Observational study of a gauze medication contaning Rigenase® and polyhexanide in the treatiment of venous leg ulcers (<6cm²) and perilesional skin

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ABSTRACT

The *Triticum Vulgare* Extract (TVE) is a particular wheat extract patented by Farmaceutici Damor. TVE (Rigenase®) has been shown to have an important bio stimulation effect promoting the tissue repairing process in vitro. In this context, an observational study was developed to access the effects of a gauze based on Rigenase® and polyhexanide in the treatment of venous ulcers (area <6 cm² and not beyond the dermal layer) and of damaged perilesional skin whose damage could have also been determined by iatrogenic cause. Inclusion and exclusion criteria were identified and a medication protocol was applied. The study showed that the product based on Rigenase® and polyhexanide is effective in the treatment of venous ulcers and damaged perilesional skin.

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INTRODUCTION

The *Triticum Vulgare* Extract (TVE) is a particular wheat extract patented by Farmaceutici Damor. Several in vitro studies demonstrated its ability to modulate the inflammatory process by acting on metalloproteinase 9 (MMP-9)[1] and on the release of various mediators of inflammation like Nitric Oxide (NO), Interleukin-6 (IL-6), Prostaglandin E2 (PGE2) and Tumor Necrosis Factor-alfa (TNF-alfa).[2] Moreover, TVE is able to stimulate cellular chemotaxis by inducing the synthesis of fibronectin and the hyaluronic synthetase 2 expression,[3] exerting a direct action on the generation and remodeling of the extracellular matrix.[4] In damaged tissues (burns and/or chronic lesions), the Reactive Oxygen Species (ROS) are responsible for the oxidative stress, which contributes to obstacle the process of tissue repairing. TVE has a scavenging effect on ROS, thus exerting an antioxidant activity. These recent scientific findings underlined the bioactive features of TVE, able to exert pro-proliferative, anti-inflammatory and antioxidant activities.[5]

This active substance is contained in cream and gauzes formulations. By mistake, in the management of acute and chronic lesions, the bio stimulating ability of TVE is considered less important than the non-adherence features of the gauze support in which it is contained. In fact, this kind of medication, is generically described as "non adherent and/or traditional medication". A nonspecific definition able to mystify the user that is not able to

attribute specific functions of this medication on wound management.

With the precise intent of overcoming this usage limits, it was appropriate to evaluate its efficacy in specific clinical conditions related to wound management.

First of all, the correct clinical conditions for the product application were identified, considering the high variability related to chronic ulcers and to perilesional skin during the tissue repairing process.[6] It was not possible to select deep, high exudating and/or infected wounds, since the product is not able to manage infected and high exudating wounds.

These findings are at the basis of the choice of two clinical conditions linked one to one other, like the management of venous ulcers and of perilesional skin, which can request different clinical approaches during the tissue repairing process.

The choice of these conditions was also determined by the necessity to evaluate the performance of the gauze under compressive bandage, which represents the gold standard for the treatment of venous ulcers and their complications.[7]

Since there were no clinical trials performed with this product in this condition, it was decided to proceed with an observational study with the precise intent to evaluate the performance of the gauze under compressive bandage, the ability of stimulating the granulation process, if it can cause tissue maceration on the lesion margin and the healing of perilesional skin. Any other adverse event that would limit the use of the product was reported.

The study design involved several clinical operators belonging to different specialties. This choice was made to better evaluate the product performance, also taking into consideration the setting in which it can be used.

MATERIALS AND METHODS

Objective

This study aims to evaluate the effectiveness of a gauze product based on Rigenase® and polyhexanide in the management of venous ulcers, ($6cm^2$ wide and thickness not beyond the dermal layer, Figure 1) and the ability to provide the healing of the damaged perilesional skin (also by iatrogenic cause, Figure 2), with particular attention to the possible occurrence of adverse events. Observation time was predetermined.

