Topical treatment with a matrix containing mesoglycan in association with hyaluronic acid in the management of chronic skin ulcers of the lower limbs

Rolando Tasinato,[1] Paolo Zangrande[2]

[1]General Surgery Unit, ASL 3 Serenissima, Hospital of Mirano (VE); [2]Emergency Unit, ASL 3 Serenissima, Hospital of Mirano (VE), Italy

ABSTRACT

A chronic skin ulcer in the lower limbs represents the epiphenomenon of pathologies that may involve, at various levels, the venous, arterial, lymphatic and nervous systems of the leg, which must be identified and adequately treated. Recently, there has been increasing evidence that glycosaminoglycans (GAGs) play a role in the re-epithelialization of chronic skin ulcerative wounds of the lower limbs, particularly as regards ulcers of venous and arterial vascular origin. In this paper we report our experience in the treatment of chronic skin ulcers with debridement according to the TIME Wound Bed Preparation protocol with application of a bioactive dressing containing GAGs and hyaluronic acid, compared to a technique using a standard dressing involving the cleansing of the wound with 10% povidone iodine solution.

INTRODUCTION

Chronic skin ulcers of the lower limbs reflect a varied group of pathological situations in which multiple etiopathogenetic factors affect and radically condition treatment strategies. This treatment must necessarily be diversified according to the basic pathology that underlies the ulcerative event, even though some principles remain valid for a shared approach to the various types of injury.[1,2]

A chronic skin ulcer in the lower limbs thus represents the epiphenomenon of pathologies that may involve, at various levels, the venous, arterial, lymphatic and nervous systems of the leg, which must be identified and adequately treated.

Diversified strategies which, however, agree that careful debridement associated with the cleansing and disinfection of the bed of the wound and the perilesional skin are essential prerequisites for the promotion of adequate re-epithelialization, with the primary aim of reducing healing times.

The consequences in terms of social and health care and the significant economic implications associated with these conditions and patient management are common occurrences because the problem of chronic ulcerative lesions impacts heavily on the annual budget of social and health authorities.[3] While many randomized multicenter trials have shown that topical or systemic antibacterial treatment does not in fact influence the modalities and times of recovery,[4] in more recent years multicenter clinical experience has shown a marked advantage in the topical antibacterial treatment of these lesions.

Recently, there has been increasing evidence that glycosaminoglycans (GAGs) play a role in the re-epithelialization of chronic skin ulcerative wounds of the lower limbs, particularly as regards ulcers of venous and arterial vascular origin.

In this paper we report our experience in the treatment of chronic skin ulcers with debridement according to the TIME Wound Bed Preparation protocol with application of a bioactive dressing containing GAGs and hyaluronic acid, compared to a technique using a standard dressing involving the cleansing of the wound with 10% povidone iodine solution.

MATERIALS AND METHODS

From January 2017 to April 2017, 63 patients suffering from chronic lower limb skin ulcers were treated con-

Correspondence: Rolando Tasinato, General Surgery Unit, ASL 3 Serenissima, Hospital of Mirano, Via Don Giuseppe Sartor 4, 30035 Mirano (VE), Italy.
E-mail: rolandotasinato@libero.it

Key words: Chronic skin ulcers; Mesoglycan; Hyaluronic acid; Debridement.

Contributions: RT: general surgeon, angiologist, phlebologist with experience in the treatment of diabetic foot; PZ: general surgeon and vascular ultrasounds expert.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Received for publication: 7 February 2019.
Revision received: 6 March 2019.
Accepted for publication: 15 May 2019.

Italian Journal of Wound Care 2019; 3(2):44-48
doi:10.4081/ijwc.2019.48

secutively at the Wound Management Outpatient Clinic of Surgery and General Surgery of the Hospital Unit ASL 3 Serenissima of Mirano (Venice).

The group consisted of 29 men and 34 women of average age 68.1 years (range 32-91) referred to and assessed at our Wound Care clinic set up within the General Surgery unit with an adjoining vascular surgery and interventional hemodynamics facility.

Patients were selected after appropriate clinical assessment, color Doppler study, in many cases also implemented by angio computed tomography or angiography, and evaluation of transcutaneous oximetry.

This is done in order to formulate a correct diagnosis before starting the patient on specific treatment of the underlying condition that we summarized in Table 1.

Once the patient had been admitted, the lesion was photographed and measured by sketching the edges on a transparent sheet of acrylate and carrying out a centimeter estimate of the area (Figure 1).

The impressions so obtained could be catalogued and compared in the subsequent controls, obtaining a rapid display of any progress made in terms of reduction or otherwise in the wound area in the course of treatment.

As part of a more general study on the ulcers that come to our observation in the outpatient clinic, we divided the 63 patients randomly into two groups A and B diversified on the basis of the type of topical treatment used on the wound.

