Case Series

Fifty-Patient Study Evaluating the Efficacy of Modified Collagen With Glycerin in Periwound Skin Management

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Abstract

The management of chronic nonhealing ulcers pose a great challenge because they are associated with morbidity and increased costs. This report presents the observations of standard management along with application of modified collagen with glycerin (MCG) in the periwound area for management of nonhealing wounds. This observational report included 50 patients (33 male, 17 female) aged 24 to 94 years having nonhealing wounds. All wounds were treated using standard treatment protocols (TIME concept), whereas the periwound severity was assessed using the Harikrishna Periwound Skin Classification (HPSC). All patients received once-daily application of MCG lotion directly in the periwound areas and compression bandaging until there was complete wound healing. Patient compliance was ensured by regular follow-up and counseling. All diabetic patients were counseled to ensure glycemic control during the entire follow-up period. The criteria used for wound healing were based on clinical observation, and proper epithelialization of the wound was the end point. The median age of the wounds was 12.0 weeks (95% CI = 8.00 – 58.08). Majority of the non-healing wounds were diabetic foot ulcers with age of wound between 4 weeks to 15 years. The median time to complete wound healing was 12.71 (95% CI = 10.00-16.67) weeks. Standard treatment protocol of TIME principle with periwound area assessment based on HPSC 2015 and treatment accordingly with topical application of MCG along with additional measures has shown complete healing of nonhealing wounds. However, further large-scale comparative studies are needed to substantiate these effects on a larger population.

Keywords

periwound skin classification, shortening healing time, strengthen skin integrity, modified collagen and glycerin

Background

Nonhealing wounds are defined as wounds that do not improve after 4 weeks of standard treatment and supportive measures in a timely manner,[1] and these commonly include diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), nonhealing surgical wounds, pressure ulcers, wounds related to metabolic disorders, or wounds that repeatedly break down. Management of nonhealing wounds poses a great challenge because they are associated with underlying disorders and are prone to complications, including secondary infections and risk of amputation.[2] Also, in a planned systematic review protocol, chronic nonhealing wounds are reported to present a substantial economic burden to the health care system, and cause significant reductions in quality of life (QOL) and precede often serious events such as limb amputation or even premature death.[3]

One of the important steps in the process of wound healing is collagen synthesis,[4] and application of collagen dressings has been reported to enhance the wound healing process through multiple mechanisms in the preclinical setting.[5] These include induction of a transient inflammatory response followed by increased vascularization, leading to accelerated collagen deposition.[5] Collagen also may stimulate wound granulation by increasing mobilization of cells into the wound through increasing cell signal induction.[6]

The triangle of wound assessment propagated by Carolyn Dorsett and Keith Harding during the EWMA conference, which was published in the *International Wound Journal*, mentions the assessment of the wound bed preparation itself and emphasizes the importance of wound edges and the periwound.[7,8] The periwound area, also termed *the defensive zone that contains the wound*[7] is critical for the wound healing process, and an unhealthy periwound area is reported to

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Table 1. Harikrishna Periwound Skin (HPS) Classification, 2015.

HPS Class	Periwound Condition
Class 0	Normal
Class 1	Fibrous tissues/tissue at risk
Class 2A	Exudate centered with desiccation
Class 2B	Exudate centered with maceration
Class 2C	Exudate centered with allergy
Class 3	Inflammation without infection
Class 4	Inflammation with infection
Class 5	Atypical (senescent cells/cancer/subcutaneous emphysema)

be one of the major causes of nonhealing.[9] Thus, a healthy periwound—that is, the absence of any abnormalities surrounding the wound area is also important in the successful healing process. Collagen-containing topical formulations are recommended for improving wound healing. This article reports the user experience of standard wound management along with application of modified collagen with glycerin (MCG) on the periwound area in the treatment of nonhealing wounds of various etiologies at a wound care specialty clinic at the Internal Medicine Department Hospital, Kuala Lumpur.

Methodology

This study was conducted at Wound Care Unit, Department of Internal Medicine, Kuala Lumpur Hospital, and all study-related documents and informed consent forms were reviewed by the institutional review board.

