Use of chlorhexidine in wound healing and granulation tissue formation

Edgar G. Wagner, Juan M. Sala
Orthopedics Department, Hospital Regional de Comodoro Rivadavia, Chubut, Argentina

ABSTRACT
Introduction: Wounds with dressing defects pose a great challenge when choosing a good treatment that may reduce the risk of infection and promote granulation tissue formation. **Objective:** To demonstrate the usefulness of chlorhexidine digluconate (CHG) for granulation tissue formation. **Materials and methods:** Eighteen wounds (16 patients) that met the inclusion criteria were included. Wound cleansing was performed in outpatients with 20% CHG-impregnated cloths every 48-72 h, until the proper tissue granulation was achieved. Photographs of the clinical evolution of the wounds were taken. **Results:** The adequate wound granulation mean was of 9.2 days (4-25 days) regardless of wound size or presence of comorbidities. There were no clinical signs of infection in any wound during the healing period. **Conclusions:** CHG treatment is an appropriate method to be considered for outpatient injuries, which reduces the hospital costs borne by the health-care system.
Level of Evidence: III.
Key words: chlorhexidine, wounds, granulation tissue, skin dressing defect.

Uso del gluconato de clorhexidina en la curación de heridas y su potencial formación de tejido de granulación

RESUMEN
Introducción: Las heridas con defectos de coberturas suponen un gran desafío a la hora de elegir un buen tratamiento que reduzca el riesgo de infección e incremente la capacidad de granulación del tejido. El objetivo de este estudio fue demostrar la utilidad del digluconato de clorhexidina para la granulación de tejidos. **Materiales y Métodos:** Se incluyeron 18 heridas de 16 pacientes que cumplían con los criterios de inclusión. Se realizaron curaciones ambulatorias con gasas embebidas en digluconato de clorhexidina al 20%, cada 48-72 h, hasta lograr la adecuada granulación de tejido y se tomaron fotografías de la evolución clínica de las heridas. **Resultados:** Se observó una adecuada granulación de las heridas en una media de 9.2 días (rango 4-25 días), independientemente del tamaño o de la comorbilidades. Ninguna herida presentó signos clínicos de infección durante el período de curación. **Conclusiones:** El uso de digluconato de clorhexidina es un adecuado método por tener en cuenta para tratar heridas, de forma ambulatoria, y así disminuir los costos hospitalarios del sistema de salud.
Palabras claves: Clorhexidina; heridas; tejido de granulación; defecto de cobertura.
Nivel de Evidencia: IV

INTRODUCTION

The antiseptic properties of CHG have been known since the 1950s.[1] CHG common applications include from oral hygiene to preoperative surgical preparation and the prevention of hospital-acquired infections due to multi-drug-resistant organisms.[1,2] CHG is a bisbiguanide and exists as a cationic form at physiological pH that binds to the negatively charged bacterial cell wall, altering the osmotic equilibrium of the bacterial cell and resulting in the leakage of cytoplasmic contents.[3,4] CHG is water-insoluble, thus the commercial CHG for clinical applications is usually formulated with gluconic acid to form water-soluble salts.[3,4]

Received on April 21st, 2019. Accepted after evaluation on November 30th, 2019 • Edgar G. Wagner, MD • edgar.gw@hotmail.com
How to cite this paper: Wagner EG, Sala JM. Use of chlorhexidine in wound healing and granulation tissue formation. *Rev Asoc Argent Ortop Traumatol* 2020;85(2):139-146. https://doi.org/10.15417/issn.1852-7434.2020.85.2.985

Esta Revista está bajo una Licencia Creative Commons Atribución-NoComercial-Compartir Obras Derivadas Igual 4.0 Internacional. (CC-BY-NC-SA 4.0).

