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CASE SERIES

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Healing of complex venous ulcers through oxidative stress management

Resumen

El exceso de radicales libres en el entorno de una herida contribuye de forma significativa al estancamiento de la misma en la fase inflamatoria, fa- voreciendo la aparición de una herida de difícil cicatrización. Se genera una situación de estrés oxidativo, puesto que las enfermedades de base que suelen presentar los pacientes con heridas crónicas dificultan en gran medida el retorno a una situación de balance oxidativo. Esto incide directamente sobre la capacidad de respuesta del tejido, ya que se afectan directamente estructuras celulares y la matriz extracelular del entorno. En este trabajo se ha aplicado un tratamiento antioxidante para el control del exceso de radicales libres en el entorno de la herida, con el fin de conseguir la activación en el caso de úlceras crónicas de etiología vascular venosa. Para ello, se ha aplicado un apósito antioxidante con componentes de origen natural, una matriz absorbente de algarrobo y una solución antioxidante con cúrcuma y acetilcisteína, indicado para la fase inflamatoria de las heridas y la adecuada terapia compresiva. Para la evaluación de la evolución de las úlceras se utilizó la escala RESVECH 2.0. Transcurridas 2-3 semanas, el apósito antioxidante consiguió la activación de la herida, lo que se reflejó en el mantenimiento del lecho de la úlcera libre de tejido desvitalizado, la inducción de la formación de tejido de granulación y la activación de los bordes perilesionales. A partir de ese momento, se aplicaron apósitos de cura húmeda convencionales, llegando hasta la cicatrización total de las heridas en las semanas 5-6 desde el inicio del tratamiento.

PALABRAS CLAVE: APÓSITO ANTIOXIDANTE; ESTRÉS OXIDATIVO; RADICALES LIBRES; HERIDA CRÓNICA; ÚLCERAS VENOSAS.

HEALING OF COMPLEX VENOUS ULCERS THROUGH OXIDATIVE STRESS MANAGEMENT: CASE SERIES

Summary

The excess of free radicals in the wound environment significantly contributes to the arrest of the wound in the inflammatory phase, favouring the appearance of a hard-to-heal wound. An oxidative stress condition is generated, as the comorbidities that patients with chronic wounds frequently present hinder the return to an oxidative balance. This fact affects the ability of the tissue to respond to an injury, since cellular structures and extracellular matrix of the environment are affected. In this work, an antioxidant treatment has been applied, to control the excess of free radicals in the wound environment, in order to achieve the activation of chronic ulcers from venous vascular etiology. This antioxidant dressing has two components from natural origin, an absorbent matrix from carob tree and an antioxidant solution containing curcumin and acetylcysteine, and is indicated for the inflammatory phase of the healing process of wounds. The appropriate compressive therapy was also applied. RESVECH 2.0 scale was used as wound evolution assessment. The results showed that after 2-3 weeks of treatment, the antioxidant dressing achieved the activation of the wound, which was reflected in the maintenance of a wound bed free from devitalized tissue, the induction of the formation of granulation tissue and the activation of the perilesional edges. After that, conventional moist wound healing dressings were applied, reaching wound closure after 5-6 weeks from the beginning of the treatment.

KEY WORDS: ANTIOXIDANT DRESSING, OXIDATIVE STRESS, FREE RADICALS, HARD-TO-HEAL WOUNDS, VENOUS ULCERS.

Introduction

The oxidative stress present in a damaged tissue is due to an excess of the levels of free radicals and reactive oxygen and nitrogen species, which are not managed properly during the process of tissue repair[1-3]. These radicals are produced by the same inflammatory cells that go to the damaged area, as first antibacterial defence line and as signalling molecules for the regulation and activation of healing[4,5]. Once their mission is completed, the concentration of free radicals must decrease until reaching basal levels[6,7]. Factors such as bad habits or patient processes (diabetes, ischemia, venous disease), decrease the physiological antioxidant defences and the levels of these molecules remain elevated[8–11] longer than necessary.