Study Participants

A total of 50 patients (33 male and 17 female) between 24 and 94 years of age (median age = 56 years, 95% CI = 53-59 years) having nonhealing wounds for at least a duration of 4 weeks were included for this observational report, and there were no specific exclusions. The wound etiology was confirmed based on detailed history, clinical examination, ankle brachial index, ultrasound imaging, and laboratory findings. Informed consent was obtained from all patients prior to their inclusion for therapy. The periwound area (ie, the skin within 4 cm of the wound edge as well as any skin under the dressing) was assessed based on a new classification called the Harikrishna Periwound Skin Classification (HPSC), which was presented in the International Biotherapy and Wound Conference, Kuala Lumpur, Malaysia (2015) and at the Fifth WUWHS (World Union of Wound Healing Societies) Congress, Florence, Italy (2016). It categorises wounds based on the health of the periwound region, with class 0 as healthy skin and classes 1 to 5 depicting the different statuses of the periwound area (Table 1).[10] This suggested classification is based on the now widely accepted theory of triangle of wound assessment, which considers the 3 factors of wound bed, wound edge, and periwound skin as important factors in the healing of wounds.[7] Among the 3 factors, the periwound area has been one of the most important factors, and rehydration of dry skin and avoidance of exposure to exudate/moisture in this area can improve wound healing.[11]

Study Treatments

Wound management was done with standard treatment protocols[12] in line with the TIME concept of wound bed preparation where tissue (T) debridement was done for any nonviable tissue, necrotic tissue, and presence of any slough or eschar; presence of any infection (I), whether local or systemic was treated with topical application of silver dressing or systemic antimicrobials; moisture (M) balance was maintained using foam as a secondary dressing, which conforms to standard wound care practice; and wound edges (E) were managed by proper dressings. In addition to wound management, treatment was focused on periwound management with topical application of MCG lotion (Stimulen lotion, Southwest Technologies, Kansas City, MO) directly in the periwound areas during all dressings in all patients. The amount of lotion used varied depending on the wound size and the periwound class, per the HPSC 2015 (Table 1). Patients with inflammatory lesions received systemic anti-inflammatory agents. DFU patients received offloading, and those having VLU received compressive dressings. Patients came for follow-up, whereby dressing change was done 2 to 3 times a week according to the severity. Patients were provided the dressing material for regular daily application at home and were instructed and trained to apply the treatments. Patients were followed up weekly till complete wound healing or clinically significant improvements were observed. Patient compliance was ensured by regular follow-up and counseling. Patients with class 4 wounds were given systemic antibiotics for control of infection. All patients continued their other treatments for underlying conditions per their primary physician's prescriptions. All diabetic patients were counseled to ensure glycemic control during the entire follow-up period. Clinical safety of MCG was assessed based on the local reactions and irritation after application of MCG.

Assessments

The criteria used for wound healing were based on clinical observation, and proper epithelialization of the wound was the end point.[13,14] Epithelialization was assessed based on clinical and photographic evidence. Wound closure was decided based on the criteria of complete closure of wound gap, nonvisibility of wound bed, absence of any exudate, and approximation of wound margins. Wound size was not

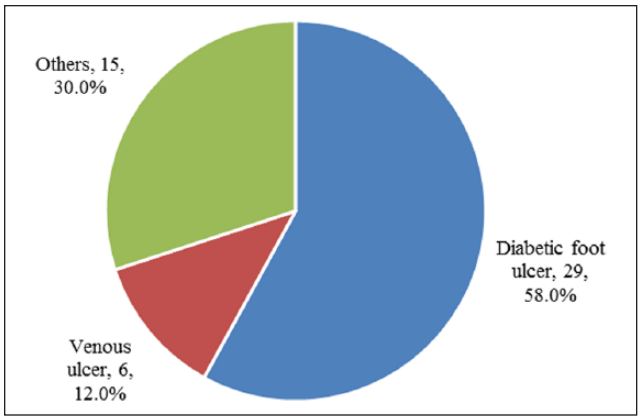

Figure 1. Wound types in patients (percentage, n = 50).

