Polihexanide – Perspectives on Clinical Wound Antisepsis

A. Kramer^a N.-O. Hübner^a O. Assadian^a G. Mulder^b

^aInstitute of Hygiene and Environmental Medicine, Ernst Moritz Arndt University Greifswald, Greifswald, Germany;

^bWound Treatment and Research Center, Department of Surgery/Division of Trauma, University of California San Diego, San Diego, Calif., USA

Disruption of the integrity of the skin is common experience with the resulting wound repair process being a well-orchestrated and complex phenomena. An undisrupted defined sequence of tissue repair, in combination with local and systemic biochemical, immunological and biophysical factors makes normal closure of the wound possible. When intrinsic or extrinsic factors delay the process delayed secondary closure may result in scar formation.

Chronic wounds or ulcers result when the disruption in the skin remains open for many weeks or more. The chronic wound may result in increased associated morbidity including infection and amputation, as well as psychological distress. Prolonged bacterial presence is a significant concern as this may lead to chronic inflammation, infection and, in many lower extremity wounds, amputation.

One of the most serious disruptive factors of wound healing is infection. The prevention of wound infection is one of the most responsible tasks in medical care, its early recognition one of the most difficult, and the therapy of manifest wound infection one of the most rewarding. With every application of an antiseptic in wound treatment, the therapist treads the narrow path between the benefit of the antimicrobial effect and the risk of reducing the patient's self-healing powers, e.g. as a result of

the cytotoxicity of the antiseptic. This area of conflict has always been the driving force in the development of new antimicrobial substances and wound coverings.

Despite the lack of knowledge about microorganisms until relatively recently, the search for substances with an antiseptic action is as old as medicine itself, and follows a fascinating path of hope, success, failure and resultant new solutions. Initially, antiseptic wound treatment, first and foremost inaugurated by Lister (1867), marked a turning point in antiseptic prophylaxis and the therapy of contaminated wounds. But hardly 20 years later, 'Listerism' started to be criticized, mainly on account of the toxicity of the carbolic acid that he used for antisepsis.

After the discovery of penicillin by Alexander Fleming in 1923 and the introduction of antibiotics on the market in 1947, the prevention and therapy of wound infections by means of antiseptics declined in importance almost to the point of insignificance as a result of the sensational initial successes obtained with the use of the well-tolerated and highly effective chemotherapeutic agents and the local and systemic side effects of the antiseptics available at the time. Only with the widespread development of resistance of the wound infection pathogens to antibiotics, the associated necessity of restricting their use to essential indications, and the replacement of antiseptic substances with a narrow therapeutic margin (hydrogen per-

oxide, organic mercury compounds, dyes, sulfonamides, iodine-containing antiseptics based on iodine/potassium iodide, nitrofurans, quinolones and phenolic compounds such as hexachlorophene) by better tolerated substances such as PVP-iodine and chlorhexidine did wound antiseptics start to undergo a renaissance. Additional aspects that contributed to the replacement of topical use of antibiotics on wounds were their comparatively high sensitization potential when applied topically [1–4], the potential possibility of the induction of bacterial resistance to topically used antibiotics [5–7] and the higher cytotoxicity, in some cases considerable, of topically used antibiotics [8, 9].

However, as soon as PVP-iodine was introduced, the demand arose for antiseptics with comparable efficacy but better tolerability [10]. Good [11] combined polihexanide, which until then had only been used as a disinfectant, with polyethylene glycol 4000 in order to achieve improved wetting when used on wounds. With this development, a product introduced under the name Lavasept®, the triumphal march of this substance has begun. In 1994, the convincing results achieved up to then with this combination were published by Willenegger [12] under the title ‘Local antiseptics in surgery – revival and advance’. In the same year, in an editorial the possibilities of preventing postoperative wound infections, including ventilation-associated pneumonia, and of therapeutic peritoneal lavage by means of local use of polihexanide while refraining from the use of antibiotics [13] were demonstrated.

The active substance polihexanide stands out from the previously known antiseptic substances due to one crucial characteristic: in comparison with Ringer’s solution, polihexanide is the only currently known wound antiseptic to significantly promote wound healing in the use concentration [14, 15, 27]. In the bacterially infected cell culture, the pathogens are killed without cell proliferation being prevented [16]. Despite this property which is surprising for a microbicidal substance, the efficacy requirements of an antiseptic are not only fulfilled, but polihexanide surpasses both chlorhexidine as well as triclosan and PVP-iodine in microbicidal efficacy, albeit with a clear time dependency [17]. Further, polihexanide has good skin and mucous membrane tolerability, including the eye, and has negligible cytotoxicity [18]. This is shown in a biocompatibility index >1 [19]. Efficacy against intracellular microorganisms is also a feature, which is why polihexanide is used for the treatment of *Acanthamoeba* keratitis [20].