CHG has broad-spectrum activity and is highly effective against a wide variety of Gram-positive microorganisms, such as *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus* [MRSA]) and coagulase negative *Staphylococcus*. It also demonstrates activity against Gram-negative bacteria, fungi and, to a lesser extent, mycobacteria. It is sporostatic, but not sporicidal.[3,4] It has a rapid onset, approximately 20 seconds, and a prolonged residual effect.[2] The antimicrobial activity of CHG has been documented to persist up to 48 hours of contact with skin.[4] It is bacteriostatic at low concentrations (0.0002% to 0.5%) and bactericidal at higher concentrations (>0.5%).[3,4]

One of its most significant characteristics is its *in vitro* activity against enveloped viruses, including herpes simplex virus, HIV, cytomegalovirus, influenza virus, and respiratory syncytial virus); however, it has lower activity against non-enveloped viruses.[3]

The beneficial effect of CHG on the granulation tissue formation in wound areas has been proven by some studies, mainly animal model studies (rabbits and pigs).[5]

Our Department of Orthopedics has a non-systematized positive record concerning skin dressing defects in patients treated with 20% CHG-impregnated cloths.

The aim of this study is to demonstrate the usefulness of CHG in healing wounds (infected and non-infected) and generating granulation tissue that would allow for an epithelialization procedure, a skin flap or graft or a referral to a plastic surgery specialist. To the best of our knowledge, there are no local or international studies on this particular subject.

MATERIALS AND METHODS

This is an observational retrospective study on all adult and pediatric patients of both sexes that were admitted to our department between 1/7/2017 and 21/12/2018 due to skin dressing defects.

All wound dressing changes were performed by the author of this study. The inclusion criteria were: all patients of both sexes who had skin dressing defects of different origins (e. g., surgical wound infection sequelae or wound dehiscence) as well as different trauma injuries that precluded wound dressing. The exclusion criteria were: all patients of both sexes who had epidermal wounds without dermal involvement and had achieved primary wound closure or were on a treatment to promote wound epithelialization, and patients who had soft-tissue lesions due to high-energy trauma or lacerated injuries, and had achieved primary wound closure. The study variables (Table 1) were: Demographic variables (sex) and Clinical variables (comorbidities, type and mechanism of injury, injury size, wound healing time).

For all patients admitted into the examination room for wound dressing changes, the physician follows the following procedural steps:

1. Patients' personal details are recorded and the consultation is entered into the medical record.
2. A wound picture is taken to document its evolution.
3. Wound cleansing is performed with abundant normal saline and 20% CHG soap (Laclorhex, 4g chlorhexidine digluconate 20% solution, Laboratorio Sertex S.R.L, Rosario, Santa Fe, Argentina) (Figure 1).
4. Dressing composed of 20% CHG-impregnated cloths is placed.
5. Bandaging is applied

The wound dressing changes were performed with CHG-impregnated cloths (20%) every 48-72h until the amount of granulation tissue detected allowed for a skin flap or graft procedure, a secondary wound closure using vaseline or silver sulfadiazine cream or a referral to a plastic surgery specialist.

The wound dressing changes included the same procedural steps taken at the first consultation plus wound toilet using a scalpel to remove fibrin from the wound before applying the 20% CHG-impregnated cloths (Figures 2-4).

The protocol of the study was approved by the Education, Training and Research Committee and the Bioethics Committee of our Center.

Table 1. Study variables

Wound	Comorbidity	Wound size (cm)	Total healing time (days)	Treatment onset	Treatment end	Sex	Wound cause
1	No	10 x 6	9	10/26/2017	11/4/2017	M	traumatic amputation
2	DM, HBP, HF, single-kidney patient	6 x 4	8	8/19/2017	8/27/2017	F	wound dehiscence
3	Osteomyelitis	5 x 3	25	10/1/2017	10/25/2017	M	fistula due to Osteomyelitis
4	No	12 x 4	17	9/14/2017	10/1/2017	M	wound dehiscence
5	DM	4 x 3	13	9/6/2017	9/19/2018	M	wound dehiscence
6	anticoagulated	6 x 4	12	3/16/2018	3/28/2018	F	Compartment Syndrome
7	DM	7 x 5	6	9/28/2018	10/3/2018	M	Traumatic degloving injury
8	No	5 x 4	7	8/8/2018	8/15/2018	M	gunshot wound
9	No	7 x 3	5	8/31/2018	9/4/2018	M	gunshot wound
10	No	10 x 4	5	8/31/2018	9/4/2018	M	gunshot wound
11	No	25 x 18	8	8/5/2018	8/13/2018	F	Morel-Lavallée syndrome
12	No	13 x 5	5	10/5/2018	10/10/2018	M	Traumatic degloving injury
13	DM	4 x 5	10	10/14/2018	10/24/2018	M	diabetic foot
14	DM	6.5 x 3	11	12/10/2018	12/21/2018	M	diabetic foot
15	No	5 x 5	7	12/10/2018	12/17/2018	M	Traumatic degloving injury
16	No	4 x 3	7	12/13/2018	12/21/2018	M	Intraoperative thermal injury
17	No	7.5 x 4	7	12/13/2018	12/21/2018	M	Intraoperative thermal injury
18	No	3.5 x 1	4	12/15/2018	12/19/2018	F	wound dehiscence

