



Oxygen in wound healing: a review

Efficacy, tolerability and acceptability of a new, flexible lipidocolloid dressing

Doxycycline in the treatment of a high output lymphatic fistula

Case study: a rare presentation of mucormycosis

Singlet oxygen for cleansing and disinfecting stagnating wounds

Does cetuximab pose an additional risk during radiotherapy?

Telemedicine in the management of chronic wounds

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Subscription rates 2010/11:

Annual subscription (12 issues)
UK personal (cheque/c. card):* £102.00
UK personal (direct debit):* £94.00
UK institutional: £395.00
Europe personal:* €174.00
Rest of world personal:* \$274.00
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indexed on several databases, including:

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CINAHL The Cumulative Index to
Nursing and Allied Health Literature;

RCN The Royal College of Nursing
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Published by:

MA Healthcare Ltd,
St Jude's Church, Dulwich Road,
London SE24 0PB



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Printing by Pensord
ISSN 0969-0700



Evidence debate: let's listen to both sides

During the past few years, a trickle of correspondence and editorial opinion pieces, published in the nursing press, has grown into a full-blown debate about what constitutes evidence in wound care.

There seem to be two sides in the argument, with some saying that the randomised controlled trial and Cochrane meta-analyses should form the basis for clinical decision-making and others arguing that, for practical, logistical and financial reasons, this is an unachievable goal. The reason we are in the midst of this debate is, of course, because dressings are classed as devices, and so are not regulated, meaning that in many instances RCT evidence isn't a prerequisite for their launch. Should we aim for more — and better quality — RCTs, or consider a pragmatic approach, as advocated by EWMA's Patient Outcome Group document,¹ that will improve the quality of research in general, even if it remains at a lower levels of the evidence hierarchy?

In view of this, having a debate, and listening to the strong arguments on both sides is healthy, and we must hope that this concludes with a consensus that helps us to move the discipline of tissue viability nursing forward and improve clinical practice. Better patient outcomes must be the result!

So what is the role of journals in all this? It is definitely not to take sides, but rather to make sure that the proponents on both sides of the debate have the chance to air their views. We have recently published two supplements which argue that, while meta-analyses and RCTs constitute the most robust form of evidence, that an alternative approach is also needed. However, I will also be inviting those associated with the Cochrane Wounds Group, and other key supporters of the evidence hierarchy, to explain how they believe practitioners and researchers can overcome the obstacles to conducting studies that achieve a high level of evidence, referred to by the Patient Outcomes Group and others in various articles. Should we have a trials' register? Who should we lobby for funding? The questions go on and on.

Ultimately, as I said in last month's editorial, our shared objective — indeed, our passion — must be to improve the quality of research in wound care. To achieve this, we must work together, and ascertain how industry, higher education, clinicians and key opinion leaders, including those from the Cochrane Wound Group if they so wish, can work together to produce guidance that can make this a reality.

I Gottrup, F. Apelqvist, J. Price, P. Outcomes in controlled and comparative studies on non-healing wounds: recommendations to improve the quality of evidence in wound management. J Wound Care 2010; 19: 6, 235-268.

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Measuring parameters such as changes in fibrin, slough and granulation tissue (as assessed by computer analysis of digital photographs) and also levels offensive wound odour, rated by patients and clinicians on a five-point scale, the results of this cohort study indicate that singlet oxygen has a role in wound cleansing, disinfection, reducing inflammation and promoting wound healing. G. Kammerlander, O. Assadian, T. Eberlein, P. Zweimüller, S. Luchsinger, A. Andriessen

R 160 Role of oxygen in wound healing: a review of evidence

A literature search was performed using Ovid and the Cochrane Database, revealing 1568 relevant studies (although only 2 randomised controlled trials were found). This review of the evidence found that oxygen is vital throughout wound healing, especially in the inflammatory and proliferative phases. It is suggested that oxygen supplementation can enhance bacterial killing and angiogenesis, reduce surgical site infection. A.C. Chambers, D.J. Leaper

P 166 Wound healing following combined radiation and cetuximab therapy in head and neck cancer patients