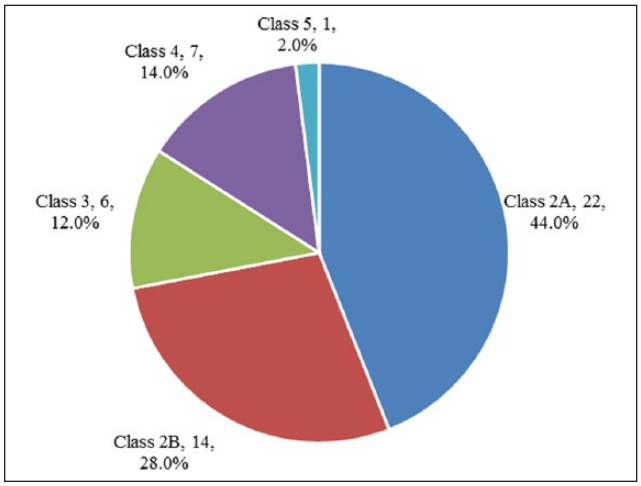

Figure 2. Periwound skin class (percentage, n = 50).

measured as a part of efficacy assessment. Clinical safety of MCG was assessed based on the local reactions and irritation after application of lotion. Wound assessments were made by different nurses who were trained for wound assessments and were supervised by a senior wound nurse.

Statistical Analyses

Data for time are presented as means and medians, whereas discrete data are presented as counts with percentages. This being an observational data study and there being no hypotheses, only descriptives are presented for the data. All analysis is done using Windows-based proprietary software Stata Version 13.1 (StataCorp LP, College Station, TX).

Results

The patient distributions based on wound type and periwound class are displayed in Figures 1 and 2, respectively. A majority of the patients had DFUs with wound age ranging from 4 weeks to 15 years (median = 12 weeks; 95% CI = 8.00-58.08 weeks). Of the 50 patients, 29 (58.0%) had DFUs, 6 (12.0%) had venous ulcers, and 15 (30.0%) had other nonhealing wounds. Other wound types included pressure injuries (n = 3), cellulitis (n = 3), necrotizing fasciitis (n = 2), postoperative fungating mass in breast (n = 1), infected foot ulcer (n = 1), dorsal multiple skin eruption (n = 1), osteomyelitis (n = 2), surgical site infection (n = 1), and abscess (n = 1). The distribution of patients according to the HPSC 2015 is presented in Table 2. About 36 (72.0%) patients had exudate-centered wounds, and 13 (26.0%) had inflamed wounds.

The median time to complete wound healing in all patients was 12.71 weeks (95% CI = 10.00-16.67). Table 3 shows the median and mean time for complete wound healing in different wound types and periwound class types. The time to heal was longer for venous ulcers (Figure 3) and relatively shorter in male compared with female patients. However, this hypothesis was not tested in the analysis. Patients with venous ulcers need longer times to heal even for HPS class 2 wounds.

It was observed that with standard care of the wound ensuring a healthy wound bed with adequate moisture and careful management of the periwound site with MCG lotion, the wounds experienced full closure in the clinical course. Figures 4 to 12 represent the wound images taken before starting MCG lotion application and at the time of complete healing.

Discussion

Wound healing is a complex process requiring highly coordinated biochemical processes at the wound site and immune responses needed for restoring tissue integrity. Along with this complex processes involving cellular players, wound healing also requires a number of coordinated biochemical pathways and reactions that lead to collagen synthesis and disposal of damaged tissues.[4] Also, the availability of micronutrients and amino acids is critical for wound healing, and systemic supplementation of vitamins, iron, and thyroid hormones are known to improve wound healing.[15,16] However, there are challenges in their use for augmenting wound healing because of the existence of several biochemical and physiological barriers. The treating clinicians hence face challenges in the treatment of nonhealing wounds probably as a result of various coexisting factors and comorbidities. However, as reported in a recent consensus document, technology in the form of devices and techniques may offer aid in accurate diagnosis, predicting wound healing outcomes, and prevention of recurrences.[17] Thus, successful wound healing may require appropriate use of diagnostic aids for correct diagnosis to identify factors that delay wound healing, treat all aspects of wound area, and have a standardized care approach.[17]

Table 2. Wound Type and Harikrishna Periwound Skin Class Before Treatment.