Figure 1. 20% chlorhexidine digluconate soap used in this studt (Laclorhex, 4g chlorhexidine digluconate 20% solution, Laboratorio Sertex S.R.L, Rosario, Santa Fe, Argentina).

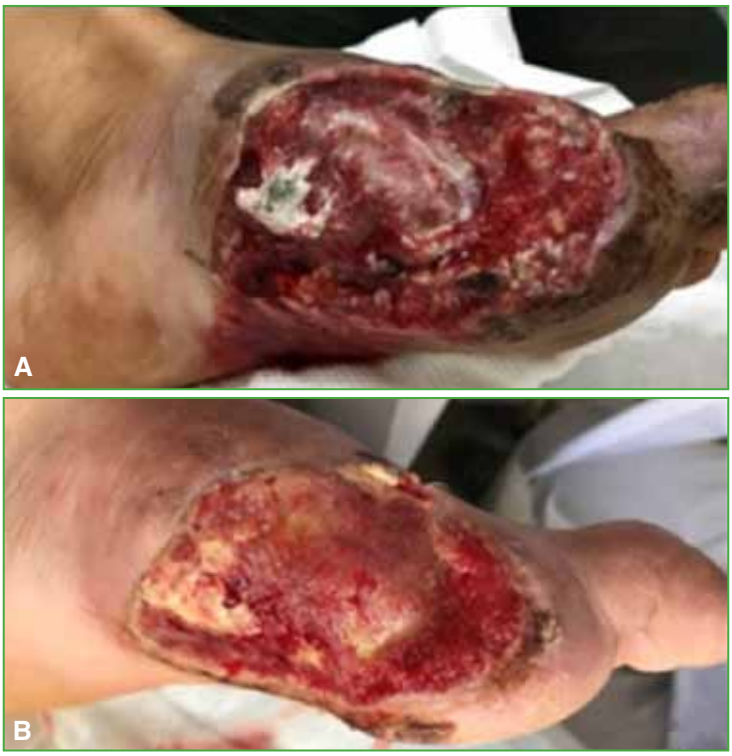

Figure 2. Traumatic amputation wound. **A.** Foot wound due to a motor vehicle accident with hallux amputation. **B.** Day 9 after 20% chlorhexidine digluconate treatment, case eligible for an epithelialization procedure, a skin flap or graft or a referral to a plastic surgery specialist.

