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**EVALUATION OF THE EFFECTIVENESS
OF A HYPEROXIDIZED OIL-BASED MEDICATION
IN THE TREATMENT OF SKIN LESIONS:
OBSERVATIONAL STUDY**

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E D I Z I O N I · M I N E R V A · M E D I C A

Evaluation of the effectiveness of a hyperoxidized oil-based medication in the treatment of skin lesions: observational study

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Aim. Aim of the study was to demonstrate the effectiveness, in the management of recalcitrant wounds, of a hyperoxidized oil-based gel with film-forming and protective functions.

Methods. The study involved 50 patients with recalcitrant not infected and/or necrotic chronic ulcers. All patients had 0.7 minimum ABPI value; terminal and/or cancer and/or under immunosuppressive therapy patients were excluded. The dressing consisted in a uniform gel layer applied on the lesion, after cleansing with a 0.05% sodium hypochlorite chloroxidating solution. The dressing was changed every 48 hours (or every 24 hours, in case of hyperexuding wound). The effectiveness was assessed by the evaluation of the WBP score changes and area reduction (*via* the Visitrak™ Digital System) after an observation period of 4 weeks.

Results. All patients achieved area improvement; WBP score improved in more than 90% of the B score patients; pain reduction was reported by all patients: more than 55% of the total number of patients limited the use of analgesic drugs and in 6 cases (12%) they discontinued the antalgic therapy.

Conclusion. The dressing showed an actual effectiveness, promoting granulation and accelerating epithelialization; no patient suffered from allergy/intolerance and all of them reported a decrease in pain, until complete relief.

KEY WORDS: Oils - Wounds and injuries - Oxygen.

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Among the already general and local well-known factors that can affect the complex tissue repair process (whose deficiency or absence may slow down or interrupt the sequence of the related progressive phases and make the wound chronic), oxygen can be for sure considered a key element.

Arterial lesions (for instance resulting from obliterative arterial diseases and obstructive vascular complications in diabetes) tend to get chronic due to the poor oxygen concentration which perfuses ulcerated tissues and perilesional regions, thus *de facto* seriously impairing the creation of new vital tissue and the survival of the portion already affected by the ulcerative phenomenon.¹ However, going beyond the pathophysiological mechanism which is the basis for the etiology in "ischemic" lesions, an in-depth insight into the repair process points out how oxygen plays a fundamental role nearly in any stage of wound healing.²

Throughout the inflammatory phase of the tissue repair process, for instance, oxygen is involved in the cascade mechanism of

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caspace, which governs the phenomena of “programmed cell death” in damaged cells (apoptosis), and in the creation of superoxide anions (O_2^-) and the so-called singlet oxygen (O^-), which take part in the tissue and cell destruction processes generated by free radicals.³ Cells involved in the inflammatory phase require high oxygen concentration, in order to allow cellular respiration and to preserve the related activities each of them is intended for (phagocytosis of macrophages, degranulation of mast cells); finally, diapedesis too (which involves macrophages, fibroblasts and monocytes) is strictly oxygen-related.⁴ The following phase, *i.e.*, the creation of granulation tissue, basically depends on oxygen, essential for fibroplasia, angiogenesis and the creation and deposition of the new extracellular matrix. To conclude, also in scar remodeling the level of oxygen proves to be fundamental for enzymatic reactions which determine the realignment of collagen fibers in the extracellular matrix, the deposition of elastic fibers and their retraction, hence favoring a more homogenous tissue regeneration and better scar results.²

Therefore, almost any phase in tissue repair is oxygen-dependent, to the extent that, when the level of this element decreases, the consequences in terms of time and effectiveness of the process are remarkable. Besides, we must not undervalue the antimicrobial power of oxygen, which deploys a bacteriostatic and bactericidal action (by means of macrophages and, indirectly, thanks to the free radicals which are generated) on anaerobes and pyogenic bacteria, and also on obligate aerobes, unable to survive high oxygen tensions.⁵

In the light of the above premises, a significant aim in the treatment of skin lesions is to ensure an adequate level of oxygen in the wound bed.