Participants

Several operators were enrolled, including nurses and doctors, managing patients with venous ulcers and/or damaged perilesional skin.

General exclusion criteria have been identified. Precisely: i) Ankle-brachial index <0.9; ii) Presence of bilateral edema of the lower limbs appeared in the previous 30 days or more; iii) Primary and/or secondary unilateral lymphedema; iv) Therapy for Deep Vein Thrombosis (DVP); v) Insulin-dependent diabetes; vi) Antibiotic therapy in progress or suspended less than 7 days before enrollment; vii) Antifungal therapy in progress or suspended less than 7 days before enrollment; viii) Therapy with antihistamine drugs.

Local exclusion and inclusion criteria have been identified for each individual clinical condition.

Venous ulcers

Local exclusion criteria: i) Infection; ii) Ulcer with no/moderate/heavy exudate; iii) Presence of necrosis; iv) Slough and/or other (non-healing ulcers); v) Retroflexed, hyperkeratotic, macerated, undermined margins.

Local inclusion criteria: i) Ulcer area <$6cm^2$; ii) Depth limited to the dermal layer; iii) Cleaned ulcer; iv) Poorly exudating ulcer; v) Active margins.

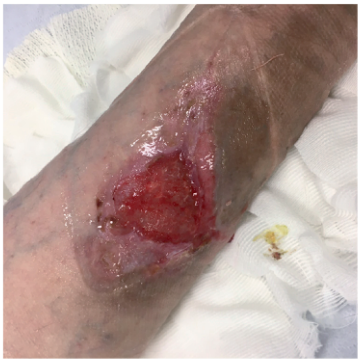

Figure 1. Venous ulcer.

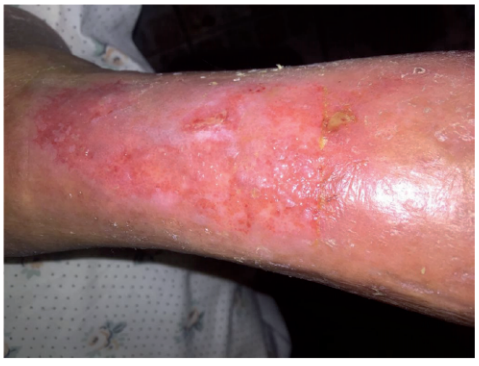

Figure 2. Perilesional skin.

Damaged perilesional skin of venous ulcers (also for iatrogenic causes)

Local exclusion criteria: i) Cellulitis; ii) Erysipelas; iii) Mycosis.

Local inclusion criteria: i) Phlebostatic erythema; ii) Dermal/phlebostatic hypodermatitis; iii) Skin lesion determined by contact allergy; iv) Scratching injuries; v) Iatrogenic lesions (deriving from compressive bandage, dressing or other local procedure); vi) Ulcerative lesions of venous origin even with dimensions > 6cm^2.

In addition, the treatment protocol for skin ulcers management was defined: i) Cleansing and antisepsis with 0.05% sodium hypochlorite solution or chlorhexidine in aqueous solution; ii) Application of 2 gauzes (Fitostimoline® Plus); iii) Covering with a sterile gauze; iv) Compressive bandage; v) Dressing change every 2 days.

A treatment protocol for the management of perilesional skin was also defined: i) Cleansing and antisepsis with 0.05% sodium hypochlorite solution or chlorhexidine in aqueous solution; ii) Application of Fitostimoline® plus gauzes on the perilesional skin; iii) If the wound is moderately of highly exudating, application of advanced dressings to the bottom of the wound (Figure 3); iv) Covering with a sterile gauze; v) Compressive bandage; vi) Dressing change every 2 days.

The observation time for skin ulcers was scheduled to be of 15 days; for the perilesional skin it was scheduled to be of 7 days.

Observation timing is not the only difference between the two treatment protocols; in case of the management of perilesional skin, in fact, there is the possibility to apply advanced medication if the wound is moderately/highly exudating.