In group A we adopted a standard technique: cleansing of the ulcerative wound with 5-minute contact with physiological solution, debridement of the bed with mechanical removal of the biofilm by cleansing with gauze and subsequent double application of 10% povidone iodine of both the ulcerative bed and the perilesional skin for a distance of at least 5 cm from the edge of the wound. There followed an occlusive flat dressing associated with elastic bandage in the case of phlebostatic ulcer.

Group B patients were treated similarly, but after cleansing and disinfection we used a bioactive dressing (matrix containing biofilm based on mesoglycan in association with hyaluronic acid).

The matrix containing the biofilm has a two-fold effect: GAGs, as components of the extracellular matrix, promote the response of cytokines that are responsible for the mechanism that reconstructs the injured tissue. In addition, biofilm also acts as a protective barrier on the wound and helps to maintain a microenvironment conducive to the healing process.

In this group too, patients were treated with: cleansing of the ulcerative lesion by 5-minute contact with saline solution, debridement of the wound bed with mechanical removal of the biofilm by cleansing with impregnated gauze and subsequent application of the matrix with biofilm containing mesoglycan on the ulcerative bed with contact time of at least 3 minutes before proceeding to the flat occlusive dressing or elastic bandage in the case of a phlebostatic ulcer.

The dressing was applied every 2-3 days. In the initial phases, especially in the case of secreting lesions, the dressing was renewed even every two days on the basis of the extent of secretion; on average from 1 to 3 times a week depending on the case. By contrast, in the final stages, with re-epithelialization almost complete, the dressing was replaced even after 4-5 days.

Clinic accesses and the clinical progress of the patients were recorded on each occasion in a special digitized clinical diary, accompanied by photographic images.

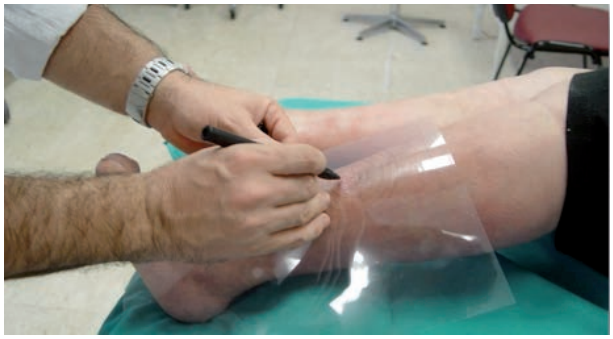

Figure 1. Technique adopted at our clinic for the dimensional assessment of ulcerative wounds.

Table 1. Stratification of patients on the basis of the type of skin ulcer for which they were treated in the outpatient clinic.

Type of ulcer	Patients (total)	Males	Females	Average weeks of treatment	Cases reaching re-epithelialization (%)
Phlebostatic	26	10	16	7.2	94.8
Ischemic	17	9	8	9.5	79.3
Neuropathic	8	3	5	5.9	92.2
Post-traumatic	4	3	1	5.6	96.4
Burn	2	1	1	3.5	98.8
Vasculitic	2	0	2	11.4	74.2
Mixed	4	2	2	9.1	88.6

The overall management of the patients also benefited from the help of the A.D.I. staff (home nursing care) who looked after application of the protocol at home, especially as regards patients who were difficult to transport, reporting data in the clinical record.

RESULTS

Of the initial 65 patients, 63 (93.6%) completed randomization, 32 of them in group A and 31 in group B. Overall, in both randomized groups, treatment was well tolerated.

In group A in 2 cases (6.3%) we observed phenomena of skin hypersensitization linked to the presence of the iodine compound or its excipients.

In group B, only in 1 case (3.2%) did we observe allergic/erythematous skin reactions leading us to suspend treatment, which in 96.8% of cases was well tolerated.

As far as pain symptoms are concerned, all randomized patients were evaluated for pain at each access on an 11-item numeric rating scale (NRS). In the graph below we report the average measurements of pain symptoms in the two groups of patients (Figure 2). The analysis shows an almost similar trend in terms of duration and intensity of pain.

DISCUSSION

We would stress the importance of the reduction in the average pain symptoms in the group of patients undergoing topical dressing with biofilm containing mesoglycan and hyaluronic acid, pain reduction evaluated at around 2.5 NRS items compared to the control group treated with standard dressing.

The pain reduction is noted particularly in the hours following the dressing session. This effect resulted in a 21.6% reduction in the intake of analgesics *per os* in group B patients compared to group A.

With regard to the rate of re-epithelialization and consequently wound healing times, even in a situation of heterogeneous wound types, an improvement was observed in healing times in the group of patients treated with biofilm containing mesoglycan and hyaluronic acid compared to the group treated with the standard method.