While, conversely, such a condition proves to be intuitive in the case of overt arterial diseases (which require an early echo-Doppler examination of the vascular aspect and a specialist clinical assessment, with a view to validating the possibility of

revascularization), sometimes the same tissue oxygenation index is to be guaranteed even in the treatment of etiologically different lesions (with the exception of those neoplastic wounds which cannot be surgically cured and whose typical therapeutic indication aims at interrupting or decelerating the growth of tumor tissue, often by means of silver nitrate or potassium permanganate applications), due to the manifold implications of this element in the healing process.⁶

The hyperbaric chamber is an oxygen treatment option (an adjuvant therapy to advanced medications) to be taken into account in those cases where the vascular access is sufficiently patent to allow blood flow up to the lesion, considering that, intrinsically, the high pressure generated is naturally expected to increase the oxygen percentage as dissolved in plasma.⁷ In those cases where such treatment does not have applicable indications (unsolvable vascular occlusions) or cannot be implemented (non-moveable, claustrophobic patients or suffering from other contraindications), the direct delivery of the necessary oxygen percentage to the tissue to be treated is mandatory.⁸

Taking the non-effectiveness of a direct delivery of local gaseous oxygen in normobaric conditions for granted (as extensively evidenced in literature), a few other treatment options with these purposes can be further considered.⁹

The topic application of oxygen-release formulations (cold creams, ointments) can grant the lesion a correct “extra quantity” of this element, both in those cases where it totally lacks (critical and subcritical arterial diseases) and also in those where the deficiency is due to the increased local metabolism (considerable phenomena of phagocytosis resulting from tissue resorption and/or destruction of micro-organisms, radiant treatment of neoplastic wounds).¹⁰

Since the major need of any skin lesion is the availability of large quantities of oxygen in order to permit those necessary metabolic processes as neoangiogenesis and re-epithelialization,¹¹ the purpose of this

study was to prove the effectiveness of a hyperoxidized oil-based medication as primary treatment for acute and chronic skin lesions. A secondary aim was to evaluate its capability to accelerate the repair processes,¹² mainly through an analysis not only of the ability to stimulate the creation and/or proliferation of the granulation tissue, but also of the variation in the wound bed preparation (WBP) score.¹³ The ease of use and administration (in particular the eligibility to be considered a "self-medication"), the patient's comfort, intended as the potential to affect pain perception in terms of decrease/control, and the low frequency in wound colonization during treatment were taken into account.

Materials and methods

The study included patients with acute or chronic skin lesions, who had already turned 18 and, in the case of female patients, who were not pregnant. The recruitment was discontinued as soon as the share of 50 enrolled skin lesions was achieved. The material under evaluation was a hyperoxidized oil-based gel dressing fulfilling film-forming and protective functions, even from a thermic viewpoint; the existing international literature positions the product among oxygen generators and recognizes its capabilities to accelerate re-epithelialization, assist proliferation of fibroblasts and stimulate endogenous neoangiogenesis through an increased creation of cytokines and growth factors, which it is supposed to induce. In addition it can control microbial growth thanks to its highly oxidizing properties.¹⁴

Notwithstanding the observational nature of the study, the inclusion/exclusion criteria adopted proved to be rather rigorous indeed, starting from the primary and absolute prerequisite to complete a detailed etiological diagnosis prior to classifying the lesion as eligible and, above all, prior to evaluating any other criterion. The need to recruit only lesions whose etiological diagnosis can be regarded as certain

depends on the fact that it is most likely that, upon completion of the diagnosis, an adequate causal therapy is provided;¹⁵ this is definitely fundamental with a view to being able to decrease the variables which may affect the analysis of the result to the minimum value. For the same reason the Ankle Brachial Pressure Index (ABPI)¹⁶ of each patient was evaluated in order to avoid including in the study lesions which might be influenced by a basal state of severe hypoxia; hence, a hypoxic condition resulting from an arterial disease cannot be resolved by a causal non-surgical therapy. No doubt any etiology shall be treated and local hypoxia, common in any chronic skin lesions, can be reduced by means of an adequate therapy. In presence of bedsores local hypoxia depends on capillary occlusion due to compression¹⁷ and a revised distribution of loads by means of positioning and technological surface becomes the obvious choice for therapy, consequential and suitable as it is (as well as rather easily implementable in order to have the patient enrolled in the study), whereas in presence of severe arterial diseases exclusively surgery might restore an acceptable oxygenation in the area affected by the lesion: this is the reason why an ABPI value <0.7 was considered as a key exclusion criterion. Borderline arterial disease, if treated by means of vasodilators and antiplatelet agents, was not considered as an exclusion criterion.