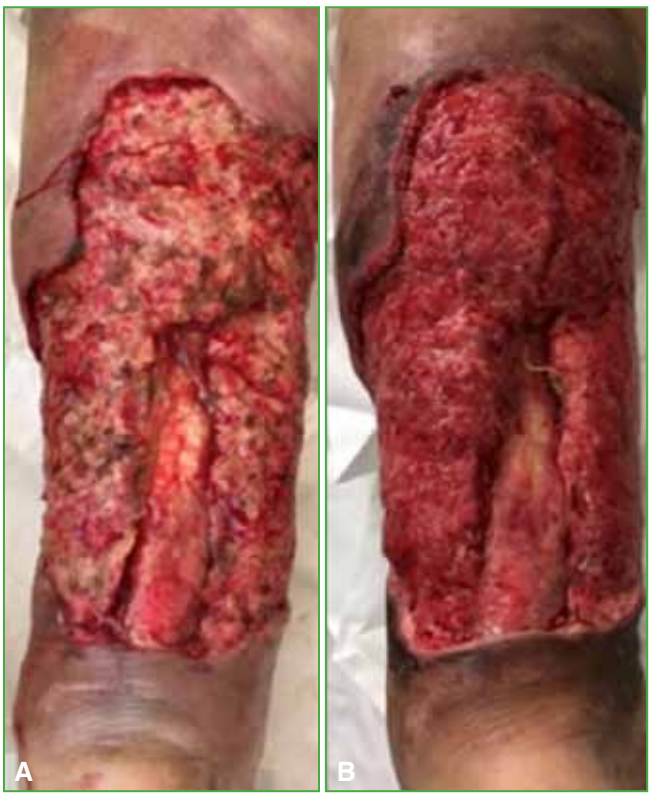

Figure 3. Morel-Lavallée injury. **A.** Postoperative Escharotomy, beginning of the chlorhexidine wound dressing change treatment. **B.** Day 8 after chlorhexidine digluconate treatment, case eligible for an epithelialization procedure, a skin flap or graft or a referral to a plastic surgery specialist.

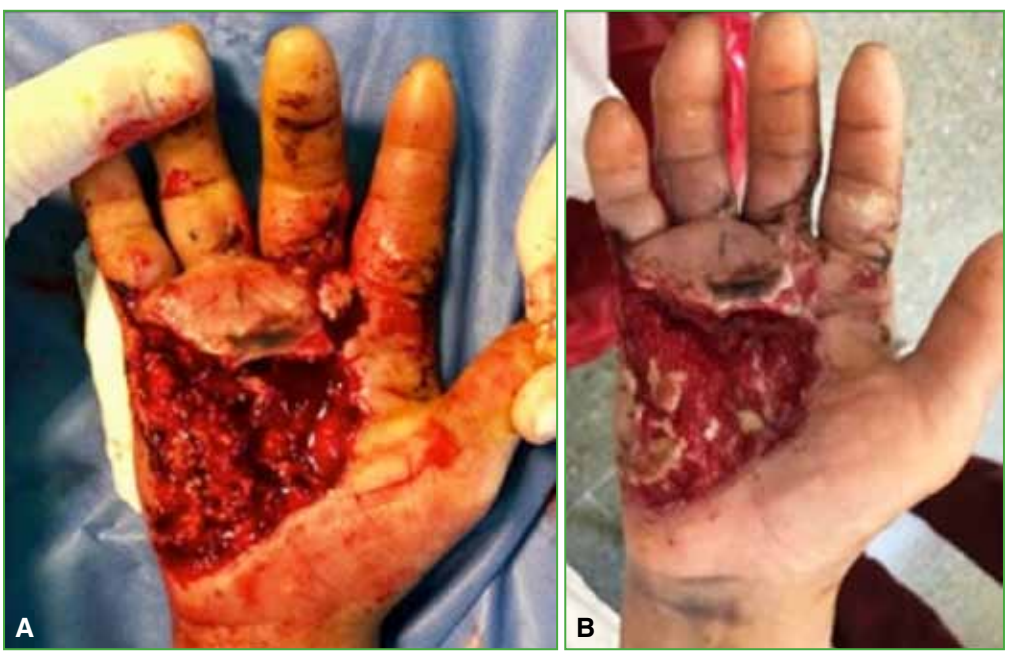

Figure 4. Hand wound due to a crushing injury in a bakery bread-making machine. **A.** Day 1 after Escharotomy, beginning of the wound dressing change treatment. **B.** Day 6 after chlorhexidine digluconate treatment, case eligible for an epithelialization procedure, a skin flap or graft or a referral to a plastic surgery specialist.

RESULTS

During the study period 16 patients who met the inclusion criteria were attended at our Center, with a total of 18 wounds with skin dressing defects. Four (25%) were females and 12 (75%) were males.