While prior radiation is a known risk factor for wound complications, it is unknown whether anti-EGFR therapy poses an additional risk for the wound healing process. By performing a retrospective chart review, this study set out to determine if cetuximab treatment increases the risk of wound healing complications when used in association with radiotherapy. N.R. Dean, L. Sweeny, P.M. Harari, J.A. Bonner, V. Jones, L. Clemons, H. Geye, E.L. Rosenthal

P 171 Case report: doxycycline instillation used to treat a high-output lymphatic fistula secondary to needle puncture

Doxycycline has been used as a sclerosing agent in the treatment of recurrent pleural effusion and pneumothoraces but little is currently known of its use in the closure of lymphatic fistulae. This paper presents an unusual case in which instillation of doxycycline was used to treat patient who had developed the unusual complication of a high-output lymphatic fistula, following a femoral needle puncture. K. Singh, M.L. Wang, V. Rubinshteyn, C. Sücco, J. Deitch

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P 176 Mucormycosis of the anterior chest wall presenting as a soft tissue tumour

This report describes a case of the mucormycosis that presented as a non-healing ulcer over the chest wall (an extremely rare site for this lesion) which appeared to be a soft tissue tumour. The ulcer was managed successfully with high doses of intravenous Amphotericin B and aggressive surgical debridement.

S.K. Jain, R.C.M. Kaza, R. Tanwar

R 180 Use of a new, flexible lipidocolloid dressing on acute and chronic wounds: results of a clinical study

This paper documents the efficacy, tolerability and acceptability of a new, flexible lipidocolloid dressing on acute and chronic wounds. An open, non-comparative, multicentre clinical trial recruited patients from 11 centres, including surgical, burns and rehabilitation units, and paediatric, geriatric and dermatology wards. In terms of efficacy and tolerability, the dressing was found to be similar to a less flexible dressing from the same family, although when considering acceptability, the new, flexible dressing was found to be superior.

S. Meaume, J. Perez, H. Descamps, V. Voinchet, P. Jault, V. Saunier, S. Bohbot

P 187 Telemedicine in the management of patients with chronic wounds

This article presents a telemedicine system that has been introduced in southern Jutland, Denmark. Using 'low-tech' equipment, such as camera-equipped mobile phones and normal desktop computers with an internet connection, health professionals have been able to communicate and collect data in a clinical database more effectively. This system aims to improve interdisciplinary collaboration, through facilitating the interaction between health professionals and also other parties that are involved in the provision of care, such as administrative staff and local reimbursement authorities. R. Jelnes

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This year's cover
theme is professions.

A clinical evaluation of the efficacy and safety of singlet oxygen in cleansing and disinfecting stagnating wounds

- **Objective:** This cohort study evaluated the clinical efficacy of singlet oxygen, ActiMaris (AM) a hypertonic (3%) ionised (pH 9.8) sea water solution. It was assumed that when used for wound cleansing, disinfection and the reduction of inflammation, AM would be safe and effective.
- **Method:** Between May 2008 and May 2009, ambulant patients presenting at one of four wound healing centres were included in the study. Patients had critically colonised and/or infected, malodorous wounds, covered with slough/fibrin or wounds showing inflammation of the periwound skin. Wounds were assessed in terms of percentage changes in fibrin, slough and granulation tissue, they were assessed clinically and high resolution digital photographs were scored by a physician who was blinded to treatment allocation. Results were compared at baseline (week 0) and following 42 days of AM treatment (week 6).
- **Results:** Seventy-three patients were included in the analysis. Dressing changes were at 2-day intervals on average, and the median treatment period was 46.04 days (range: 3–197). At 42 days, 33% (n=24) of included wounds had healed, 57% (n=42) had improved and 10% (n=7) remained stagnant. Cleansing and wound disinfection with AM was effective. In 31 patients (42%) wounds had showed clinical signs and symptoms of critical colonisation and/or infection at day 0, whereas at day 42 the infection was completely eradicated. Inflammation was reduced in 60% (n=44) of cases and patients did not report pain or discomfort when using AM.
- **Conclusion:** The use of singlet oxygen was shown to be safe and the results of this study indicate AM to be useful for wound cleansing, disinfection, reducing inflammation and promoting wound healing.
- **Conflict of interest:** The centres were supplied with the study product by the sponsor. The authors have no financial interest in writing this article.