In response to an excess of free radicals there is a neutrophil recruitment, an activation of the secretion of pro-inflammatory cytokines that keep the wound in a persistent inflammatory state[12–14], with an altered cellular response and the healing process slows down producing a hard-to-heal wound[15–18]. Table 1 shows the effects of this oxidative stress on the wound. The main objective of this work is to present the effect of an antioxidant wound dressing with components from natural origin on five cases of complex venous wounds. This wound dressing was used in order to eliminate the excess of free radicals in the wound environment, achieve wound activation and overcome the inflammatory phase, by controlling oxidative stress and its harmful effects. Also, as a secondary objective, an estimate of the cost-benefit of the use of this wound dressing, indicated for the inflammatory phase of complex wounds of different etiology, was calculated.

Material and Methods

Design

This is a case series study of patients referred to the advanced chronic wound specialist of the Poniente Health District, Almería (Andalusian Health Service, Spain), where they were examined and treated with the antioxidant wound dressing throughout the first semester of 2018.

Description of cases

Patients included in the study had wounds from venous etiology over three months in evolution, with local clinical signs of infection, moderate exudate, presence of devitalised tissue in the wound bed (fibrin and slough) and torpid evolution (table 2).

EFFECTS OF OXIDATIVE STRESS ON THE WOUND **1**

Persistent inflammatory environment[13]
Direct damage of free radical son cell membranes, proteins and DNA[1,2]
Decreased mitochondrial activity, energy deficit in the cell[20]
Induction of fibroblasts senescence[21]
Inhibition of the migration capacity of keratinocytes[22]
Induction of metalloproteinase synthesis[23]
Decreased activity of endogenous antioxidants[1]

Source: this manuscript.

Description of the wound dressing

The antioxidant wound dressing consists of an absorbent plant matrix of carob seeds that is moistened with a solution containing turmeric and N-acetylcysteine, providing a moist environment and a high antioxidant capacity provided by all its components. The matrix can be trimmed to fit the wound bed.

Description of lesion management techniques

In all cases a sharp debridement was performed, followed by the application of the antioxidant wound dressing as primary dressing and polyurethane foam as secondary dressing, in order to keep the antioxidant wound dressing on the wound bed, and help with the management of the exudate.

The matrix was cut to fit the shape of the wound bed. Perilesional skin was protected with a barrier film to prevent maceration due to exudate. The antioxidant wound dressing was maintained on the wound an average of 3-4 days. Once the advanced chronic wound specialist considered that normal wound healing process had been reactivated – wound bed with no devitalised tissues, active edges, and induction of proliferative phase – the ulcers were treated with conventional moist wound healing dressings. The evolution for the ulcers was evaluated by means of the RESVECH 2.0[19] scale at each wound dressing change. This scale has 6 items related to wound dimension, depth of affected tissues, state of wound edges, type of tissue in the wound bed, level and type of exudate and signs of infection-inflammation.

The application of the scale allowed us to obtain quantitative data on the evolution of the wound.

Age	40	80	41	70	65
Wound etiology	Post-thrombotic venous vascular ulcer	Post-thrombotic venous vascular ulcer	Varicose venous vascular ulcer	Post-thrombotic venous vascular ulcer	Post-thrombotic venous vascular ulcer
Time in evolution	4 MONTHS	2 YEARS	6 MONTHS	2 YEARS	12 MONTHS
Pathologies	• Crohn disease • Hypothyroidism • Obesity • Venous insufficiency	• Beta thalassemia minor • Arterial hypertension • Gilbert's syndrome • Microcytosis • Diabetes Mellitus	• Diabetes Mellitus • Chronic pancreatitis • Liver disease • Mixed hyperlipidemia • Portal hypertension • Venous insufficiency • Barrett's esophagus	• Venous insufficiency • Repeated stroke	• Arterial hypertension • Left popliteal artery aneurysm • Gonarthrosis • Dyslipidemia • Morbid obesity • Venous insufficiency • Osteoarthritis • Hyperuricemia
Primary wound dressing	Antioxidant wound dressing				
Secondary wound dressing	Polyurethane foam				
Frequency of wound dressings changes	Every 72 h	Every 72 h	Every 72 h	Every 72 h	Every 72 h
Compressive therapy	Multilayer bandage (JOBST® Compri 2-BSN)				Non-elastic compression system (Circaid)
Compressive therapy after healing	Compression stockings (Ulcer care)				Non-elastic compression system (Circaid)

Source: this manuscript.