Although for polihexanide, as well as for all wound antiseptics, only data with limited meaningfulness from randomized, controlled, double-blind studies exist, in the overall evaluation based on the findings in vitro, in ex vivo models, in experimental animals and the results of therapy in human medicine, the substance became established as the therapy standard for chronic wounds and is considered to be the agent of first choice for poorly healing chronic or very sensitive wounds. Polihexanide-based wound antiseptics are also suitable for the antiseptic primary care of traumatic contaminated wounds [21] and for the treatment of infected wounds, including irrigation-suction drainage. Finally, polihexanide is used with success in wound dressings for moist wound cover [22]. In an evaluation of the level of knowledge, in an independent consensus recommendation from the year 2004, polihexanide was classified as the agent of choice for poorly healing and chronic wounds [23]. With the collaboration of representatives of the Austrian Wound Association, the German Society for Wound Healing and Wound Treatment and the Chronic Wound Initiative, in 2009 a further experts’ recommendation for the treatment of critically colonized or locally infected acute and chronic wounds with polihexanide was given as a further step towards the substance becoming the therapy standard [24]. Actually, this recommendation is in print in 10 European journals. Polihexanide is also recommended as an antiseptic substance in two AWMF guidelines [25, 26]. A document from a consensus meeting on contribution of PHMB to wound management will be published in the next issue of *Wound International* [28].

The decision regarding the selection of the wound antiseptic appropriate to the indication can only be made on the basis of knowledge, experience and evidence. This supplement is intended to provide assistance in that the substance polihexanide is examined critically and with regard to practical aspects by an international team of authors.