singlet oxygen; redox system; stagnating wounds; wound cleansing; wound disinfection

Chronic and stagnating wounds often provide an ideal habitat for microbial colonisation, which together with the lack of a host response, can impair healing.^{1,2} Furthermore, the environment within such wounds can be ideal for bacterial proliferation, especially in the presence of necrotic or sloughy tissue.^{2,3}

The removal of devitalised tissue is generally accepted as a necessary precondition for the formation of new tissue.^{4,5} Devitalised tissue can mask infection, act as a physical barrier to healing and may impede normal matrix formation, angiogenesis or the development of granulation tissue.⁶ Devitalised tissue contributes to the production of inflammatory cytokines, which in turn leads to the overproduction of matrix metalloproteinases (MMPs).^{6,7}

The value of chronic wound cleansing, including debridement, is a basic principle in the modern approach to wound management.^{7,8} It is a part of

wound bed preparation — it gently and continuously removes debris and exudate, preparing the wound bed for wound closure.^{1,2,5}

Topical antimicrobial substances such as silver, povidone iodine or polihexanide are increasingly used to treat multi-resistant wound infections.^{7–9} Antiseptics have a lower potential to induce bacterial resistance compared with antibiotics, although overuse of these products may reduce their efficacy.^{7,8}

In recent years, there has been debate over the appropriateness and efficacy of various different methods of wound cleansing and disinfection. In Europe we differentiate between debridement (removal of dead tissue) and cleansing (removal of senescent cells and exudate). However, this distinction is not made everywhere. There are grey areas. For instance, in the management of stagnating wounds, the removal of an excess of MMPs may be done by absorbent dressings and not just by sharp debridement.^{4,5}

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For wound cleansing, a variety of strategies are currently applied, such as short rinsing, or leaving a dressing impregnated with an antimicrobial in place for approximately 20 minutes (the so-called 'wet-to-dry' phase) before applying the usual dressing regime.^{5,9} Antimicrobials have a time to onset, so a better effect can be expected when applied for 20 minutes, rather than a quick rinse. We previously published this method in *JWC* and it has since been widely practiced in Continental Europe and is currently gaining favour in the UK.

To use these tissue friendly solutions in a moist wound healing dressing, of course, gives an even better effect. However, for this study we used AM the same way as polyhexamethylene biguanide (PHMB) or other antiseptic solutions would be used, applying best practice — the wet-to-dry phase.

The wet-to-dry phase is a multi-phase concept, which starts with an active cleansing phase, the 'wet' phase, in which a cleansing fluid is applied to the wound for 20 minutes to one hour, followed by a short resting phase, the 'dry' phase. During the dry phase, the wound is covered with a gauze dressing and peri-wound skin integrity is restored. Cleansing fluid evaporates during both phases, resulting in the release of wound debris, exudate and pathogens, which saturate the gauze dressing during the dry phase. Next, a moist wound healing dressing, usually an alginate, foam or Hydrofiber, is applied. If local infection is present, then an antiseptic may be used as the cleansing agent during the wet phase and an antiseptic dressing might be used afterwards, instead of an absorbent dressing. The aim of the wet-to-dry phase is not to create an optimal healing environment or temperature (although excessive cooling off is to be prevented), but rather to cleanse the wound and reduce itching and inflammation.⁵

There are currently no conclusive data to show which strategy, out of continuous treatment with an antimicrobial combined with a dressing, or a short cleansing phase using an antimicrobial before dressing application is the most effective strategy for wound disinfection.⁹

However, it has been suggested that the antimicrobial carrier used and the time during which the antimicrobial can become activated can influence the results obtained with the treatment.^{5,9}

Singlet oxygen

Singlet oxygen, a form of molecular oxygen (O₂) which is less stable than the normal triplet oxygen, is a reactive oxygen species (ROS). ActiMaris (AM) (QuantumMedis Est, Vaduz, Liechtenstein) is an ionised (pH 9.8) solution of sea water with active singlet oxygen, that has been used as an antimicrobial for wound disinfection in Austria, Switzerland and Germany.^{10,11} It is hypertonic (3%) and thus draws water out of cells by osmosis.¹¹⁻¹³