Cost-benefit Analysis

An estimate of the cost of treating the wounds and a comparison between costs before and after treatment with the antioxidant wound dressing. The cost estimate per treatment included the expenses associated with the consumables, used wound dressings, antibiotics and hourly costs of the professionals who treated the wound (nurse, primary care doctors and specialist).

Results

Five patients with hard-to-heal ulcers from venous vascular etiology were included. Table 2 shows the characteristics of patients and lesions.

Average age of patients was 59.2 ± 17.9 years. Patients presented ulcers of 4 to 24 months in evolution. They also had basal diseases that made the healing process of lesions more difficult. All wounds were treated according to the protocol described in the methodology with wound dressing changes every 72 hours in all cases. All patients were treated with compression therapy (multilayer bandage or non-elastic compression system), which remained after healing.

Figure 1 shows the images of the evolution of wounds throughout treatment with antioxidant wound dressing, polyurethane foam and compressive therapy.

The wound management protocol of the study achieved permanent elimination of devitalised tissues from the wound bed, since there was no re-deposit of slough and fibrinous tissue after the initial debridement, preventing their effect in wound evolution. Application of the antioxidant wound dressing in addition to an adequate management of the exudate and the appropriate compressive therapy promote the formation of new granulation tissue and the activation of the perilesional edges, that started to progress (Figure 1).

Total wound closure was achieved after 5-6 weeks of treatment with a decrease in RESVECH of 53.4 ± 8% during the first 2-3 weeks of treatment (Figure 2).

In addition, the estimate of the cost-benefit calculated in these 5 cases, indicated that treatment with antioxidant wound dressing produced savings between 152.52 and 2499.20 euros, with an average of 1652,31 ± 1235.92 euros (Figure 3).

Discussion

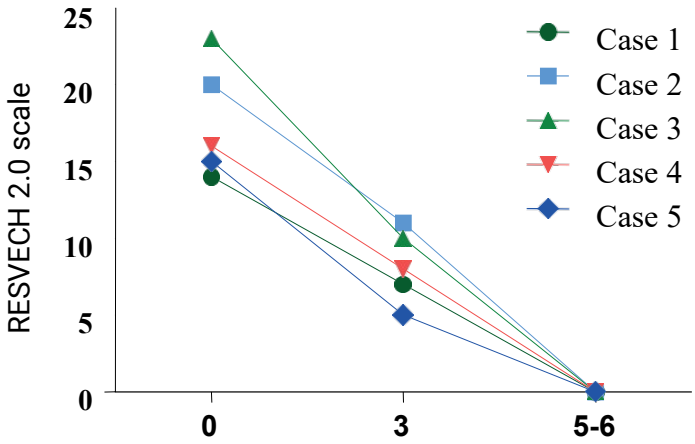
Control of oxidative stress in the wound has been described in recent years as a relevant factor to consider for achieving activation of hard-to-heal wounds[16].

Images of the evolution of the wounds during the treatment with tha antioxidant wound dressing, poliurethane foam and compressive therapy. Source: this manuscript.

Patients with complex lesions are frequently exposed to an oxidative stress situation, due in part to their basal pathologies (diabetes mellitus, venous or arterial insufficiency, hypertension, etc.) that are a continuous source of free radicals[8–11], and also in part to the decrease of physiological antioxidant defences (enzymatic and non-enzymatic antioxidation)[1]. These circumstances interfere with returning effectively to a situation of oxidative balance or homeostasis[3]. The excess of free radicals has different effects on the cells responsible for the healing process, as there are direct damages on different cellular structures (membranes, DNA, proteins)[1,2], and on the extracellular matrix (collagen, hyaluronic acid) [23] ,which affect response capability of tissues.