Finally, data collection forms were written for each clinical condition (Appendix).

RESULTS

Venous leg ulcers

Seventy-six (76) patients with venous leg ulcers were enrolled. Of these, 22 males with a mean age of 63 years (range: 51-95); 52 females with a mean age of 52 years (range: 52-97). According to the obtained results, the patients were divided into 4 groups following the clinical condition of the lesion: lesion healed, improved, stationary, worsened. Twenty-six (26) patients (35% of all the patients enrolled) were healed. In 30 patients (41%), the lesion improved, while in 14 patients (19%) it was stationary. In 4 patients (5%), the lesion worsened during the treatment period (Figure 3).

Adverse events

Maceration of the perilesional skin: 5 cases in the "stationary lesion" group, 4 cases in the "worsened lesion" group.

Appearance of necrosis: 2 cases, in the "stationary lesion" group.

No cases of contact allergy during product application were reported.

Damaged perilesional skin

Sixty (60) patients affected by venous leg ulcers with damaged perilesional skin were enrolled.

Of these, 21 males with a mean age of 73 years (range: 60-87) and 39 females with a mean age of 75 years (range: 52-91). Fifteen (15) patients (25% of all the patients enrolled) were healed. In 26 patients (43% of all the patients enrolled) the lesion improved, while in 16 patients (27% of all the patients enrolled) it was stationary. In 3 patients, (5% of all the patients enrolled), it worsened during the treatment period (Figure 4).

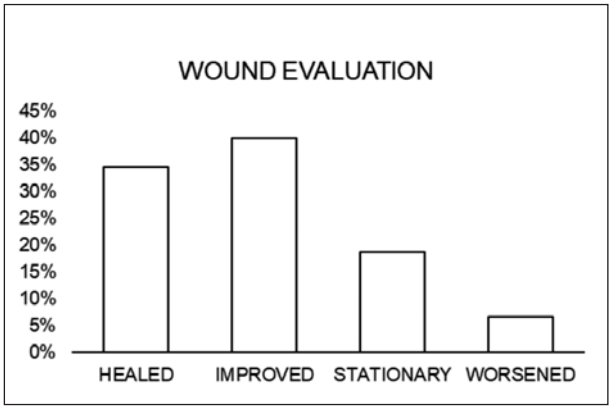

Figure 3. Wound evaluation.

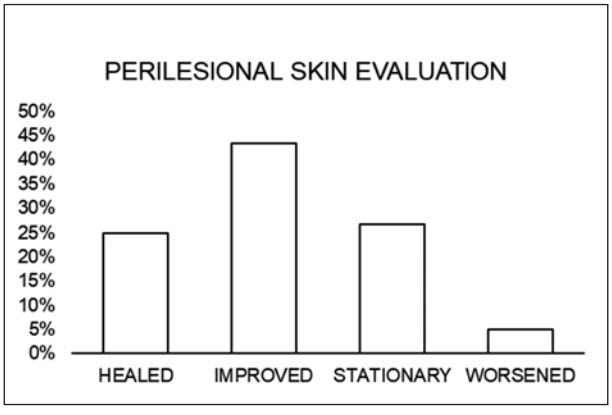

Figure 4. Perilesional skin evaluation.

Adverse events

In 3 cases of the "worsened lesion" group, maceration of perilesional skin was observed.

No case of contact allergy during the product application were reported.

DISCUSSION

The observational and multicenter study design, certainly widened the limits of clinical studies on ulcerative skin lesions. In fact, this study design is related to the impossibility of selecting patients with similar general health state, social and welfare conditions in addition to the defined exclusion and inclusion criteria. Therefore, it is necessary to make a first reflection on the reason why the observation time was so short. This choice was the most useful in order to evaluate the efficacy of the product in the management of two clinical conditions that were observed separately, even if they often coexist in the real life settings. This design allowed to evaluate the effectiveness of the gauzes based on Rigenase® and polyhexanide in the management of perilesional skin, even in presence of ulcerative lesions larger than 6cm^2. In fact, in presence of normal/hyper-exudating wounds, the management of exudate was obtained by applying a different medication (Figure 5 and 6).