ROS are implicated in cellular activity to a variety of inflammatory responses.¹²⁻¹⁴ Effects of ROS on cell metabolism have been well documented for a variety of species.¹⁴⁻¹⁶ These include not only roles in apoptosis (programmed cell death) but also in other mechanisms such as the induction of host defences.¹² This can be explained with the redox system. ROS generated within cells or, more generally, in a tissue environment, can damage cells and tissues. Aerobic organisms can carefully control the generation of ROS and other oxidative stress-related radical and non-radical reactive intermediates (that is, aerobic organisms can maintain redox homeostasis), and 'make use' of these molecules under physiological conditions, to modulate signal transduction, gene expression and cellular functional responses ('redox signalling').

When AM is in contact with the wound bed, singlet oxygen is released slowly, as during the Krebs cycle in mitochondria.^{10,11,14} At a high pH (9.8), AM's singlet oxygen interacts with hydroxide groups as a redox system,^{11,13,14} which occurs through a series of complex electron transfers.¹⁵ Redox signalling can have positive effects, such as the induction of host defence.^{11,12,14-16} AM's clinical activity is based on these mechanisms reducing inflammatory reactions, promoting neovascularisation, granulation and epithelialisation in stagnating wounds.^{10,11}

In AM, active oxygen is bound and stabilised between sodium and chloride ions (NaOCl) in water or gel.^{10,11} Bacteria and viruses do not have an efficient defence against singlet oxygen.¹¹ Singlet oxygen, has been shown to have microbicidal activity against *Staphylococcus aureus* and *Escherichia coli* *in vitro*, and also when applied to chronic wounds *in vivo*.^{10,11} When in contact with skin and/or wounds, active oxygen induces a reaction by binding electrons from other cells or substances.^{10,11} This destroys the sulphate groups of bacterial membranes in seconds, and the bacteria are soon engulfed.

The fast onset of activity makes AM especially suitable for wound rinsing.^{10,11} AM is available as a solution, a forte solution and a gel. The solution and the gel are indicated for cleansing contaminated wounds and those at risk of infection. The forte solution is indicated for critically colonised and clinically infected wounds. AM has a low concentration of sodium oxichlorit (0,2%) and both the solution and gel are alkaline (pH 9); the forte solution and gel are hypertonic (3,0%).

The product may be combined with various dressings, such as alginates, hydrofibres and foams, for continuous application.^{4,5,10,11} Due to excellent tissue compatibility and an absence of irritation, ubiquitous application is possible on the skin, mucous membranes, cavities, the middle ear and cartilage and beneath semi-occlusive and occlusive dressings.^{10,11} AM may be used for acute wounds, chronic

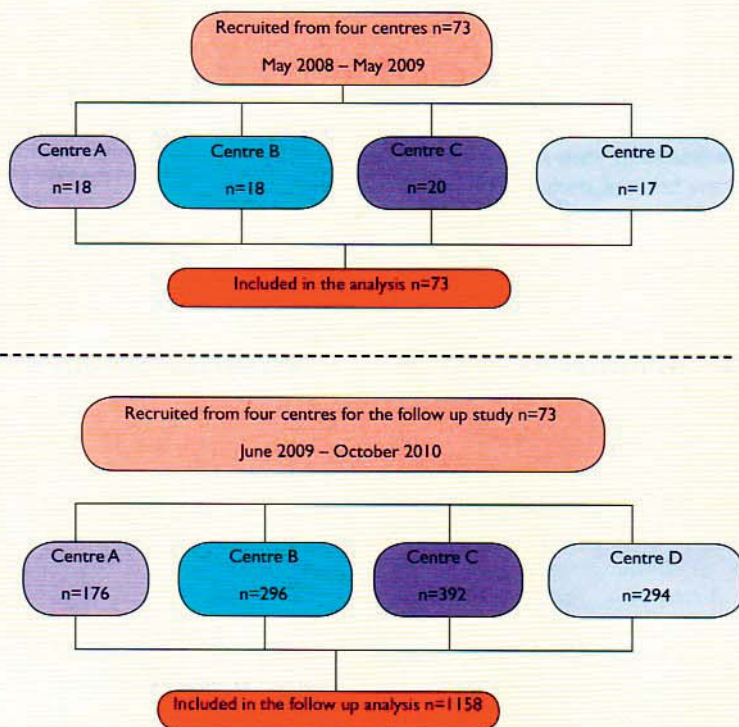


Fig 1. Patient flow chart

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ulcers and burns.^{10,11} The active oxygen product may bleach dark clothes and it is contraindicated in individuals who are allergic to sea salt.

