Introduction

Biofilms refer to an accumulation of microorganisms (bacteria, protozoa, and other viruses) embedded in an extracellular polymeric substance (EPS) that can be attached to biological or non-biological surfaces. Biofilm generally comprises 10% to 20% microorganisms and 80% to 90% EPS, offering protection against chemical and neutrophil attacks [1]. Formation of biofilms at the base of a wound can lead to chronic infection and a persistent immune response in the host, which may result in inhibition of the wound healing process. Additionally, antibiotics cannot efficiently penetrate through the protective layers built by microbial cell aggregates, thus losing effectiveness [2]. For these reasons, biofilms are increasingly being recognized as a major obstacle to wound healing; moreover, eradicating biofilms in chronic wounds is a difficult and critical challenge in medical fields. Since the concept of biofilms was established, many related therapeutic strategies have been studied [3]. Surgical debridement is one of the most effective treatment methods for eradicating biofilms. However, while being invasive, this method is still unable to completely eradicate biofilms,
which may re-form quickly despite repeated debridement [4].

Many antiseptic agents have been applied to treat biofilms, such as povidone-iodine (PVP-I), silver, and chlorhexidine. Most of these agents have potential cytotoxicity or no clinical benefit in improving wound healing. However, some studies have reported the advantages of polyhexamethylene biguanide-betaine (PHMB-B) as it is not cytotoxic and supports wound healing [5,6].

In this report, we present a case of managing chronic wound biofilms using PHMB-B combined with silver sulfadiazine ointment in a patient with advanced breast cancer, leading to successful flap coverage without infection. This study was approved by the Institutional Review Board of Dankook University Hospital (IRB No. 2023-02-002). Upon being informed regarding submission of this case study for publication, the patient provided written informed consent.

Case

A 46-year-old female was referred to the plastic surgery department for reconstruction after a palliative mastectomy by general surgery. The patient first found a lump suspected of breast cancer in 2017 but left it untreated for 2 years. Breast cancer was diagnosed in 2019, and it was found to have already spread to the bones, lungs, and brain. The patient’s left breast presented with a 10×20 cm open wound with a foul odor (Fig. 1A). Palliative chemotherapy and radiotherapy were performed nine and two times, respectively. The patient’s metastasized brain cancer showed improvement, but the size of the tumor in the left breast did not decrease significantly. In addition, the chronic wound on the patient’s left breast worsened. Despite the use of antibiotics and antiseptics, the secretion of odorous wound exudate increased. Several pathogens,

**Fig. 1.** Clinical photographs of chronic wounds. (A) Left breast cancer with chronic open wounds. (B) After palliative mastectomy. (C) After surgical debridement. (D) Before initial polyhexamethylene biguanide-betaine (PHMB-B) dressing combined with silver sulfadiazine ointment. (E) One week after PHMB-B dressing combined with silver sulfadiazine ointment. (F) Two weeks after PHMB-B dressing combined with silver sulfadiazine ointment.
such as *Acinetobacter baumannii*, *Corynebacterium* species, and *Pseudomonas aeruginosa* had been identified in wound cultures. Clinically, it was suspected that the chronic wound had microbial infiltration and biofilm growth.

A palliative total mastectomy was performed in November 2021. After mastectomy, the wound was measured to be approximately 30×30 cm, with continued excessive secretion of foul-smelling wound exudate (Fig. 1B). No cancer cells were found on the mastectomy resection margin, but the patient was positive for lymphovascular invasion. Accordingly, negative pressure wound therapy was not carried out due to concerns about tumoral recurrence or seeding; instead, PVP-I wet gauze dressing was applied every day. Meanwhile, intravenous vancomycin was administered, corresponding to bacterial culture results. Three days after palliative mastectomy, additional surgical debridement was performed to mechanically remove the remaining infected tissue, including the thick EPS of the biofilm (Fig. 1C). Postoperatively the daily PVP-I wet gauze dressing routine was changed to twice daily, but the wound retained its foul-smelling exudate and did not improve significantly. *P. aeruginosa* was the only microorganism identified in wound cultures. The patient also complained of severe pain with PVP-I dressings. Three days later, we switched the dressing to silver sulfadiazine ointment twice a day and also changed the intravenous antibiotics to tigecycline. However, silver sulfadiazine ointment alone was not effective in eradicating the biofilm; the necrotic slough with foul-smelling wound exudate still remained (Fig. 1D). Four days after the initiation of silver sulfadiazine ointment dressings, we additionally applied PHMB-B, a combination of 0.1% polyhexamethylene biguanide (PHMB) and 0.1% betaine (Prontosan, B. Braun Medical Inc.), using PHMB-B soaked gauze for 15 minutes before the application of silver sulfadiazine ointment (Fig. 2). A reduction in necrotic slough and foul-smelling wound exudate was observed during the first week of using PHMB-B dressing combined with silver sulfadiazine (Fig. 1E).