In the case of phlebostatic ulcers (32 consecutive patients), the re-epithelialization time in group B was on average 11.9 days shorter than in the group of patients treated with iodine compound (Table 2).

For the other types of ulcers also, the average re-epithelialization time of group B was lower, even if the smaller percentage of cases was such as not to allow us for the moment to extrapolate statistically significant data as in the case of phlebostatic ulcers, the largest group in our preliminary evaluation series.

From a bacteriological point of view, we observed that the two dressing procedures were substantially similar as regards the effectiveness of the antiseptic action of povidone iodine.

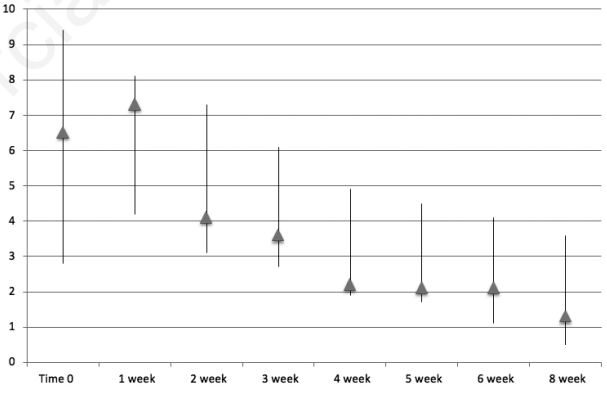

Figure 2. Average findings of pain symptoms measured on an 11-item NRS scale during outpatient evaluations of a total of 63 patients randomized into the two groups.

Table 2. Clinical findings and calculation of average re-epithelialization times in the two groups of patients in the study.

	Group A - Treatment with polyvinylpyrrolidone iodine	Group B - Treatment with Prismaskin bioactive matrix
Total re-epithelialization time in days from first access to outpatient clinic	42.4 days	31.6 days
Fever	2 cases	1 case
Pain higher than 5 NRS	12 cases	2 cases
Resort to pain-killers	18 cases	5 cases
Intolerance to dressing procedure	2 cases	1 case
Patients requiring more than 3 accesses per week to clinic	13 cases	4 cases
Number of cases not re-epithelialized after 15 weeks of treatment	5 cases	2 cases

NRS, numeric rating scale.

The number of cases in which we observed the onset of fever or bacterial superinfection was substantially the same in the two groups (Table 3).

More interesting is the analysis of the data emerging from cultures carried out on swabs in direct contact with the wound bed which have shown that after 4 weeks of treatment there is an increase in wounds contaminated by fungi, microbial forms that are recalcitrant to the action of iodine compounds.

The assessment of other clinical parameters, in particular the presence of painful nocturnal symptoms, the consequent resort to painkillers and the number of accesses to the outpatient clinic for a fresh dressing in the two groups of patients, has documented that patients in group B (topical dressing with biofilm based on mesoglycan and hyaluronic acid) show fewer pain symptoms, particularly after the dressing session, than patients in group A (Figure 3).

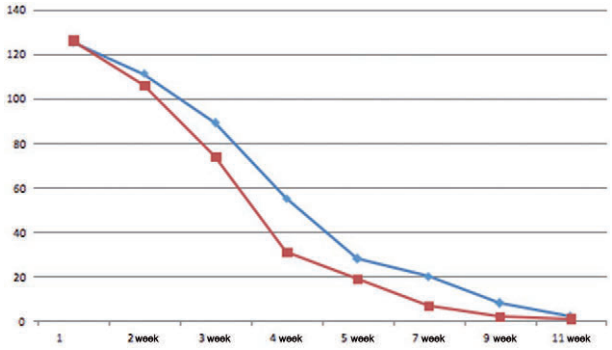

Figure 3. Comparative evaluation of the trend of ulcer re-epithelialization in the two randomized groups. Group A (red line): patients treated with polyvinylpyrrolidone iodine. Group B (blue line): patients treated with the bioactive matrix containing mesoglycan in association with hyaluronic acid.