Rigenase® and polyhexanide-based gauzes were used as a primary dressing for the treatment of ulcerative lesions when the inclusion criteria related with sizing and depth were matched. These kind of lesions are usually poorly exudating (Figure 7 and 8).

Compression bandage therapy is considered as the gold standard in the treatment of venous leg ulcers and in their complications. The medication based on Rigenase® and polyhexanide has retained its non-adhesion capacity under compression bandage and has not undergone processes of dehydration and/or bacterial contamination.

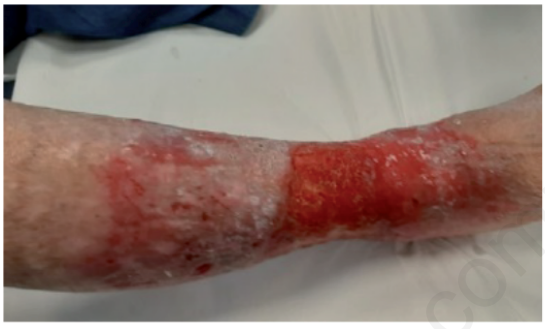

Figure 5. Exuding venous ulcer.

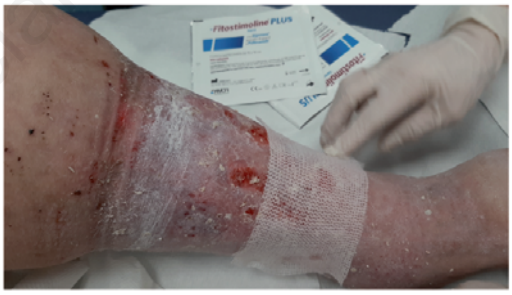

Figure 7. Hypoexuding venous ulcer.

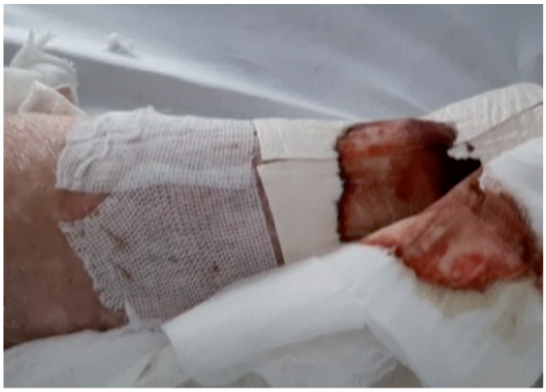

Figure 6. Use of advanced dressing.

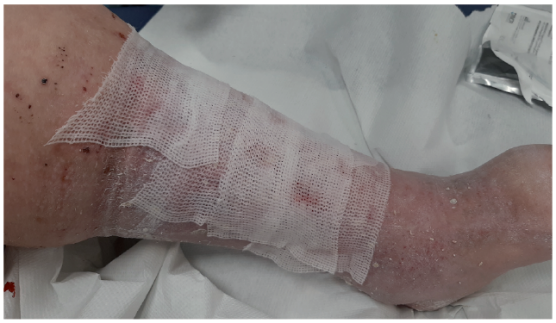

Figure 8. Primary dressing.

This feature allowed the operator to remove the dressing very easily, without producing any damage to the lesion (Figure 9 and 10) and it was found decisive in both the clinical conditions evaluated in this trial.

The short timing of wounds observation determined the impossibility of including healing as a parameter in the evaluation forms. However, healing of the lesion has been included in the "other results" item and it was reached by a surprisingly high number of clinical cases. In the venous ulcer group, 76% of patients were classified as healed or improved. While in the perilesional skin group, 68% of patients were classified as healed or improved (Figure 11 and 12).

