

Topical oxygen wound therapies for chronic wounds: a review



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Chronic wounds are an increasing problem in our ageing population and can arise in many different ways. Over the past decades it has become evident that sufficient oxygen supply is an essential factor of appropriate wound healing. Sustained oxygen deficit has a detrimental impact on wound healing, especially for patients with chronic wounds. This has been proven for wounds associated with peripheral arterial occlusive disease (PAOD) and diabetic foot ulcers (particularly in combination with PAOD). However, this is still under debate for other primary diseases.

In the past few years several different new therapeutic approaches for topical oxygen therapies have been developed to support wound healing. These tend to fall into one of four categories: (1) delivery of pure oxygen either under pressurised or (2) ambient condition, (3) chemical release of oxygen via an enzymatic reaction or (4) increase of oxygen by facilitated diffusion using oxygen binding and releasing molecules. In this review article, the available therapeutic topical oxygen-delivering approaches and their impact on wound healing are presented and critically discussed. A summary of clinical data, daily treatment recommendations and practicability is provided.

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The most common chronic wounds are leg ulcers, foot ulcers and pressure ulcers.^{1,2} In most cases, patients with such wounds suffer from peripheral arterial occlusive disease (PAOD), chronic venous insufficiency (CVI) and/or diabetes mellitus, or, in the case of pressure ulcers, immobility.

It is generally accepted that, in patients with PAOD and diabetic foot syndrome, a disturbance in the vascular system results in a sustained inadequate supply of oxygen and finally chronic hypoxia. These conditions dramatically increase the probability of developing a chronic wound.^{3,4}

In patients with PAOD, the relationship between oxygen deficiency and reduced arterial perfusion has been well known for decades.⁵ Depending on the degree of the reduction, the hypoxia reaches a critical threshold below which wound healing is significantly decreased. This stage of PAOD is termed chronic critical ischaemia.

In the case of neuropathic diabetic foot ulcers, traumatic repetitive pressure load is a common trigger of ulceration as the patient does not sense the pressure due to polyneuropathy. In addition, patients with diabetic foot syndrome have a func-

tional vascular impairment^{7,8} due to a thickening of the basal membrane and endothelial capillary swelling.⁹ As a result of the neuropathy, the endothelium-dependent regulation of the vascular lumen is affected by nitric oxide (NO) and the neuronal regulation of the precapillary arterioles is deregulated.¹⁰ As a result of such dysfunctions, an adequate reaction in the foot—increased blood flow in response to an injury, for example—cannot be achieved.^{11–13} Although the feet of patients with diabetes seem phenotypically healthy, such underlying structural and molecular changes may prevent a sustained oxygen supply when needed after an injury.

In addition, there is increasing evidence that similar pathophysiological aspects regarding inadequate oxygen supply are relevant to other primary diseases like CVI.^{14–16}

In patients with CVI, hypoxia is mainly caused by venous hypertension and hypervolaemia. The chronically elevated ambulatory pressure in the veins and the upstream venules causes structural changes in the blood vessels. This leads to the demise of capillaries, which is seen as reduced capillary density.^{17,18} The oedema associated with

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venous stasis further increases distances between capillaries and results in slower diffusion of oxygen from the remaining capillaries to the tissue cells.¹⁹⁻²²

It is well known that wound healing is accompanied by an increase in metabolism in the skin tissue and therefore requires considerably more oxygen than intact skin. In the different phases of wound healing, numerous biochemical and cellular processes are highly dependent on a sufficient supply of oxygen,^{3,4,24-27,30} including energy metabolism,³¹ reactive oxygen species (ROS) generation, infection control,³²⁻³⁴ signalling,³⁵⁻³⁷ and construction of the extracellular matrix (ECM) or remodeling of collagen.³⁸⁻⁴²

Therefore, it makes sense that the status of the oxygen supply to a wound represents an important determinant for the course of healing. There are well-established methods available to determine this status^{28,29} but it should be noted that it is important to determine the oxygen partial pressure over the whole wound area in order to identify the hot spot(s) of limited oxygen supply as reported by Barnikol and Pötzschke.¹⁴

As oxygen plays a crucial role in wound healing, supplying additional oxygen to the chronic wounds may help promote healing.^{3,4,23,24}

Various approaches have been developed to improve the local oxygen supply, resulting in a wide range of adjuvant oxygen therapies.