Periwound Skin Class[a]	Diabetic Foot Ulcer (n = 29)		Venous Ulcer (n = 6)		Others (n = 15)		All (n = 50)	
	n	Percentage	n	Percentage	n	Percentage	n	Percentage
Class 2A	13	44.83	2	33.33	7	46.67	22	44.00
Class 2B	10	34.48	2	33.33	2	13.33	14	28.00
Class 3	3	10.34	2	33.33	1	6.67	6	12.00
Class 4	3	10.34	0	0.00	4	26.67	7	14.00
Class 5	0	—	0	—	1	6.67	1	2.00

[a]Harikrishna Periwound Skin Classification 2015: class 0, normal; class 1, fibrous tissues/tissue at risk; class 2, exudate centered (2A, desiccated; 2B, macerated; 2C, allergy); class 3, inflamed without infection; class 4, infection; class 5, atypical.

Table 3. Time to Wound Healing (weeks).

	n	Mean	SE	Median	95% CI for Median		*P*[a]
					Lower	Upper	
Wound type							
Diabetic foot ulcer	29	13.74	1.22	11.29	10.00	15.24	.165
Venous ulcer	6	20.59	5.23	16.00	8.89	39.64	
Others	15	13.50	2.33	15.29	4.61	20.43	
Periwound skin class							
Class 2A	22	15.63	1.97	14.21	9.39	19.74	.251
Class 2B	14	15.64	1.88	15.42	10.65	20.73	
Class 3	6	15.67	4.42	12.57	8.22	27.17	
Class 4	7	9.35	2.47	10.00	1.71	16.61	
Class 5	1	2.71	—	—	—	—	

[a]Kruskal-Wallis test.

For wound dressings, the TIME principle (tissue debridement, infection/inflammation, moisture, and edge) is widely followed and results in good wound healing.[18,19] In our study, wound bed preparation was done using standard protocols per the TIME concept, where care was taken to address the tissue, infection, moisture maintenance, and edge dressing. Wound edges are also important to healing because unhealthy edges that are undermined or rolled are difficult to heal and a potential cause of chronic wounds.[12,20]

The triangle of wound assessment propagated by Carolyn Dorsett and Keith Harding during the EWMA conference, which was published in the *International Wound Journal* mentions the assessment of the wound bed preparation and emphasizes the importance of wound edges and the periwound.[7,8] In a UK National Health Service trust survey, it was observed that 70% of patients with nonhealing wounds have surrounding skin that is dry, macerated, excoriated, and inflamed,[9] and this unhealthy periwound area is one of the major causes of nonhealing. Integrity of the periwound area is of paramount importance in determining the speed of wound healing, and poor management of the periwound area leads to poor wound healing.[5,7] Thus, the importance of the periwound area in the process of wound healing is now widely accepted. It is said that problems in this area are very common and may delay wound healing, cause pain and discomfort, enlarge the wound, and also lead to deterioration in the patient's QOL.[7,11] A healthy periwound ensures good blood supply to the wound margins, thus ensuring a good healing process. A classification of the periwound area based on the periwound status—namely, the Harikrishna Periwound Skin Classification (HPSC) 2015—was suggested and presented at the Fifth WUWHS Congress, Florence, Italy (2016). This classification categorizes wounds based on the health of the periwound region into 5 categories, from class 1 to class 5, depicting the status of the periwound area (Table 1).[10] It is suggested that for rapid and healthy wound healing, it is important to assess all wounds carefully, so that specific and customized therapies can be used. A management plan has been suggested based on the triangle of wound assessment to address issues in the wound bed, wound edge, and periwound skin.[7] In our study, it was observed that the healing time for class 2 was longer than the healing time for class 3, which probably could be a result of the macerated state of the periwound region in class-2 wounds, which requires a longer time to heal.