![Fig. 2.](image1.png) Clinical photographs of polyhexamethylene biguanide-betaine (PHMB-B) dressing. (A) PHMB-B irrigation. (B) PHMB-B wet gauze applying for 15 minutes before silver sulfadiazine ointment treatment.

![Fig. 3.](image2.png) Clinical photographs of the patient. (A) After palliative mastectomy. (B) Before pedicled transverse rectus abdominis myocutaneous (TRAM) flap coverage. (C) Three weeks after pedicled TRAM flap coverage.
Clinical improvement was consistently observed over 2 weeks, and no microorganisms were identified in follow-up wound cultures (Fig. 1F). In this manner, the wound bed was sufficiently cleaned and prepared for flap coverage in approximately 3 weeks. Subsequently, pedicled transverse rectus abdominis myocutaneous flap breast reconstruction was successfully performed without complications (Fig. 3).

Discussion

Chronic wounds can occur when wound healing does not progress in an orderly and timely manner. This delay or failure in chronic wound healing increases the likelihood of wound infection [7]. Therefore, maintaining the bioburden of a wound at a level where the host remains in control is important for avoiding wound infection [8]. In a persistent wound infection state, planktonic bacteria first attach to the wound surface and form microcolonies which eventually develop into mature biofilm [2]. A recent systematic review and meta-analysis showed that the prevalence of biofilm in chronic wounds was 78.2%, suggesting that biofilm was present in most chronic non-healing wounds [3]. The unique EPS of biofilm composed of polysaccharides, DNA, and proteins enables bacteria to survive from the assaults of external substances and antibiotics [1,2]. From the perspective of the wound, biofilms secrete substances that maintain a chronic inflammatory state, which results in delayed wound healing [1,8]. In addition, although wound culture results may demonstrate only one organism in biofilm, multiple microorganisms may be present in deeper parts of the wounds. In particular, *P. aeruginosa* embedded in the deep layers of biofilm may be missed in standard wound swab cultures [9].

Recent guidelines for detecting biofilms have suggested the use of scanning electron microscopy and confocal laser scanning microscopy as the most reliable methods. However, these techniques are impractical for clinical use and require specialized knowledge [7]. Macroscopic detection of biofilms in wounds can be challenging due to the presence of debris, slough, and exudate, which may be confused with biofilms. However, the presence of biofilms in wounds can be inferred using certain clinical indicators, such as treatment failure despite using appropriate antibiotics or antiseptics, delayed wound healing, repeated cycles of infection or exacerbation, excessive moisture, and wound exudate [4]. In this study, the secretion of odoruous exudate increased in the chronic wound of the patient despite the use of antibiotics and antiseptics, thus suggesting microbial infiltration and biofilm growth.

Wound bed preparation (tissue management, control of infection/inflammation, moisture balance, and advancement of the epithelial edge of wound) is important for biofilm treatment. These principles suggest to maintain a healthy wound bed with a combination of necrotic tissue removal including EPS of biofilm, wound cleansing using antiseptics, and antimicrobial therapy [10]. Mechanical removal via debridement and biofilm suppression with antiseptic agents is considered an effective method in managing wounds with biofilm. This therapeutic strategy enhances further reduction of microorganisms and inhibits the regrowth of the biofilm [4]. Many antiseptic agents have been suggested for the treatment of biofilm. PVP-I is an iodine-release agent with a broad spectrum of antimicrobial activity and antibiofilm efficacy [3]. However, some studies have reported that PVP-I showed inferior results compared to PHMB in terms of biocompatibility, and was less effective in reducing the wound size than silver dressings [11]. Silver-containing products have a broad antimicrobial spectrum of activity against multidrug resistant strains. However, they may have some disadvantages regarding tissue irritation, delayed wound healing, and pseudo-eschar formation [12].