Recent case studies and clinical trials suggest that local oxygen therapies⁴³⁻⁴⁷ are promising and valid options in the toolbox of adjunctive oxygen therapies (Fig 1).

Here we describe the different delivery routes of topical oxygen, the available clinical data and the possibility of implementing such approaches into daily wound care treatment recommendations.

Topical oxygen supply in the treatment regime of chronic wounds

The question arises as to how to specifically improve the local oxygen supply in order to promote the oxygen-dependent processes of wound healing in a targeted manner.⁴³ Although gaseous oxygen can diffuse through any permeable surface, only a very minor amount of oxygen used in wound healing enters the body via the skin and wound exudate. This is related to the thickness of the skin and the liquids in the wound bed which act as an oxygen diffusion barrier.⁴⁸

Oxygen therapies are most commonly based on supply of dioxygen O_2 , the most stable form of oxygen. Ozone (trioxygen, O_3), a very reactive gas (oxidation), and nascent oxygen (singlet oxygen), a short-lived free radical of oxygen, are mainly used for disinfectant purposes and not in long-term therapies due to their cytotoxic side effects. Any topical oxygen therapy needs to overcome two major intrinsic issues:

- Diffusion between the gas phase of oxygen and the solid or liquid phase of the skin and the wound exudate which serve as barriers
- Movement of oxygen within the liquid phase of the wound bed to the cells that require the oxygen, through transfer and diffusion processes.

Considering the first issue (oxygen diffusion at the boundary between the gas phase and liquid wound exudate), oxygen is dissolved at very low amounts in water and wound exudate-like liquids. Its solubility and the speed of dissolution can be influenced by increasing the partial pressure and varying the temperature and salt content.

For example, the solubility of oxygen in fresh water is 14.6mg/l (14.6 part per million (ppm)) at 0°C, normobaric pressure (760mmHg) in a 100% oxygen atmosphere. An increase to 795mmHg (+4.6% increase in pressure) results in an increase to 15.6mg/l (+6.8% additional oxygen). If the normobaric pressure is maintained at 795mmHg and the temperature increased to 30°C (+10%) the oxygen content decreases to 7.9mg/l (-46%).⁴⁹ Therefore, an increase in temperature results in a decrease of oxygen in water, while an increase of the oxygen partial pressure leads to increases of oxygen in a solution.

Once the oxygen is dissolved the second issue concerns the diffusion limitations. The molecular oxygen (O_2) has to diffuse to the sites of consumption such as fibroblasts, immune cells and proteins building the ECM. In chronic wounds the blood flow at the wound area is often disturbed and the diffusion distance for oxygen is significantly increased from the blood vessels. In this situation, the improvement of oxygen content in the wound area by topical approaches should have a beneficial impact on physiological processes in wounds. Topical approaches aim to generate a local increase of

Fig 1. Different topical and systemic approaches of additional oxygen supply to a chronic wound are available. The topical approaches are discussed in this review in more detail

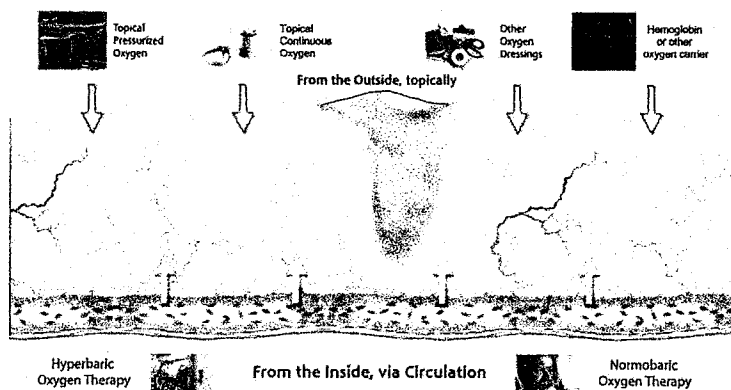
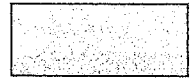


Table 1. Comparison of different medical devices for topical oxygen supply.