The most frequently observed adverse event was the maceration of the perilesional skin. It was mainly observed in the venous leg ulcer group. This event was likely linked to an inappropriate medication procedure by the operator: the usage of the Rigenase® and polyhexanide based medication is inappropriate if a significant amount of exudate is present.

In the venous ulcer group 24% of patients were classified as steady/worsened after treatment. In the perilesional skin group 32% of patients were classified as steady/worsened after treatment. The comparison of adverse events justifies cases classified as "worsened" but it is not completely justifying the cases classified as "stationary", particularly frequent in the perilesional skin group. As part of a correct evaluation of this result, it is not possible to exclude that clinical failure was determined by mistakes in the clinical procedure. Finally, no

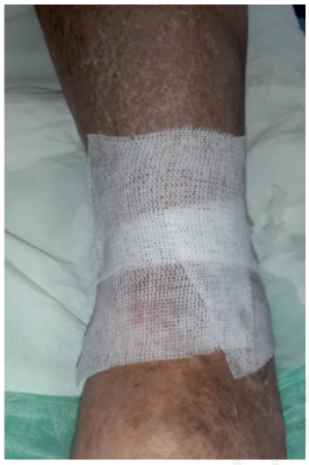

Figure 9. Application of the gauze.

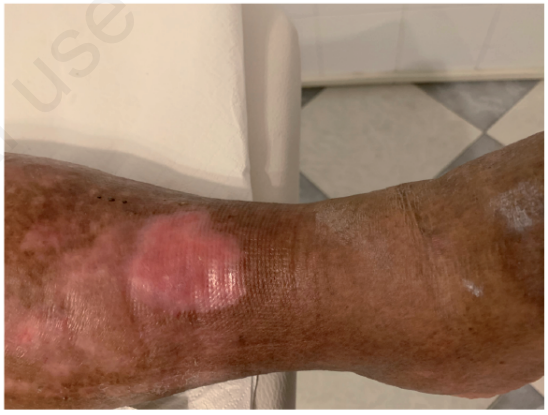

Figure 11. Healed venous ulcer.

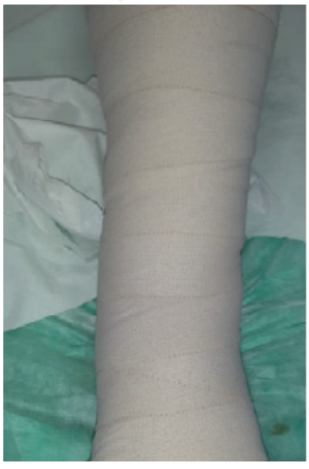

Figure 10. Application of compression therapy.

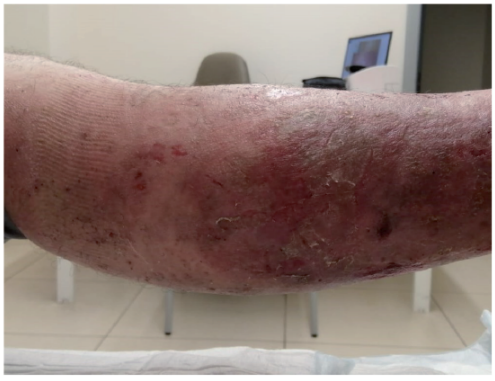

Figure 12. Healed perilesional skin.

cases of contact allergy during the product application were reported.

CONCLUSIONS

The results obtained demonstrate the effectiveness of the gauzes containing Rigenase® and polyhexanide in the management of venous ulcerative lesions (area <6cm^2) and of damaged perilesional skin. The clinical efficacy is obtained if a correct selection of the lesion is done, together with the applying of a valid protocol for the management of this clinical condition. The gauzes containing Rigenase® and polyhexanide were highly tolerated: contact allergy was never reported and the occurrence of adverse events was extremely rare.

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