Most dressing changes were performed in patients having wound dehiscence after a surgical procedure (4 cases, 23%), followed by traumatic degloving injuries (3 cases, 17.5%), gunshot wounds (3 cases, 17.5%), intraoperative thermal injury (2 cases, 12%), diabetic foot (2 cases, 12%), Morel-Lavallée syndrome (1 case, 6%), Compartment Syndrome (1 case, 6%), and traumatic amputation (1 case, 6%).

The patients' underlying conditions were grouped into 3 categories: no comorbidities, one comorbidity, and more than one comorbidity. Six patients (38%) had 1 comorbidity, 9 patients (56%) had no comorbidities, and only 1 patient (6%) had more than one comorbidity.

The wound healing time was considered until the end of the CHG-dressing change treatment, that is, until the amount of granulation tissue detected allowed for an epithelialization procedure, a skin flap or graft or a referral to a plastic surgery specialist. The average wound healing time was 9.2 days (range, 4-25). The size of the wounds was measured by taking the greatest distance in two planes, length and width. Wound depth was not considered.

No relation was found between the variables of comorbidities, wound size and total wound healing time in relation to the granulation tissue formation.

DISCUSSION

To the best of our knowledge, to date there are no previous studies on the treatment of wounds with skin dressing defects (infected and non-infected) that had been successfully treated with CHG to promote granulation tissue formation as well as to prevent a potential infection. The antiseptic properties of CHG have been well documented in the literature, and its applications include decreasing the risk of infection in surgical procedures, promoting granulation tissue in periodontal surgeries and preventing hospital-acquired infections.[1-4,6-8]

In a 1984 study with rabbit corneal abrasion models, Bowes Hamill *et al*. reported that 2.0 and 4.0% chlorhexidine gluconate irrigations decreased the re-epithelialization rate, but this rate was not affected with concentrations of 1%.[9] In a similar study, in a model of wound infection in guinea pigs (Platt and Blucknall, 1984), chlorhexidine gluconate irrigations completely prevented infection and did not increase the time of wound healing.[10]

On the other hand, Archer *et al*. reported in their 1990 study that chlorhexidine gluconate treatment in wounds in pigs showed an exhibited delayed healing of 75% as well as a reduction of infilling with new connective tissue; however, chlorhexidine gluconate was the only treatment to eradicate all bacteria[5], which is significant to prevent any type of infection in wounds requiring dressing changes on a daily basis. In 1963, Winter *et al*. demonstrated that an occlusive dressing doubles the rate of re-epithelialization when compared to wounds exposed to air.[11]

Our literature review produced no papers on wound treatments with CHG, which is a limiting factor in comparing these study findings with those of other authors. In addition, the low population size, the different types of injuries and the different comorbidities result in very diverse healing times.

The longest healing time was in patients with clinical evidence of wound infection, thus we conclude that the infectious condition should be simultaneously treated in order to achieve and expedite an adequate granulation tissue formation. The greatest delay in granulation belonged to a wound from an active fistula associated with leg Osteomyelitis due to an open fracture.

No wound became infected during the wound dressing change process and that the surgical wounds that had presented evidence of infection and were treated with CHG had their symptoms neutralized and healed without any significant complication.

It is worth mentioning that in our public health system most patients may find it difficult to access an expedite, effective and state of the art treatment for wound dressing changes. Using CHG results in an adequate treatment for wounds with skin dressing defects that promotes granulation tissue formation and allows for the institution of another treatment based on epithelialization or skin flap or graft, or a referral to a plastic surgery specialist, while decreasing the risk of infection thanks to the already mentioned CHG properties.

No relation was found between wound size, healing time and the presence of comorbidities; thus, patients with comorbidities may be treated with CHG and be expected to achieve the same outcomes in the same amount

of time. CHG enables wound dressing changes to be an outpatient procedure, with patients attending dressing change appointments every 48-72h. This scheme significantly decreases hospitalization costs and, consequently, the health-related expenses of the public health system.