Medical device		Oxygen content	Oxygen supply	Oxygen release	Oxygen uptake & release	Ulcer type			
Company	Product name	System	Pressurised	Normobaric		Diabetic foot	Arterial leg	Venous leg	Pressure
Aortl Ltd.	two ₂	Oxygen enrichment and pressure unit (chamber or disposable bag)	●			●	●	●	●
OxyCare GmbH	O ₂ TopiCare System	Oxygen enrichment and pressure unit (chamber or disposable bag)	●			●	●	●	●
GWR Medical Inc.	TO ₁	Oxygen enrichment and pressure unit (Bag; O ₂ Boot & O ₂ Sacral)	●			●	●	●	
Ogenix Inc.	EpiFLO	Oxygen enrichment unit and supply material		●		●	●	●	●
InotecAMD Ltd.	Natrox	Oxygen enrichment unit and supply material		●		●	●	●	●
OxyBand Technologies Inc.	OxyBand	Absorbant hydrocolloid patch with permeable oxygen-emitting reservoir			●	●	●	●	●
Halyard Health Inc.	OxygeneSys Continuous	Oxygen foam dressing with permeable oxygen-emitting reservoir			●	●	●	●	●
Halyard Health Inc.	OxygeneSys On Demand	Oxygen foam dressing with hydrogen peroxide doping			●	●	●	●	
Crawford Healthcare Ltd.	Oxzyme	Dual layer hydrogel with hydrogen peroxide doping			●	●	●	●	
Tenax Therapeutics Inc.	Oxycyte	Oxygenized perfluorocarbon (PFC) topical gel				●	●	●	●
SastoMed GmbH	Granulox	Stabilised purified haemoglobin solution				●	●	●	●



oxygen concentration at the wound site. Unlike systemic oxygen therapy, topical oxygen does not rely on an (impaired) vascular system to deliver the oxygen to the wound site. It also has reduced risks compared to systemically increasing oxygen via hyperbaric oxygen therapy.

Since the late 1930s, local delivery of oxygen to wounds has been used with varying success and, recently, several different types of device supporting the local oxygen supply have been introduced to the wound-care sector, supported by *in vitro* experiments and *in vivo* animal model data. For example, *in vitro* experiments revealed an increase of vascular endothelial growth factor (VEGF) transcripts in macrophages and endothelial cells after hyperoxia,⁵⁰⁻⁵² while *in vivo* data showed an increase of the VEGF protein.⁵³

It must be noted that topical oxygen therapies are seen as different to hyperbaric oxygen therapy as they have different physiological and biochemical effects. Therefore, they are not seen as equivalent therapies.⁵⁴ This article focuses on topical treatment, specifically on topical pressurised oxygen therapies in the form of topical continuous oxygen therapy, oxygen-releasing wound dressings, and oxygen-diffusion enhancers.

Topical pressurised oxygen therapy

Devices for facilitating local topical pressurised oxygen therapy such as small chambers or bags were developed in contrast to large and costly hyperbaric chambers. These can be used easily in daily practice. The aim was to increase flexibility and reduce some of the proposed side effects, such as fatigue or light-headedness and the more severe problems of the middle-ear, lung failure, fluid in the lung or seizures, of hyperbaric therapy.

There are currently several products marketed using a combination of a small pressure chamber with oxygen-providing wound dressings, and oxygen-diffusion enhancer units (Table 1). Current clinical evidence for the effectiveness of these systems is based on case reports and clinical studies primarily published in the last two decades. Several authors have reported improved healing in different wound types.^{44,55} Most of the studies reported are not randomised and/or controlled, but instead use wounds which were therapy resistant. Blackman et al. reported that a group of difficult-to-treat patients with severe diabetic foot ulcers treated with a pressurised oxygen therapy revealed that they 'were significantly more likely to heal and during a shorter period of time' than wounds in patients of the control group.⁵⁵ In another study Gordillo et al. demonstrated that the use of pressurised topical oxygen therapy had a significant impact on wound-size reduction while also showing that VEGF expression was increased at the wound boundary.⁵³ Tawfik and

Sultan found in a study assessing treatment refractory venous leg ulcers a significantly higher healing rate in the oxygenised group (89%), compared to the control group treated with a moist wound dressing (35%).⁴⁴ Several other reports similar results in hard-to-heal wounds.^{45,56,57}

Therapy recommendation

Gordillo and Sen recommend such systems to be used daily for 90 minutes, for 4 consecutive days followed by 3 days without treatment.⁴³ During treatment the wound dressings should be removed. Furthermore, conditions for O₂ delivery should be optimised by removing necrotic tissue from wound surface, minimising oedema, and keeping the affected area warm and the patient well hydrated. This treatment can be performed for several weeks or months. An improvement of wound healing within 6-8 weeks should be used as an indicator to maintain therapy.⁴³