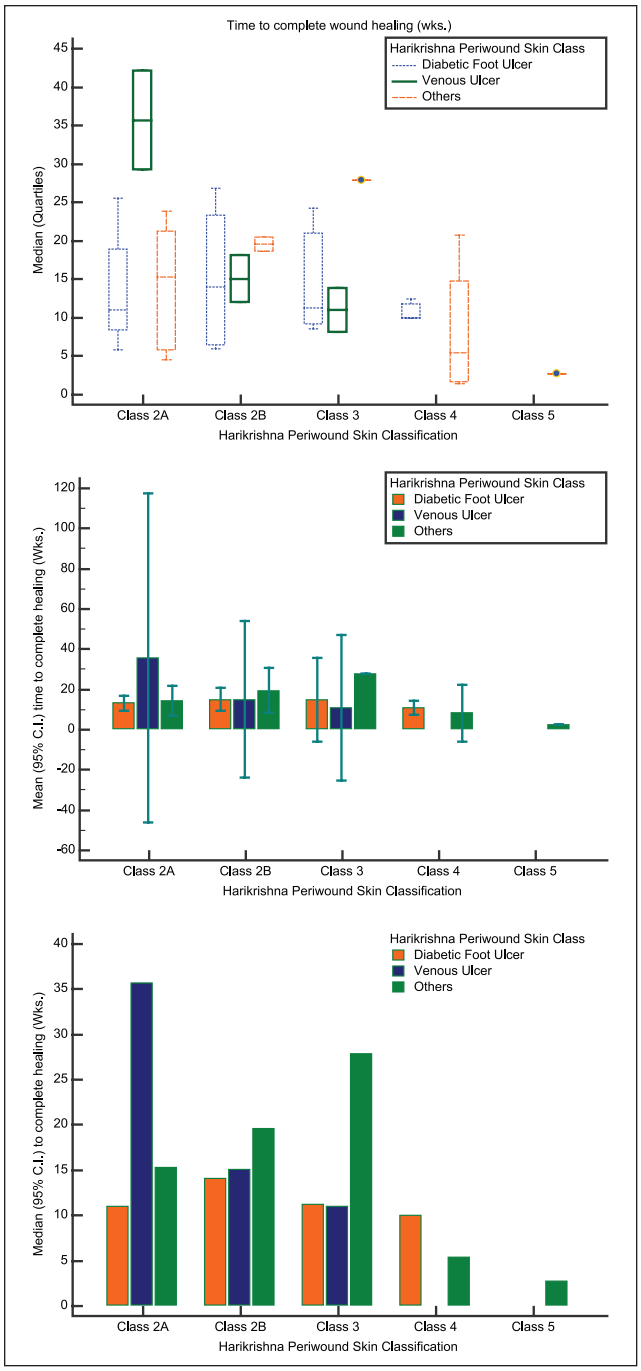

Figure 3. Box plot for time to complete wound healing (median weeks) in different wound types: First is box plot showing median with quartiles; the second has mean values with 95% CIs, and the third has median values.

Figure 4. A 56-year-old male patient with a 7-week-old wound of diabetic foot ulcer.

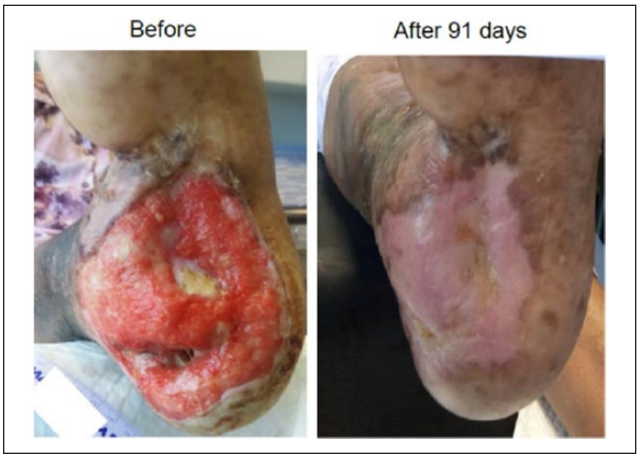

Figure 5. A 59-year-old female patient with a 15-year-old diabetic foot ulcer.