CONCLUSIONS

From a management viewpoint, topical cleansing and the application of a bioactive matrix containing mesoglycan in association with hyaluronic acid has proved to be effective from both a clinical and management point of view in relation to safety and ease of use.[5-7]

In particular, the introduction of the dressing using a bioactive matrix (Figure 4) containing mesoglycan has not substantially modified or interfered with the other procedures and guidelines that we have long adopted in our Hospital for the management of patients with chronic ulcers of the lower limbs. The dressing with GAGs, specifically, integrates very effectively with the TIME wound bed preparation protocol that for about 3 years we ourselves have adopted and promoted among the various inter-hospital services and centers that deal with the management of these patients.[8]

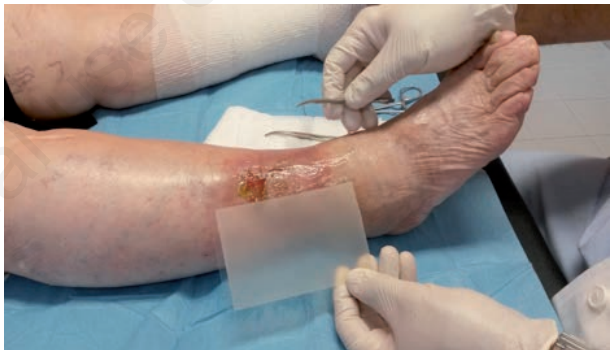

Figure 4. Example of a bioactive membrane dressing containing mesoglycan in association with hyaluronic acid. The membrane is laid on the ulcerative wound in direct contact with the wound bed. Thereafter, the patient is treated with a simple occlusive dressing associated or otherwise with an elastocompressive bandage according to the guidelines laid down for the specific type of wound.

Table 3. Microbial strains isolated at time zero (date of first access to outpatient clinic) and after 4 weeks of treatment in the two groups of patients. Note that after 4 weeks mycotic forms start to be a significant presence. This occurrence has proved to be particularly frequent in patients who had been treated with topical or systemic antibiotic therapy.

Frequency of microbial strains isolated at time zero		Frequency of microbial strains isolated after 4 weeks of treatment	
Pseudomonas Aeruginosa	****	*Fusobacterium*	****
Staphylococcus Aureus	***	*Streptococcus Epidermidis*	**
Other *Staphylococci*	**	*Peptostreptococci*	**
Proteus Mirabilis	***	*Klebsiella Sporigens*	**
Escherichia Cloacae	**	*Acinetobacter*	**
Enterobacter Sporigenes	**	*Candida Albicans*	***
Enterococcus Fecalis	**	*Escherichia Coli*	**
Clostridium Sporigens	*	*Candida Sporigens*	**
Candida Sporigens	**	*Epidermophyton*	**

, **, *, **** the asterisks represent the relative frequency of the microbial groups found (from 1 to 4) in ascending order.*

In particular, we have noticed that matrix solubilization leaves no evident deposits or residues on the bed of the wound, so enabling direct assessment of the wound bed, and does not require any further debridement maneuvers other than those aimed at removing the sludge that may have reformed between one dressing and another.

From an economic point of view too, this dressing has proved to be much more advantageous than most of the therapeutic options currently available in the treatment of chronic skin ulcers.

Also as regards the training of nursing staff, in particular staff from the ADI Department of our own hospital, the bio-active membrane containing mesoglycan has proved to be easy and intuitive to use, needing only very short learning times.

The significant cost curtailment, its applicability in many clinical situations, its effective pro-re-epithelializing action, especially with regard to chronic skin ulcers of phlebostatic origin, as well as the product's optimal safety profile has led us to include GAGs bioactive matrix as an effective dressing in the list of therapeutic options for the management of patients with chronic skin ulcers of the lower limbs.

REFERENCES

1. Nelson EA, Ruckley CV, Dale J, Morison M. The management of leg ulcers. J Wound Care 1996;5:73-6.
2. Makrantonaki E, Wlaschek M, Scharffetter-Kochanek K. Pathogenesis of wound healing disorders in the elderly. J Dtsch Dermatol Ges 2017;15:255-75.
3. Humbert P, Mikosinki J, Benchikhi H, Allaert FA. Efficacy and safety of a gauze pad containing hyaluronic acid in treatment of leg ulcers of venousor mixed origin: a double-blind, randomised, controlled trial. Int Wound J 2013;10:159-66.
4. Meaume S, Ourabah Z, Romanelli M, et al. Efficacy and tolerance of a hydrocolloid dressing containing hyaluronic acid for the treatment of leg ulcers of venous or mixed origin. Curr Med Res Opin 2008;24:2729-39.
5. Dissemond J, Böttrich JG, Braunwarth H, et al. Evidence for silver in wound care - meta-analysis of clinical studies from 2000-2015. J Dtsch Dermatol Ges 2017;15:524-35.
6. Frantz RA, Bergquist S, Specht J. The cost of treating pressure ulcers following implementation of a research-based skin care protocol in a long-term-care facility. Adv Wound Care 1995;8:36-45.
7. Gao AL, Cole JG, Stoecker WV. Unna boot central gauze technique for chronic venous leg ulcers. Dermatol Online J 2017;23.
8. Bennett LL, Rosenblum RS, Perlov C, et al. An in vivo comparison of topical agents on wound repair. Plast Reconstr Surg 2001;108:675-87.