Topical continuous oxygen therapy

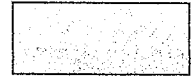
Topically applied continuous normobaric oxygen therapy to wounds is different to pressurised therapy, as it does not increase pressure and does not need a pressure chamber. Several different devices are currently marketed (Table 2). Portable units generate pure oxygen and provide a continuous flow of oxygen to the wound 24 hours a day and 7 days per week. Occlusive dressings and oxygen supplying tubes or battery-operated oxygen extraction units may be changed at planned wound-care visits. Animal studies have revealed that this method can promote healing in different wound models.^{58,59}

In the clinical setting, several case reports and clinical studies show promising results for chronic wounds.^{46,60-63} Lowell et al. presented a series of four cases with non-healing leg or foot ulcers.⁶¹ All wounds were therapy resistant and had failed to improve under standard care. In addition, the wounds were very painful. The authors reported that all wounds closed under the new therapy and the wound-related pain stopped. Wo et al. evaluated transdermal continuous topical oxygen therapy (TCOT) for its effect on chronic wound healing in nine patients. After 4 weeks of treatment the wound surface area and wound infection were significantly reduced.⁶² Kemp and Hermans tested the therapy in patients with recalcitrant diabetic foot ulcers.⁶³ The patients had previously failed other therapies including HBOT, negative pressure or low-intensity laser therapy. Using continuous topical oxygen therapy 12 out of 14 wounds healed. Additional case reports support the encouraging results for this treatment. Again, in most cases hard-to-heal wounds were selected.^{46,60} Further additional clinical studies are currently reported as ongoing on www.clinicaltrials.gov.

Table 2. Comparison of treatment modalities of different topical oxygen devices.

Medical devices		Treatment details						
Company	Product name	Description	Pressure	Flow rate	Treatment period /day	Treatment frequency in days /week	Treatment location	Moist wound environment
Aoti Ltd.	two ₂	50mbar to 5mbar cycles	low > 1 bar	high	60–90 minutes	3–7	Open wound in chamber or bag	Possible
OxyCare GmbH	O2TopiCare System	2–5 l/min; 50mbar	low > 1 bar	high	60–90 minutes	3–7	Open wound in chamber or bag	Possible
GWR Medical Inc.	TO ₂	2–5 l/min; 50mbar	low > 1 bar	high	60–90 minutes	3–7	Open wound in chamber or bag	Possible
Ogenix Inc.	EpiFLO	Continuous, slow flow of pure oxygen of 3 ml/hr for 15 days through a cannula to blanket the wound	low < 1 bar	low	24 hours	7	Occlusive wound dressing	yes
InotecAMD Ltd.	Natrox	Continuous, slow flow of pure oxygen of ~12ml/hr for several days via a thin flexible tube to the Oxygen Delivery System (ODS) which is in direct contact with the wound surface	low < 1 bar	low	24 hours	7	Occlusive wound dressing	yes
OxyBand Technologies Inc.	OxyBand	Oxygen release for up to 5 days after contact with moisture within a simple occlusive wound dressing	n.a.	n.a.	24 hours	7	Occlusive wound dressing	yes
Halyard Health Inc.	OxygeneSys Continuous	Use as a foam dressing, Oxygen release for up to 5 days when dressing is moistened	n.a.	n.a.	24 hours	7	Non-occlusive wound dressing	yes
Halyard Health Inc.	OxygeneSys On Demand	Oxygen release for up to 5 days after contact with moisture within a simple occlusive wound dressing	n.a.	n.a.	24 hours	7	Non-occlusive wound dressing	yes
Crawford Healthcare Ltd.	Oxzyyme	Use as a primary dressing, in early stage wound treatment. Oxygen release when both layers are attached to each other	n.a.	n.a.	24 hours	7	Non-occlusive wound dressing	yes
Tenax Therapeutics Inc.	Oxycyte	PFC-based oil in water emulsion	n.a.	n.a.	24 hours	7	Wound bed	yes
SastoMed GmbH/InFirst Healthcare Ltd.	Granulox	Liquid spray with 10% purified haemoglobin, applied as thin layer to the wound bed covered by a non-occlusive dressing. Min twice weekly application	n.a.	n.a.	24 hours	7	Wound bed	yes

n.a. = information not applicable



Therapy recommendation

Continuous topical oxygen therapy does not require daily use of a bag or chamber and therefore can continuously deliver oxygen for 24 hours 7 days a week. In order to optimise conditions for O₂ delivery at the wound, the wound should be debrided and cleansed at regular intervals. The interval depends on the wound status and further additional therapies, with frequency adjusted accordingly, for example once daily or once per week. The dressing should be changed at each wound debridement. This therapy can be performed for several weeks or months. An improvement in wound healing within 6–8 weeks should be used as an indicator to maintain therapy.