Axel Kramer,
Ernst Moritz Arndt University, Greifswald

Nils-Olaf Hübner,
Ernst Moritz Arndt University, Greifswald

Ojan Assadian,
Ernst Moritz Arndt University, Greifswald

Gerit Mulder,
University of California, San Diego

References

- Jacob SE, James WD: From road rash to top allergen in a flash: bacitracin. *Dermatol Surg* 2004;30:521–524.
- Gollhausen R, Enders F, Przybilla B, Burg G, Ring J: Trends in allergic contact sensitization. *Contact Dermatitis* 1988;18:147–154.
- Gehrig KA, Warshaw EM: Allergic contact dermatitis to topical antibiotics: epidemiology, responsible allergens, and management. *J Am Acad Dermatol* 2008;58:1–21.
- Gette MT, Marks JG, Maloney ME: Frequency of postoperative allergic contact dermatitis to topical antibiotics. *Arch Dermatol* 1992;128:365–367.
- Alsterholm M, Flytström I, Bergbrant IM, Faergemann J: Fusidic acid-resistant *Staphylococcus aureus* in impetigo contagiosa and secondarily infected atopic dermatitis. *Acta Derm Venereol* 2010;9:52–57.
- Kinney MA, Yentzer BA, Fleicher AB, Feldmann SR: Trends in the treatment of acne vulgaris: are measures being taken to avoid antimicrobial resistance? *J Drug Dermatol* 2010;9:519–524.
- Leyden JJ: Antibiotic resistance in the topical treatment of acne vulgaris. *Cutis* 2004;73:6–10.
- Kramer A, Niedner R: Toxikologische Anforderungen an lokale Antiinfektiva; in Kramer A, Wendt M, Werner HP (eds): *Möglichkeiten und Perspektiven der klinischen Antiseptik*. Wiesbaden, mhp, 1995, pp 35–40.
- Hansbrough JF, Achauer B, Dawson J, Himmel H, Luteran A, Slater H, Levenson S, Salzberg CA, Hansbrough WB, Doré C: Wound healing in partial-thickness burn wounds treated with collagenase ointment versus silver sulfadiazine cream. *J Burn Care Rehabil* 1995;16:241–247.
- Hierholzer S, Hierholzer G: *PVP-Iod in der operativen Medizin*. Berlin, Springer, 1984.
- Good H: *Charakterisierung der Desinfektionsmittel. Aktuelle Probleme der Chirurgie und Orthopädie*. Bern, Huber, 1979, pp 87–96.
- Willenegger H: Local antiseptics in surgery – revival and advance. *Eur J Trauma* 1994;20:94–100.
- Kramer A, Willenegger H: Perioperative Antibiotikaprophylaxe – dominierende Möglichkeit zur Infektionsprophylaxe bei chirurgischen Eingriffen? *Hyg Med* 1994;19:180–182.
- Kramer A, Roth B, Müller G, Rudolph P, Klöcker N: Influence of the antiseptic agents polyhexanide and octenidine on FL cells and on healing of experimental superficial aseptic wounds in piglets. A double-blind, randomised, stratified, controlled, parallel-group study. *Skin Pharmacol Physiol* 2004;17:141–146.
- Wiegand C, Abel M, Kramer A, Müller G, Ruth P, Hipler U-C: Stimulation of proliferation and biocompatibility of polyhexanide. *GMS Krankenhaushyg Interdisziplinär* 2007;2:Doc43(20071228).
- Wiegand C, Abel M, Ruth P, Hipler U: HaCaT keratinocytes in co-culture with *Staphylococcus aureus* can be protected from bacterial damage by polyhexanide. *Wound Repair Regen* 2009;17:730–738.
- Koburger T, Hübner NO, Braun M, Siebert J, Kramer A: Standardized comparison of antiseptic efficacy of triclosan, PVP-iodine, octenidine dihydrochloride, polyhexanide and chlorhexidine digluconate. *J Antimicrob Chemother* 2010 DOI: 10.1093/jac/dkq212.
- Kramer A, Adrian V, Rudolph P, Wurster S, Lippert H: Explantationstest mit Haut und Peritoneum der neonatalen Ratte als Voraussetzung zur Verträglichkeit lokaler Antiinfektiva für Wunden und Körperhöhlen. *Chirurg* 1998;69:840–845.
- Müller G, Kramer A: Biocompatibility index of antiseptic agents by parallel assessment of antimicrobial activity and cellular cytotoxicity. *J Antimicrob Chemother* 2008;61:1281–1287.
- Behrens-Baumann W, Kramer A: Therapeutic indications for local anti-infectives. *Anti-infectives against amebic keratitis*. *Dev Ophthalmol* 2002;33:297–303.
- Roth B, Assadian O, Wurmitzer F, Kramer A: Surgical site infections after primary antiseptic cleansing of dirty-contaminated wounds by polyhexanide, PVP iodine resp. hydrogen peroxide. *GMS Krankenhaushyg Interdisziplinär* 2007;2:Doc58(20071228).
- Mulder GD, Cavorsi JP, Lee DK: Polyhexamethylene biguanide (PHMB): an addendum to current topical antimicrobials. *Wounds* 2007;19:173–182.
- Kramer A, Daeschlein G, Kammerlander G, Andriessen A, Aspöck C, Bergemann R, Eberlein T, Gerngross H, Görtz G, Heeg P, Jünger M, Koch S, König B, Laun R, Peter RU, Roth B, Ruef C, Sellmer W, Wewalka G, Eisenbeiss W: Konsensusempfehlung zur Auswahl von Wirkstoffen für die Wundantiseptik. *Hyg Med* 2004;29:147–157.
- Dissemond J, Gerber V, Kramer A, Riepe G, Strohal R, Vassel-Biergens A, Eberlein T: A practice-orientated recommendation for treatment of critically colonized and locally infected wounds using polyhexanide. *J Wound Tech* 2010;7:27–33.
- AWMF-Leitlinien-Register Nr 029/019. Massnahmen beim Auftreten multiresistenter Erreger (MRE). www.uni-duesseldorf.de/AWMF/ll/029-019.htm. 2004.
- AWMF-Leitlinien-Register Nr 037/009. Diagnostik und Therapie des Ulcus cruris venosum. www.uni-duesseldorf.de/AWMF/ll/037-009.htm. 2004.
- Gilliver S: PHMB: a well-tolerated antiseptic with no reported toxic effects. *J Wound Care/ACTIVA Healthcare* 2009;(suppl 2):14.
- Barrett S, Battacharyya M, Butcher M, Enoch S, Fumarola S, Gray D, Haynes JS, Edwards-Jones V, Leaper D, Strohal R, White R, Wicks G, Young T: PHMB and its potential contribution to wound management. *Wounds Int* 2010;1 (in press).