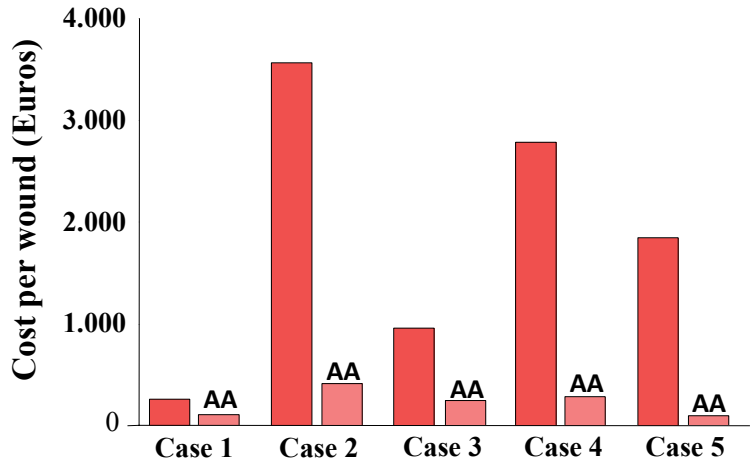
In this work, a series of hard-to-heal wounds of venous vascular etiology have been treated with an antioxidant wound dressing[24], with the objective of controlling the excess of free radicals, activating the wound and contributing to overcome the inflammatory phase. The antioxidant wound dressing consists of a galactomannan matrix of plant origin, which is obtained

2



Evolution of RESVECH 2.0 scale at treatmen beginning (0 weeks), at an intermediate point (3 weeks) and in the closure, at 5 or 6 weeks depending on the case. Source: this manuscript.

3



Estimate of the cost in euros of expenses associated with each of the cases before (left bar of each case) and after (right bar of each case) of the application of the antioxidant dressing (AA)

from the flour of carob tree seeds (Locust bean gum), and a hydration solution containing turmeric and N-acetylcysteine (NAC)[25]. The galactomannan from locust bean flour is widely used in the food industry as a thickener[26] and in traditional medicine to reduce pain and inflammation in gastrointestinal disorders. This galactomannan allows the production of an absorbent matrix with a high antioxidant capacity. Turmeric has been used for more than 2,000 years as an antioxidant, natural anti-inflammatory and to improve healing of wounds[28-30]. Finally, NAC acts synergistically with the other two components to obtain a high antioxidant capacity, and also its activity is related to the control of both bacterial and fungal biofilms[31-35].

For the treatment of the wounds in the study, the advanced chronic wound specialist of Poniente Health District, Almería (Spain), shared with co-workers the antioxidant treatment in patients with ulcers of long and/or torpid evolution, which had been previously treated with several or multiple treatments, with negative evolution, delayed healing or resistance to conventional treatments, resulting ineffective treatments in all cases.

Patients were treated by their reference nurses and supervised with follow-up and evaluation by the advanced chronic wound specialist. Data was permanently updated on both the wound follow-up program and each patient's clinical history. Initially wounds were stagnant, with presence of fibrin, slough, biofilm and devitalised tissue, and the antioxidant wound dressing helped in removing these tissues. The antioxidant treatment was not maintained until complete wound closure. Once the proliferative phase was obtained, treatments were changed to bioactive dressings or conventional moist wound healing dressings. Complete healing was achieved thanks to the maintenance of an adequate environment in the wound by controlling oxidative stress, proper management of exudate and application of compressive therapy indicated for each patient.

In spite of presenting the effect of the antioxidant wound dressing in only five cases, the results obtained were very homogeneous in terms of capacity of an adequate maintenance of the wound bed, promotion of granulation tissue formation and activation of edges, which were achieved in all cases. However, this work has limitations regarding the dispersion in patient's age and time in evolution of wounds. In addition, it is necessary to further study the effect that the antioxidant wound dressing may have on the biofilm. Although it was clinically observed that biofilm did not interfere with the evolution in these 5 ulcers, specific assays are required to define if there is a mechanism of action of the antioxidant wound dressing on the removal and formation prevention of biofilm.

Conclusions

• The control of oxidative stress in wounds is a relevant aspect to overcome the inflammatory phase, especially in complex wounds in patients with important basal diseases that affect the healing process.

• The application of antioxidant wound dressing, allows the control of the excess of free radicals in the wound, which induces the activation of hard-to-heal ulcers of venous vascular etiology.

• In the five cases included in this study, adequate maintenance of the wound bed, formation of new granulation tissue and activation of the perilesional edges were achieved, obtaining a significant reduction of the RESVECH 2.0 healing index during the first weeks of treatment. In addition, with the necessary and adequate compressive therapy, it was possible to attain complete wound closure.