Wound dressings releasing oxygen

As an alternative to the direct gaseous application of oxygen which requires the diffusion, oxygen can also be released directly in wound dressings. Two different approaches are available, either pure oxygen embedded in the dressing (Oxygeneses Continuous/OxyBand) or released after a biochemical reaction in a hydrogel (Oxygeneses on Demand/Oxyzyme).

Continuous release

In the case of oxygen-containing dressings, pure oxygen (>2800 ppm O₂) is embedded in the dressing in vesicles, and released after the dressing is liquidised by the wound exudate. *In vitro* experiments have shown that such a dressing is capable of significantly increasing oxygen levels in the wound.⁶⁴ A benefit was also seen in treating larger donor site wounds, in burn patients, compared to standard care.⁶⁵ Unfortunately, no further clinical data are available in the public domain.

Therapy recommendations

Continuous oxygen release dressings can be used as a secondary dressing and can release oxygen for up to 5 or 6 days. In order to optimise conditions for O₂ delivery at the wound, the wound should be regularly debrided and cleansed. The interval depends on the wound status. The dressing should be changed at each wound debridement.

Release on demand

With these hydrogels an increased concentration of dissolved oxygen is obtained via a chemical (Oxygeneses on demand) or biochemical (Oxyzyme) reaction. Oxygeneses on demand is an occlusive dressing and makes use of the reactivity of 0.3% hydrogen peroxide, which is converted to water and dissolved oxygen. The oxygen can diffuse via a permeable separator to the wound bed.

In contrast, Oxyzyme consists of two separate components which must be applied together to

activate the biochemical process. The first component, is a hydrogel sheet with glucose and a low concentration gel matrix with less than 0.04% w/w of iodide ions, and the second a sheet with glucose oxidase. The glucose oxidase incorporated in the second gel sheet, catalyses the oxidation of (beta)-D-glucose to D-gluconic acid and hydrogen peroxide in the presence of oxygen. The released hydrogen peroxide is thought to diffuse through the dressing and either oxidise any available iodide ions to free iodine and oxygen or, if it reaches the wound surface, is metabolised to water and oxygen. Iodine has an antimicrobial effect, while the dissolved oxygen is believed to create beneficial effects within the wound. Several case study reports demonstrated improvement in wound healing of different wound types.^{66,67}

Therapy recommendations

On demand oxygen-releasing dressings can be used from an early stage of wound care and offers additional antimicrobial properties in addition to releasing oxygen. In order to optimise conditions for O₂ delivery at the wound, the wound should be regularly debrided and cleansed. The interval depends on the wound status and further additional therapies. An improvement of wound healing within 6–8 weeks should be used as an indicator to maintain therapy.

Oxygen diffusion enhancer

Haemoglobin spray

One of the most recent products on the market is an aqueous solution containing purified haemoglobin as an oxygen carrier. For oxygen to reach the wound bed from the outside, the diffusion barrier must be at least partially opened. Such an opening in the diffusion barrier is made possible using a concept originally developed by Barnikol et al.⁶⁸ Haemoglobin, an oxygen transporter, is applied to the wound bed as an aqueous solution. Facilitated diffusion augments the movement of oxygen.⁶⁹ Haemoglobin taken from mammals is suitable as a transporter and, since it is soluble, can also transport oxygen molecules when not bound to an erythrocyte.⁷⁰ Case reports in Germany (closure of 6 from 8 wounds), the Czech Republic (closure of 5 from 5 wounds) and Mexico (closure of 9 from 9 wounds) and the UK (14 out of 17 non healing wounds showing significant improvement by week 4), all showed positive responses.^{71,72} A randomised clinical study on patients with a mixed cohort of chronic wounds (diabetic foot ulcers, venous leg ulcers, arterial leg ulcers) in Mexico revealed that in 39 out of 42 patients (93%) the treated wounds were healed using a haemoglobin spray.⁷¹ The efficacy of a haemoglobin solution in the treatment of venous leg ulcers was further demonstrated in a prospective randomised