As far as tissue evaluation is concerned, it was initially decided to include in the study lesions with A and B WBP score only, since C score, assuming the existence of a large quantity of fibrin, would have determined a situation which might allow bacterial colonization. C WBP score lesions were at any rate previously treated and, considering the good results achieved, during the final stage of the study it was agreed to exclude D WBP score lesions only, *i.e.*, those wounds showing non-viable tissue (Table I).

One of the main features of this dressing is its capability to control bacterial growth and just for this reason it was decided to exclude critically colonized and/or in-

TABLE I.—*Wound bed preparation score.*

Score	Wound bed appearance			Wound exudate
	Granulation	Fibrinous	Eschar	
A	100%	-	-	1. Fully controlled. None or minimal. No absorptive dressings required. If clinically feasible, dressings could stay on for up to a week.
B	50-100%	+	-	2. Partially controlled. Moderate amount. Dressings changes required every 2-3 days.
C	<50%	+	-	3. Uncontrolled. Very exudative wound. Absorptive dressings changes required daily or more often.
D	Any amount	+	+	

TABLE II.—*Inclusion and exclusion criteria.*

Inclusion criteria	Exclusion criteria
Acute and chronic lesions with known etiology	Acute and chronic lesions with unknown etiology
Patient aged 18 or older	Patient aged under 18
A, B and C Wound Bed Preparation score	D Wound Bed Preparation score
No severe ischemia (ABPI >0.7)	Severe ischemia (ABPI ≤0.7)
No critical colonization/infection	Critical colonization/infection
Life expectancy greater than 4 weeks	Life expectancy lower than 4 weeks
	Immunosuppressive therapies

TABLE III.—*Criteria to assist the identification of infection in granulating wounds.*

Traditional criteria	Suggested additional criteria
1. Abscess	4. Delayed healing (compared with normal rate)
2. Cellulitis	5. Discoloration
3. Discharge	6. Friable granulation tissue (easily bleeding)
(a) Serous exudate with inflammation	7. Unexpected pain/tenderness
(b) Seropurulent	8. Pocketing in the wound base
(c) Hemopurulent	8.(a) Bridging of the epithelium or soft tissue
(d) Pus	9. Abnormal smell
	10. Wound breakdown

fected lesions, since the low frequency in wound colonization during treatment was a secondary aim; it would have certainly been difficult to distinguish between the already existing colonization at the beginning of the treatment and its possible aggravation, as attributable to the product. In presence of colonized lesions, the ability of the gel to decrease the incidence of colonization/infection cannot absolutely be evaluated.

Among additional exclusion criteria were the administration of immunosuppressive drugs (with the exception of low-dose steroids) and a life expectancy lower than 4

weeks, intended as such a serious pathological status as not to allow the patient to reach treatment completion, and, above all, to perform a conditional function which might affect the result due to a pathological interference on the tissue repair process, regardless of the etiological cause of the lesion.

Table II shows an overview of the inclusion and exclusion criteria.

After preliminary preparation of the wound bed by means of an appropriate cleansing¹⁸ with a 0.05% sodium-hypochlorite-based chloroxidating solution,¹⁹ a uniform gel layer was applied on



Figure 1.—Wong-Baker FACES Pain Scale.

TABLE IV.—Pain scale subject to the use of analgesic drugs.