Collagen is the main constituent of connective tissue, is formed in abundance during tissue repair, and is regarded as one of the most useful biomaterials.[21] Collagen plays a key role in cell signal transduction and regulates cellular functions, such as cell adhesion and migration, hemostasis, and immune function.[22,23] Apart from these properties, collagen is biodegradable, has weak antigenicity, and is commonly used for topical application in wound healing.[21] Application of glycerin-based lotions has been reported to aid antimicrobial activity, which may contribute to wound healing.[24] It has been reported that a combination of collagen and glycerin is beneficial in wound healing.[5] We have also observed very good improvements in nonhealing wounds after application of the MCG lotion. Many patients included in this report had diabetic foot, where the diabetic foot triad (neuropathy, vasculopathy, and immunopathy) is responsible for nonhealing wounds.[25] The MCG application in DFU probably targets the vascular and immune pathways for these wounds.

In a swine model of chronic wounds, 21 days post-wounding, MCG-treated ischemic wounds increased the proliferating endothelial cells that formed mature vascular

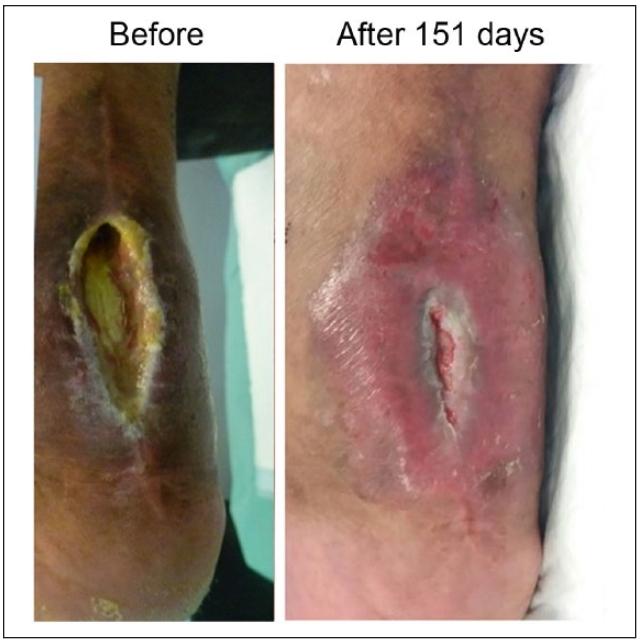

Figure 6. A 55-year-old male patient with 18 weeks of wound dehiscence.

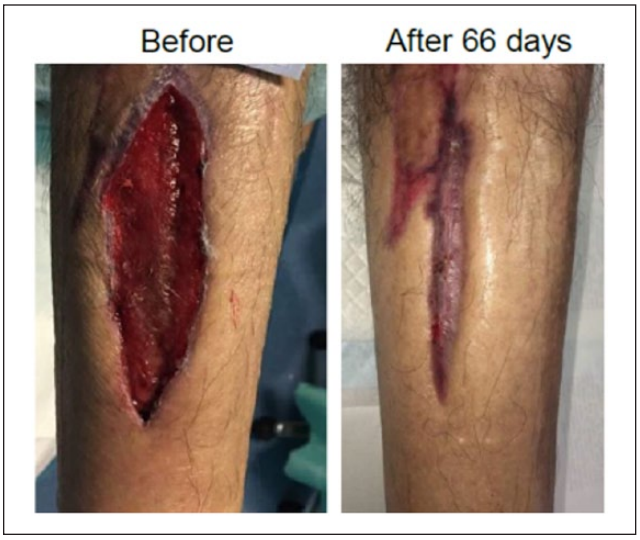

Figure 7. A 55-year-old male patient with 12-week-old necrotizing fasciitis.