single-blinded clinical study that compared haemoglobin spray with a sham product as an add-on to standard care, moist wound healing and compression.⁴⁷ The results of these studies^{47,71} illustrated a clear improvement of wound healing in comparison to a control group. A significant reduction of the average wound size by 53% after 13 weeks of treatment was observed only in the haemoglobin group. In the comparator group no reduction in mean wound size was observed. The studies mentioned above and single case reports from as early as 2005 suggest a positive impact on wound healing across of comprehensive range of chronic wound types.^{68,73,74} Besides diabetic foot ulcers and venous or arterial leg ulcers, the haemoglobin spray has shown the potential to be used in a broad spectrum of hard-to-heal wounds with similar levels of hypoxia such as pressure ulcers, secondary healing wounds (for example, wounds with post-surgical healing disturbances like infection or wounds with severe tissue loss), or burns. Results to date suggest a potent adjunctive effect of haemoglobin on the healing process in different types of chronic wounds.^{47,71}

Therapy recommendation

In order to optimise conditions for O₂ delivery at the wound, the haemoglobin spray should be applied after each wound debridement and cleansing. Dependent on the wound status and further additional therapies, the wound should be debrided and cleansed at regular intervals from once daily to once every 3 days. The haemoglobin spray can be allied with existing moist wound therapy without changing the modalities. As oxygen will be taken up from the atmosphere, a non-occlusive dressing is required. The haemoglobin spray can be used from the beginning of treatment and is recommended to be used until wound closure. An improvement in wound healing and symptoms should be observed from 4 weeks.

Perfluorocarbon

An alternative to haemoglobin might be perfluorocarbon (PFC), a synthetic oxygen carrier that does not need to be derived from blood. PFCs are molecules capable of binding and releasing oxygen in an aqueous solution and have been used as breathing fluids for deep sea diving and as a blood substitute.⁷⁵ Topical oxygen emulsion (TOE), consisting of a supersaturated oxygen suspension using PFC components as oxygen carrier aided re-epithelialisation in porcine partial-thickness excisional wounds and second-degree burns.⁴⁵ Davis et al.⁴⁵ proposed that this approach may be useful for treating chronic wounds. Recently it was demonstrated *in vitro* using fibroblast cultures, that PFC-conjugated hydrogels can control oxygen levels on a spatial scale of milli-

metres and greatly enhance cellular proliferative and metabolic responses.⁷⁶

Therapy recommendation

There is currently insufficient evidence to provide recommendations for use of this technology and there are no products marketed that could be used in wound care. At this stage clinical studies are necessary to prove the safety of the technology and to demonstrate the positive observed *in vitro* effects in animal or human experiments. Furthermore, an appropriate therapy protocol and a product viable for clinical use need to be developed.

Discussion

During the last two decades, results of various case studies and clinical trials suggest that the local oxygen therapies are promising options for enhancing wound healing. These results are supported by several experimental and clinical studies that have highlighted the key role of oxygen in wound healing in general and specifically in patients with chronic wounds. Improving the oxygen supply at the wound should be seen as an essential and important part of wound management.^{3,4,23,26} All of the described topical oxygen therapies aim to improve the oxygen supply to the hypoxic area of the wounds, so that rapid skin regeneration can take place.^{43,56,65,68} The clinical results achieved with these methods indicate that significant benefits are possible over standard care alone. The evidence base shows successful healing outcomes when standard care has failed to achieve an adequate healing response. As for many other products used in wound care management, the clinical evidence for the efficacy of topical oxygen-based treatment is still based largely on case reports and small clinical trials. In wound care, a number of different approaches and tools are required to obtain wound healing, especially if wounds are not responding to the initial treatment regime. Although not all of the trials discussed meet the highest standards of evidence, the results available support such adjunctive therapies as valuable products in modern strategies.

In addition, a major advantage of topical oxygen therapies it's ease of use. The technologies outlined in this paper can in many cases be implemented as an adjunctive therapy in future without the need to visit specially equipped facilities.

Conclusion

Topical oxygen therapy approaches are not yet widely used in the wound care community anywhere in the world. Growing evidence of its effectiveness suggests it has the potential to form a regular part of adjunctive therapies in treatment regimens to speed up healing of chronic wounds. ■

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