Lee *et al*. conducted a cost-benefit study on preoperative skin antisepsis and found that switching from povidone-iodine to chlorhexidine gluconate resulted in a net cost savings of 16-26 USD per surgical case and 349,904-568,594 USD per year for the hospital. Additionally, although chlorhexidine gluconate is more expensive than povidone-iodine, by decreasing the incidence of catheter-associated bloodstream infection, pneumonia, and superficial and deep infections, it decreases the total costs.[12]

CONCLUSION

Using 20% CHG as described herein constitutes an excellent treatment option for wounds with skin dressing defects (infected and non-infected) which promotes granulation tissue formation, decreases hospitalization costs of the public health system and reduces the probability of suffering wound infections. All the aforementioned provide the rationale supporting CHG use in wounds with skin dressing defects that had failed to be adequately treated with primary wound closure.

Conflict of interests: Authors claim they do not have any conflict of interests.

ORCID de J. M. Salas: https://orcid.org/0000-0002-8942-4701

REFERENCES

1. Rhee Y, Palmer LJ, Okamoto K, Gemunden S, Hammouda K, Kemble SK, et al. Differential effects of chlorhexidine skin cleansing methods on residual chlorhexidine skin concentrations and bacterial recovery. *Infect Control Hosp Epidemiol* 2018;1-7. https://doi.org/10.1017/ice.2017.312.
2. Wang EW, Layon AJ. Chlorhexidine gluconate use to prevent hospital-acquired infections - a useful tool, not a panacea. *Ann Transl Med* 2017;5(1):14. https://doi.org/10.21037/atm.2017.01.01
3. Maya JJ, Ruiz SJ, Pacheco R, Valderrama SL,Villegas MV. Papel de la clorhexidina en la prevención de las infecciones asociadas a la atención en salud. *Infectio* 2011;15(2):98-107. http://www.revistainfectio.org/index.php/infectio/article/view/12/24
4. George J, Klika AK, Higuera CA. Use of chlorhexidine preparations in total joint arthroplasty. *J Bone Jt Infect* 2017;2(1):15-22. https://doi.org/10.7150/jbji.16934.
5. Archer HG, Barnett S, Irving S, Middletont KR, Seal DV. A controlled model of moist wound healing: comparison between semi-permeable film, antiseptics and sugar paste. *J Exp Pathol (Oxford)* 1990;71:155-70. PMID:2331404
6. Makhni MC, Jegede K, Lombardi J, Whittier S, Gorroochurn P, Lehman RA, et al. No clear benefit of chlorhexidine use at home before surgical preparation. *J Am Acad Orthop Surg* 2018;26:e39-e47. https://doi.org/10.5435/JAAOS-D-16-00866
7. Edmiston CE Jr, Leaper D. Should preoperative showering or cleansing with chlorhexidine gluconate (CHG) be part of the surgical care bundle to prevent surgical site infection? *J Infect Prev* 2017;18(6):311-4. https://doi.org/10.1177/1757177417714873
8. Phillips PL, Young D, Chakravarthy D. The compatibility of chlorhexidine and a skin care product line. A real-world analysis of hospital-acquired infection rates. *Health Care Manag (Frederick)* 2017;36(3):288-92. https://doi.org/10.1097/HCM.0000000000000175
9. Hamill MB, Osato MS, Wilhelmus KR. Experimental evaluation of chlorhexidine gluconate for ocular antisepsis. *Antimicrob Agents Chemother* 1984;26(6):793-6. https://doi.org/10.1128/aac.26.6.793

10. Platt J, Bucknall RA. An experimental evaluation of antiseptic wound irrigation. *J Hosp Infect* 1984;5(2):181-8. https://doi.org/10.1016/0195-6701(84)90122-1
11. Winter GD, Scales JT. Effect of air drying and dressings in the surface of a wound. *Nature* 1963;197:91-2. https://doi.org/10.1038/197091b0
12. Lee I, Agarwal RK, Fishman NO, Umscheid CA. Systematic review and cost analysis comparing use of chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. *Infect Control Hosp Epidemiol* 2010;31(12):1219-29. https://doi.org/10.1086/657134.