This study is the first clinical evaluation of AM. A clinical cohort study was designed using case ascertainment to evaluate the use of singlet oxygen for cleansing and disinfecting stagnating wounds of various aetiologies, which had previously been treated with polihexanide at the clinics that participated in the study. Patients had all been treated with PHMB during dressing changes (wet-to-dry phase for 20 minutes) for at least 14 days, and did not respond sufficiently, in terms of their clinical signs and symptoms. High colonisation persisted and wounds remained stagnant.

We designed a multi-centre cohort study to evaluate the efficacy of AM for the treatment of patients with stagnating wounds of various aetiologies.

Materials and method

This multi-centre cohort study evaluated AM on the following:

Primary outcomes

- The percentage of slough in the wound bed and inflammation of the peri-wound skin, comparing day 0 with day 42
- The percentage of malodorous wounds that demonstrated a reduction in odour during the course of the study period

- A shift in wound bed tissue types, to determine the stimulation of granulation and epithelialisation, comparing the wound bed condition at day 0 and day 42.

Secondary outcome

- Ease of use, safety and suitability in deep wounds.

Patients

Between May 2008 and May 2009 ambulant patients aged over 18 years with various wound types were recruited from four complex wound healing clinics, two in Austria (centres A and B), one in Germany (centre C) and one in Switzerland (centre D) (Fig 1). The treatment protocol and level of expertise is comparable across these centres.

Local ethics committee approval was obtained and patients gave written informed consent before entry into the study. The study included patients that had presented at the centres with non-healing wounds of different aetiologies. Stagnation was confirmed before entry into the study, by demonstrating a lack of improvement despite two weeks' treatment with appropriate standard treatment. Patients had critically colonised and/or locally infected² malodorous wounds, covered with slough/fibrin and wounds showing symptoms and signs of inflammation of the peri-wound skin. In wounds with signs of infection, swabs were taken for bacterial analysis.² Patients with systemic and spreading wound infections and those with critical ischaemia were excluded.

Demographic and clinical data

At day 0, patients' general condition, nutritional status and intake, mobility status, age and risk factors were assessed, together with social status and specific factors that can delay wound healing, such as alcohol use, circulation disorders, diabetes mellitus, illicit drug use, medications and smoking.

Wound healing, reduction of wound area and wound bed condition

Wound area reduction and wound bed condition were assessed at dressing changes on days 0, 7, 14, 28 and 42. Baseline (week 0) versus day 42 (week 6)

AM treatment results were compared, looking at the percentage changes in fibrin, slough and granulation tissue. Both clinical assessment and high resolution digital photographs were used, the photos scored by two physicians, who were blinded to treatment. Photographs were analysed using a digital tool, which was applied to assess wound size and evolution of the wound bed.¹⁷

A computer program, ZWM WDSI (www.wfi.ch) was used to calculate the wound area from these digital images.¹⁷ This program includes an adapted version of the Dutch Wound Care Society (DWCS) colour classification, which was used to calculate

Table 1. Clinical characteristics of the consenting participants

Clinical Characteristics		Consenting participants (n= 73)
		Mean ± SD
Age (years)		68.8 ± 7.97
		Frequency (%)
Presence of comorbidities	Lymphoedema	8 (10.96)
	Diabetes Mellitus	8 (10.96)
	Polyneuropathy	3 (4.10)
	Peripheral arterial disease	14 (19.18)
	Hemiplegia	2 (2.74)
	Paraplegia	1 (1.37)
	Critical ischemia	1 (1.37)
	Dementia	2 (2.74)
	CVI	22 (30.14)
	Other	12 (8.76)
Wound duration (months)		0.5–221
Wound types	Mixed leg ulcer	13 (18.0)
	Arterial leg ulcer	1 (2.0)
	DFU	8 (11.0)
	Post infect.	4 (5.0)
	Trauma	5 (7.0)
	Surgical	10 (14.0)
	PU	4 (5.0)
	VLU	25 (34.0)
	Other	3 (4.0)
Wound location	Upper leg	3
	Sacrum	1
	Trunk	3
	Trochanter	3
	Abdomen	4
	Toes	7
	Foot	4
	Foot sole	7
	Heel	3
	Malleolus	22
	Lower leg	43