structures and increased blood flow to the wound.[26] Fibroblast count was markedly higher in MCG-treated ischemic wound-edge tissue. Wound-site macrophages represent key drivers of wound repair in the inflammatory phase[27] and imbalance between proinflammatory and anti-inflammatory signals in the direction of the former results in persistent wound inflammation and failure to enter the reparative phase of healing.[28] MCG is reported to enhance the macrophage recruitment to the ischemic wound site, which is indicative of a strong inflammatory response.[26]

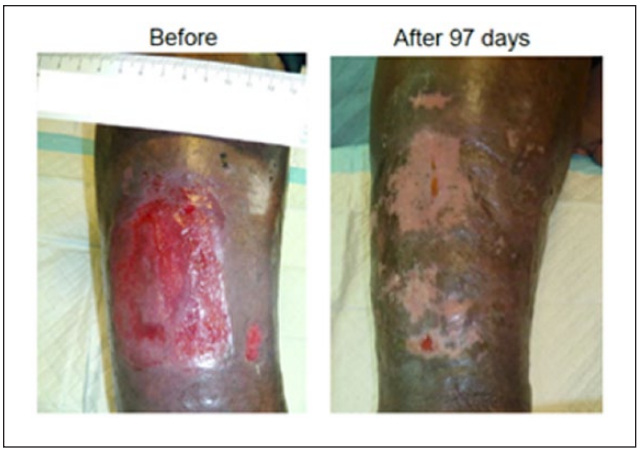

Figure 8. A 62-year-old male patient with a 2-year-old venous ulcer healed completely in 14 weeks.

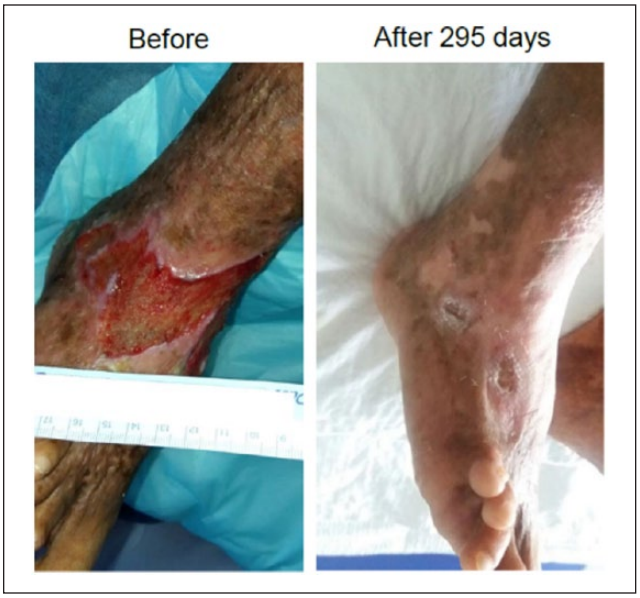

Figure 9. A 58-year-old female patient with a 25-year-old venous ulcer.

MCG possibly maintains moisture in the periwound region and has antimicrobial (fungistatic and bacteriostatic) properties. Arguably therefore MCG helps remodel skin collagen by improving type 1:3 ratio, increasing angiogenesis, and mobilising keratinocytes to move into the wound bed, thus increasing the tensile strength of the healed wound margin.[5,24] This prevents reopening of the wound because collagen deposition is known to be inadequate in ischemic wounds, which accounts for wound dehiscence and failure to close.[29] Other factors are also involved such as the wound bed, wound edge, and the size of the wound because no 2 wounds are the same. But it is noteworthy that all wounds healed with standard therapy along with MCG application in the periwound area.