PHMB, also known as polyhexamethylene biguanide has a broad spectrum of bactericidal activity and is widely used. Its structure is similar to antimicrobial peptides produced by neutrophils and keratinocytes infiltrating the wound. PHMB promotes bacterial cell wall rupture via its cationic attraction to the negatively charged bacterial surface. Furthermore, PHMB binding increases plasma membrane permeability, resulting in the loss of low molecular weight molecules. Rupture of the plasma membrane induces the release of cellular contents and leads to bacterial cell death [13,14]. The broad spectrum of the bactericidal effects of PHMB includes Gram-positive and negative bacteria and biofilm-forming bacteria [6]. Additionally, it is practically non-toxic and supports wound healing with little pain while being effective in reducing bacteria burden. It also only seldom acts as a contact allergen, carrying only a slight risk of allergic responses. According to a 2010 review, sensitization to PHMB was not observed in patients with chronic wounds for whom the contact sensitization rate with PVP-I was up to 20.0% [13].

Betaine (undecylenamidopropyl betaine) is an alkaloid surfactant that can be found in sugar beet. As a surfactant, it has a hydrophilic head and hydrophobic tail. It pulls denatured proteins and lipids coating the wound surface which subsequently can be removed by irrigation fluid as debris [8]. This action
also increases the antimicrobial activity of PHMB. The syner-
getic effect of the surfactant betaine (removing debris) and
PHMB (antimicrobial activity) acting sequentially can remove
biofilm more effectively and reduce or prevent regression of
chronic wounds. A previous study has reported the effective-
ness of a combination of 0.1% PHMB and 0.1% betaine
(PHMB-B) for treating biofilms in chronic wounds. Wounds
were soaked for 15 minutes with PHMB-B moistened gauze,
followed by active cleansing. Subsequently, an ion-releasing
silver alginate was used. The results demonstrated that using a
wound cleaner with anti-biofilm properties, such as PHMB-B,
along with a silver dressing as an antimicrobial significantly
promotes wound healing [15].

In our study, PHMB-B was used for the treatment of a
chronic wound covered with biofilm in a patient with ad-
vanced breast cancer. We used a PVP-I dressing for the first-
line choice of treatment. However, PVP-I not only showed no
clinical effects, but also induced severe pain in the patient. Due
to the continuous inflammatory phase of the wound, elevated
C-reactive protein levels, and appearance of multidrug resis-
tant P. aeruginosa on wound cultures, dressings with silver sul-
fadiazine ointment alone were planned for the second-line
choice of treatment. However, the use of only silver sulfadia-
ze ointment was ineffective in controlling the biofilm, so we
tried applying PHMB-B for 15 minutes before silver ointment
treatment. During the first 2 weeks of treatment with PHMB-
B and silver sulfadiazine ointment, the wound site biofilms
were significantly diminished, and no microorganism was
identified in subsequent wound cultures. It could be assumed
that deactivation of biofilm by PHMB-B enabled the antipseu-
domonal effect of the silver sulfadiazine ointment and antibi-
otics to be activated. Moreover, the patient did not complain
about any pain during this process.

Although the use of PHMB-B has been reported in several
different types of wounds such as venous ulcers, pressure ulcers,
diabetic foot ulcers, and burn wounds, few studies on PHMB-B
treatment combined with silver sulfadiazine on biofilm-cov-
ered chronic cancer wounds have been reported. In this study,
we report a favorable case of treatment for a chronic wound
covered with biofilms using PHMB-B combined with silver
sulfadiazine ointment in an advanced breast cancer patient.

Conflict of interest

Hong Bae Jeon, managing editor of the Journal, is the corre-
sponding author of this article. However, he played no role
whatsoever in the editorial evaluation of this article or the de-
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