No pain	Minimum pain	Mild pain	Moderate pain	Severe pain	Unbearable pain
Score: 0	Score: 1	Score: 2	Score: 3	Score: 4	Score: 5
	No analgesic	Occasional analgesics	Prescheduled analgesics	Opioid analgesics	Ineffective opioids

the lesions and their borders; the product, packaged in proper syringes to facilitate the delivery, preserves its gel status if stored at a temperature lower than 8 °C (approximately 47 °F) and, if it becomes excessively fluid due to storage in a non-refrigerated environment, can be reverted to its optimal physical status, without any alterations in quality, as soon as stored at low temperatures once again. The secondary treatment was left at the professional investigator's discretion, against the sole precondition to comply with the exudation of the lesion and to exclude any advanced, interactive or oxygen-release medications. The dressing was scheduled to be changed every other day; the possibility of a daily change was anyhow taken into account, in presence of excessive quantity of exudate.

The observation time was fixed at 4 weeks, with a number of grounded and duly controlled exceptions; at any rate those patients who could not reach the 28th treatment day were not considered as part of the study, except cases of early recovery ahead of the study deadline, protocol termination due to pain, onset of allergic reactions, manifest deterioration of the lesion. In all these specific circumstances the patient was included in the study as a statistically negative unit (related adverse event),

while in the case of study termination due to any other reason and/or non-related adverse event, such as for instance worsening of general conditions, hospitalization or death, the patient was not counted in the global case-based reasoning.

The expected measurements were identified in the iconographic documentation by means of a digital camera, the calculation of the lesion area *via* the Visitrak™ Digital System,²⁰ the WBP score data entry, the analysis of possible critical colonization/infection symptoms and the detection of pain *via* the Numerical Rating Scale (NRS)²¹ upon enrollment (T0), at first check after 2 weeks (T14) and upon final completion of the study protocol (T28). Cutting and Harding²² criteria were employed for the evaluation of the possible bacterial colonization (Table III), while, as far as pain was concerned, it was decided to resort to a Wong-Baker²³ variation based classification (Figure 1), where pain degrees are related to the use of analgesic drugs. The introduction of a new pain measurement system was aimed at trying to decrease the subjectivity of the result: likely, indications on analgesics administration may lead to a superior objectivity (Table IV).

Data were processed by means of a simple statistical system.

Results

The data collected throughout the 28-day treatment allowed us to make a complete evaluation of the hyperoxidized oil mixture taken into consideration. The definitely positive performances can be regarded as more than encouraging, particularly in terms of pain reduction and improvement of the wound bed. Before proceeding with an in-depth analysis of the results, the etiological classification of the wounds considered in the study is presented in Table V. It is advisable to recall that, although arterial lesions are part of the case-based reasoning, all the enrolled patients obtained a >0.8 ABPI result, according to the previously described inclusion/exclusion criteria.

It should be pointed out that venous ulcers enrolled in the study showed a minimum inflammatory component, considering the significant reported pain component which, in standard conditions, can be easily neglected when arising in phlebostatic ulcers (Figure 2). As it may be observed from the data in Table V, the largest percentage involves inflammatory ulcers (specifically

in the form of biopsy-diagnosed leukocytoclastic vasculitis); such a value increases from 40% to 46% if Martorell ulcers (classified as vasculitic lesions, thus inflammatory ulcers) are counted in the number (Figure 3). As for the sole post-traumatic ulcer case included in the case-based reasoning, the original etiological definition was preserved, even though the chronicization of this type of ulcer derives from the osteitis component, typical in any lesion showing an area of exposed bone; at any rate a definitely significant result was achieved in this type of lesion, where the growth of granulation buds was observed directly on the exposed bone tissue.

The results of our study consist in a series of percentage shares which we are going to individually analyze. Table VI summarizes the data referring to the average area reductions, the alterations in pain, in the use of pharmaceutical drugs and negative events, intended as adverse related/non-related events and treatment discontinuations. Table VII presents all the variations in the wound base through an evaluation of the WBP score.

As shown is Table VI, area and pain reduction are constant factors, that is to say common elements in all the patients.

The average percentage in area reduction exceeded 50% of the total cases (intended as percentage in the re-epithelialized area) and in 3 cases (6%) the complete healing was achieved within the 4-week observation time (Figure 4).