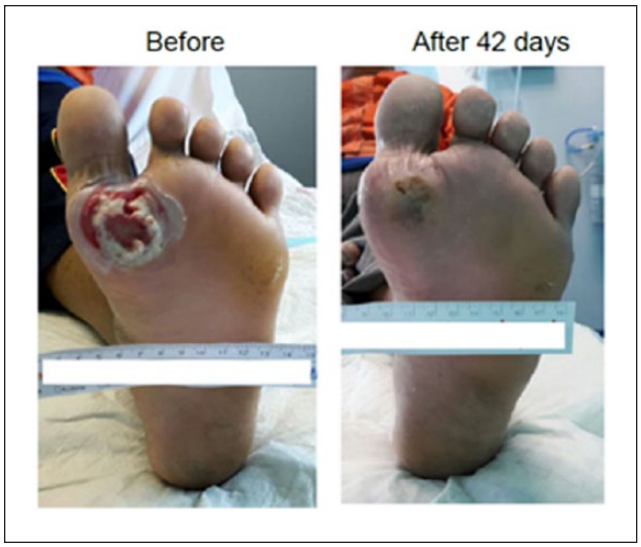

Figure 10. A 38-year-old male patient with a 2-year-old diabetic foot ulcer: complete wound closure observed in 7 weeks.

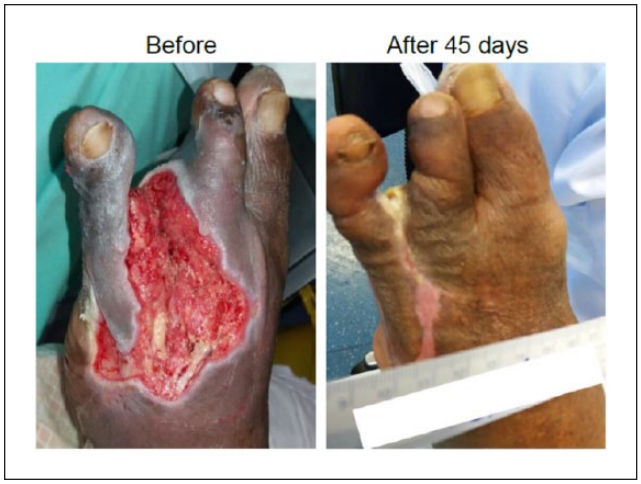

Figure 11. A 52-year-old male patient with a 12-week-old diabetic foot ulcer.

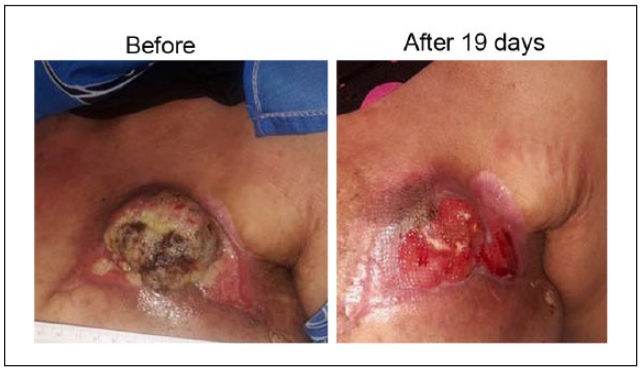

Figure 12. A 47-year-old female patient with a 4-week-old postoperative fungating mass from the breast.

Apart from local wound care, other coexisting conditions and systemic factors also have to be addressed to achieve successful wound healing and standardized care for wound treatment, as emphasized by many physicians and authors.[15-17] As reported by Mani et al,[17] DFUs usually have associated neuropathy and infection, making healing complicated, whereas venous ulcers are associated with changes in the veins, increased capillary permeability, hemosiderin deposition in tissues, skin dryness, and thickening of skin. Thus, a holistic approach that includes standardized wound care, specific systemic therapies, and supportive measures such as offloading in DFU, compressions in venous ulcers, and newer technologies such as radio frequency (electromagnetic) stimulation[30,31] may be needed for successful wound healing.

This was not a planned clinical study on all types of nonhealing wounds, and all wound sizes were included for the analysis. Wound severity assessment using HPSC classification followed by standard treatment protocol for wound management was followed in our study with special attention to the periwound skin area. This resulted in successful wound healing in all types of nonhealing wounds.

This study emphasizes the assessment and management of different scenarios according to the HPSC 2015 of the periwound skin with standard-of-care approach for the wound bed. This approach has shown complete wound healing of DFUs, venous ulcers, and other types of nonhealing wounds. However, the small sample size is a limitation; further large-scale comparative studies are needed to substantiate these effects on a larger population. HPSC2015 requires further validation, and the periwound factors in terms of wound healing should be studied extensively.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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