BIBLIOGRAPHY

1. Evans P, Halliwell B. Free radicals and hearing. Cause, consequence, and criteria. Ann N Y Acad Sci. 1999;884:19-40.
2. Di Meo S, Reed TT, Venditti P, Victor VM. Role of ROS and RNS Sources in Physiological and Pathological Conditions. Oxid Med Cell Longev. 2016:1-44. DOI: 10.1155/2016/1245049.
3. Armstrong D, Stratton RD. Oxidative Stress and Antioxidant Protection: The Science of Free Radical Biology and Disease. John Wiley & Sons; 2016. 610 p.
4. Jaganjac M, Cipak A, Schaur RJ, Zarkovic N. Pathophysiology of neutrophil-mediated extracellu- lar redox reactions. Front Biosci Landmark Ed. 2016;21:839-55.
5. El Benna J, Hurtado Nedelec M, Marzaioli V, Marie JC, Gougerot Pocidalo M A, Dang PM-C. Priming of the neutrophil respiratory burst: role in host defense and inflammation. Immunol Rev. 2016;273:180-93. DOI: 10.1111/imr.12447.
6. Niethammer P, Grabher C, Look AT, Mitchison TJ. A tissue-scale gradient of hydrogen peroxide mediates rapid wound detection in zebrafish. Nature. 2009;459:996.9. DOI: 10.1038/nature08119.
7. Rojkind M, Dominguez-Rosales J-A, Nieto N, Greenwel P. Role of hydrogen peroxide and oxida- tive stress in healing responses. Cell Mol Life Sci. 2002;59:1872-91.
8. Rasool M, Ashraf MAB, Malik A, Waquar S, Khan SA, Qazi MH, et al. Comparative study of extrapolati- ve factors linked with oxidative injury and anti-inflammatory status in chronic kidney disease patients experiencing cardiovascular distress. PloS One 2017;12:e0171561. DOI: 10.1371/journal.pone.0171561.
9. Ighodaro OM. Molecular pathways associated with oxidative stress in diabetes mellitus. Biomed Pharmacother. 2018;108:656-62. DOI: 10.1016/j.biopha.2018.09.058.
10. Liakopoulos V, Roumeliotis S, Zarogiannis S, Eleftheriadis T, Mertens PR. Oxidative stress in hemodialysis: Causative mechanisms, clinical implications, and possible therapeutic interventions. Semin Dial. 2018. DOI: 10.1111/sdi.12745.
11. Koutakis P, Ismaeel A, Farmer P, Purcell S, Smith RS, Eidson JL, et al. Oxidative stress and antioxidant treatment in patients with peripheral artery disease. Physiol Rep 2018;6:e13650. DOI: 10.14814/phy2.13650.
12. Vermeij WP, Backendorf C. Skin cornification proteins provide global link between ROS detoxification and cell migration during wound healing. PloS One. 2010;5:e11957. DOI: 10.1371/journal.pone.0011957.
13. Wagener FADTG, Carels CE, Lundvig DMS. Targeting the redox balance in inflammatory skin conditions. Int J Mol Sci. 2013;14:9126-67. DOI: 10.3390/ijms14059126.
14. Sen CK. Wound healing essentials: let there be oxygen. Wound Repair Regen 2009;17:1-18.
15. Salim AS. The role of oxygen-derived free radicals in the management of venous (varicose) ulceration: a new approach. World J Surg. 1991;15:264-9.
16. Schäfer M, Werner S. Oxidative stress in normal and impaired wound repair. Pharmacol Res. 2008;58:165-171.
17. Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D. Systematic reviews of wound care management: (2). Dressings and topical agents used in the healing of chronic wounds. Health Technol Assess Winch Engl. 1999;3:1-35.
18. Dhall S, Do DC, Garcia M, Kim J, Mirebrahim SH, Lyubovitsky J, et al. Generating and Reversing Chronic Wounds in Diabetic Mice by Manipulating Wound Redox Parameters. J Diabetes Res. 2014;2014:1-18. DOI: 10.1155/2014/562625.