A decrease in pre-existing pain, as prior to being treated, was observed in all pa-

TABLE V.—*Etiological wound classification.*

Etiology	Wounds	Percentage
Arterial ulcers	6	12%
Venous ulcers	13	26%
Mixed arterial/venous	7	14%
Inflammatory ulcers	20	40%
Martorell ulcers	3	6%
Post-traumatic ulcers	1	2%

TABLE VI.—*Results on wound area, pain and use of analgesic drugs.*

Area reduction		Pain reduction		Use of analgesic drugs	
Patient percentage	Average percentage	Patient percentage	Average percentage	Reduction	Discontinuation
100%	52.2%	100%	53.6%	56%	12%

TABLE VII.—*Evaluation of WBP score after treatment.*

Worsening		Improvement		No variation	
C Tissue	---	From C to B Tissue	12%	B Tissue	2%
B Tissue	---	From C to A Tissue	2%	Epithelialization	6%
A Tissue	---	From B to A Tissue	64%		

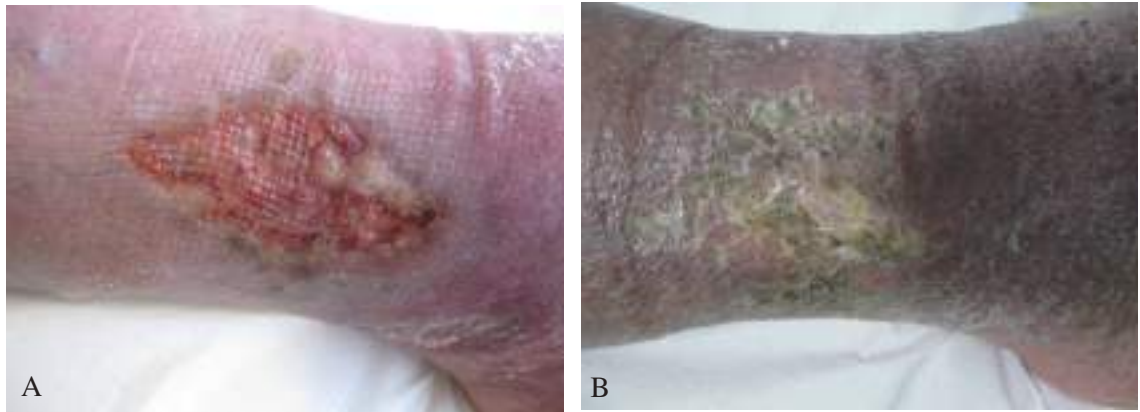


Figure 2.—A) VLU with reumatoid pattern (T0): WBP score B2: NRS 6; B) VLU with reumatoid pattern (T28): healed.



Figure 3.—A) Leukocytoclastic vasculitis (T0): WBP score B2: area 8.12 cm²: NRS 9; B) leukocytoclastic vasculitis (T28): WBP score A2: area 3.19 cm²: NRS 3.

tients; in some cases it even disappeared, from time to time, already after the first 10 therapy days. The average reduction percentage on the global volume of cases which were taken into account was identified by means of the Numerical Rating Scale in the proportion of 53.6%; this means that pain value was halved, in some cases it totally disappeared, exclusively through a topic application and without any need to resort to pharmaceutical drugs.

Indicative indeed the analysis of the use of analgesic drugs, dramatically decreased in 56% of the patients; such a statistic parameter is, however, partially incorrect: as a matter of fact, under the assumption that 12% of the patients completely discontinued the use of

analgesic drugs, the related decrease should be calculated in a 68% proportion. This rate is even more noteworthy if grounded on the particular that 32% of patients, who continued the same antalgic therapy by means of analgesic drugs, nonetheless reported an overall decrease in ulcer pain.