19. Gilkerson R. A Disturbance in the Force: Cellular Stress Sensing by the Mitochondrial Network. Antioxidants. 2018;7:126. DOI: 10.3390/antiox7100126.
20. Henderson EA. The potential effect of fibroblast senescence on wound healing and the chronic wound environment. J Wound Care. 2006;15:315-8. DOI: 10.12968/jowc.2006.15.7.26932.
21. Hu SC-S, Lan C-CE. High-glucose environment disturbs the physiologic functions of keratinocytes: Focusing on diabetic wound healing. J Dermatol Sci. 2016;84:121-7. DOI: 10.1016/j.jdermsci.2016.07.008.
22. Latifa K, Sondess S, Hajer G, Manel B-H-M, Souhir K, Nadia B, et al. Evaluation of physiological risk factors, oxidant-antioxidant imbalance, proteolytic and genetic variations of matrix metalloproteinase-9 in patients with pressure ulcer. Sci Rep. 2016;6. DOI: 10.1038/srep29371.
23. Medrano JC, Soriano JV. Development of a wound healing index for chronic wounds. Gerokomos. 2011;22:176-183.
24. Castro B, Bastida FD, Segovia T, López Casa- nova P, Soldevilla JJ, Verdú-Soriano J. The use of an antioxidant dressing on hard-to-heal wounds: a multicentre, prospective case series. J Wound Care. 2017;26:742-50. DOI: 10.12968/jowc.2017.26.12.742.
25. Castro B, Palomares T, Azcoitia I, Bastida F, Del Olmo M, Soldevilla JJ, et al. Development and preclinical evaluation of a new galactomannan-based dressing with antioxidant properties for wound healing. Histol Histopathol. 2015;30:1499-512. DOI: 10.14670/HH-11-646.
26. Barak S, Mudgil D. Locust bean gum: Processing, properties and food applications – A review. Int J Biol Macromol. 2014;66:74-80. DOI: 10.1016/j.ijbiomac.2014.02.017.
27. Dionísio M, Grenha A. Locust bean gum: Exploring its potential for biopharmaceutical applications. J Pharm Bioallied Sci. 2012;4:175-85. DOI: 10.4103/0975-7406.99013.
28. Akbik D, Ghadiri M, Chrzanowski W, Rohanizadeh R. Curcumin as a wound healing agent. Life Sci. 2014;116:1-7. DOI: 10.1016/j.lfs.2014.08.016.
29. Tejada S, Manayi A, Daglia M, Nabavi SF, Sureda A, Hajheydari Z, et al. Wound Healing Effects of Curcumin: A Short Review. Curr Pharm Biotechnol. 2016;17:1002-7.
30. Kumar A, Ahuja A, Ali J, Baboota S. Conundrum and therapeutic potential of curcumin in drug delivery. Crit Rev Ther Drug Carrier Syst. 2010;27:279-312.
31. Zhao T, Liu Y. N-acetylcysteine inhibit biofilms produced by Pseudomonas aeruginosa. BMC Microbiol. 2010;10:140. DOI: 10.1186/1471-2180-10-140.
32 Gupta P, Sarkar S, Das B, Bhattacharjee S, Tribedi P. Biofilm, pathogenesis and prevention – a journey to break the wall: a review. Arch Microbiol. 2015;198:1-15. DOI: 10.1007/s00203-015-1148-6.
33. Rasmussen K, Nikrad J, Reilly C, Li Y, Jones R s. N-Acetyl-l-cysteine effects on multi-species oral biofilm formation and bacterial ecology. Lett Appl Microbiol. 2016;62:30-8. DOI: 10.1111/lam.12513.
34. Wulf K, Arbeiter D, Eickner T, Riedel K, Schmitz K-P, Grabow N, et al. Polymer drug release system for biofilm inhibition in medical application. Curr Dir Biomed Eng. 2018;4:213-6. DOI: 10.1515/cdb- me-2018-0052.
35. Dinicola S, De Grazia S, Carlomagno G, Pintucci JP. N-acetylcysteine as powerful molecule to destroy bacterial biofilms. A systematic review. Eur Rev Med Pharmacol Sci. 2014;18:2942-8.
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