In the final analysis, the report on the variations in tissue configuration can be considered highly satisfactory: absolute improvement was observed in 100% of the total cases; 14% of unclean, C-score wounds underwent a partial cleansing (B WBP score in 6 out of 7 cases), whereas the remaining portion with a C WBP score achieved a completely clean status (A WBP score) within the 4-week treatment time; out of all

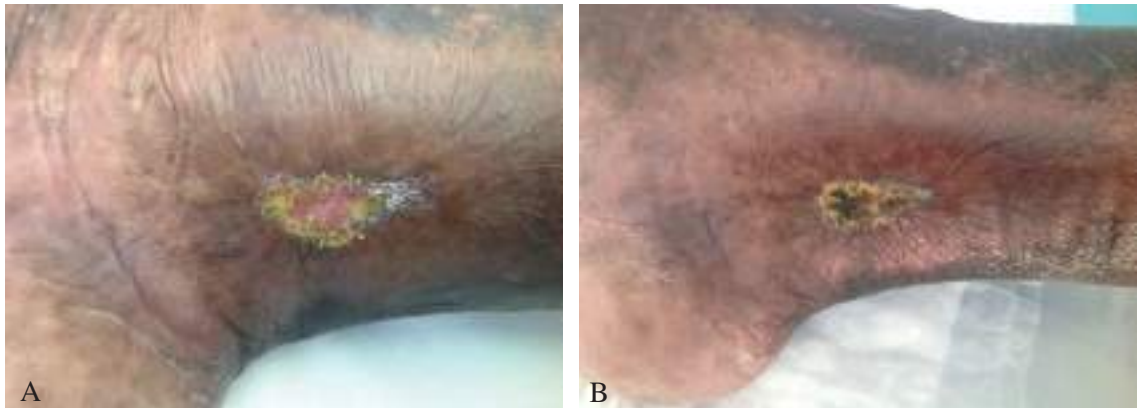


Figure 4.—A) Vasculitis in Thalasso drepanocytosis (T0): WBP score B2: area 3.44 cm²: NRS 8; B) vasculitis in Thalasso drepanocytosis (T28): healed.

the enrolled lesions with B WBP score (33), 32 achieved a clean status (64% of the total cases), while one did not show any variation in the tissue type (2%) and such a result confirms that more than 90% of the lesions which were not completely cleansed conversely achieved an optimal granulation status. Table VII does not include the data referring to 7 lesions (14%) which, starting from an A WBP score, maintained such a parameter.

Discussion

According to the results of our study, it is clear that this type of medication successfully reached the expected result, both from a qualitative and a quantitative viewpoint; granulation was unquestionably stimulated in any treated case, as evidenced by the analysis of the related Wound Bed Preparation score data; epithelialization proved to be satisfactory in quantitative terms, and this is further confirmed by a comparison between the accomplished result and the “healing rate” data as documented in literature.²⁴ Percentage values are positive on the whole and, in some cases, went far beyond expectations; all patients achieved a reduction in the wound area; more than 90% of the total lesions, which started from a WBP score other than A, attained im-

proved conditions; a complete recovery was accomplished in 3 cases (6%).

Furthermore the total absence of infective complications is to be noted: no case reported colonization/infection symptoms, thus confirming a significant preventive antibacterial activity exerted by this hyperoxidized oil-based medication.

Concerning comfort, the totality of patients showed an excellent tolerability, without any observed allergy or intolerance; exclusively in one case the treatment had to be discontinued upon the patient’s specific request a week before the fixed deadline, even though the lesion was no doubt manifestly improving: the request was merely due to the fact that the medication was to be stored at a controlled temperature in a refrigerated environment and the patient did not feel confident enough about the product’s effectiveness, once out of the refrigerator.

Pain data showed presumably the most striking success: no patient complained about pain upon application of the medication, with the exception of 2 cases reporting a transient burning pain, which spontaneously disappeared 10-15 minutes after the product was applied. The totality of the cases which were treated evidenced a substantial decrease in the pain symptomatology and some of them reported a complete pain reduction. It should be highlighted that some patients limited or discontinued the use of analgesic drugs.

Conclusions

The user-friendliness of this easy-to-apply hyperoxidized oil mixture makes it easily acceptable by caregivers and patients, who experience no difficulties when self-medicating with this product. On the basis of the achieved results and the observed appreciation, we feel confident stating that this oxygen-release mixture of hyperoxidized oils (NovoX® - MOSS S.p.A., Lesa, Novara, Italy) can be counted in the current scenario of effective medications.

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