CVI=chronic venous insufficiency; DFU=diabetic foot ulcer; PU=pressure ulcer
VLU=venous leg ulcer

the percentages of slough, necrotic, granulation and epithelial tissues present.¹⁷

Clinical assessment of wound healing was performed during dressing changes, by specialist clinicians. a scale with the following categories was used:¹⁷

- Wounds were defined as stagnating when the status of the wound bed did not change between baseline and end of the study
- Wounds had deteriorated when the clinical signs and symptoms of inflammation and/or infection increased, or when sloughy tissue and/or necrosis

had increased, or when granulation and epithelialisation did not progress

- Wounds were defined as improved when the clinical signs and symptoms of infection/inflammation^{2,5} had reduced and/or when granulation/epithelialisation had progressed.
- Wounds were defined as closed when epithelialisation was complete.

Peri-wound skin condition

The condition of peri-wound skin was assessed at dressing changes on days 0, 7, 14, 28 and 42. Baseline (week 0) results, versus those at 6 weeks' treatment were compared using a four-point scale, based on a modified physician global assessment scale (PGA).^{17,18} The presence of inflammation was evaluated using the following scores: 1 = absent, 2 = minimal, 3 = moderate, 4 = severe. Evaluation considered both the degree of redness and the area of peri-wound skin involved.

Odour assessment

Odour was assessed subjectively at dressing changes, asking both clinicians and patients to score it on a five-point scale (1=no offensive odour; 2=slight offensive odour; 3=moderate offensive odour; 4=much offensive odour; 5=severe offensive odour). Patients and clinicians were both asked if they observed any changes when comparing the odour to that smelled at the previous dressing change. Finally, patients were asked if wound odour had influenced their daily living. A five-point scale measuring quality of life in relation to wound odour was used for this (1=very good; 2=good; 3=moderate; 4=poor; 5=very poor).

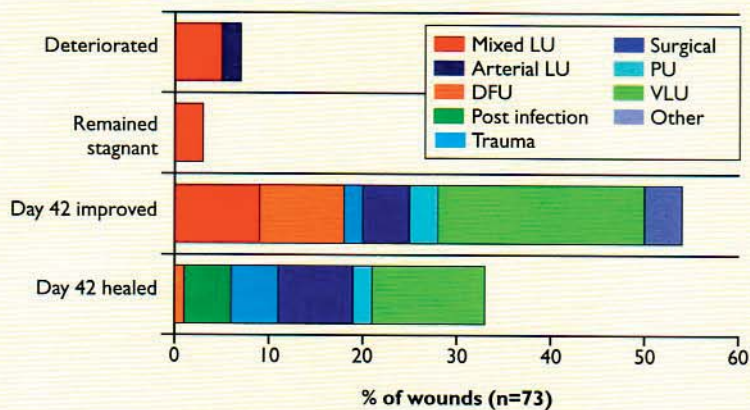
Dressing regime

Using AM as the cleansing agent, the treatment protocol used the wet-to-dry phrase. The choice of moist wound healing dressing (alginate, foam or Hydrofiber) used after the wet-to-dry phase was at the clinician's discretion. Both wound cleanser and dressing were applied in accordance with the manufacturer's instructions by experienced clinicians — the nurses and doctors at all five centres are certified wound care specialists, having completed a two-year course. The treatment period lasted a maximum of 6 weeks.

The study protocol stipulated that clinicians should treat the underlying aetiology — for instance, venous leg ulcers should be treated with compression and diabetic foot ulcers should be managed with off-loading and callus removal. The choice of primary and secondary dressing was at the discretion of the clinician, as were dressing changes (on average, these took place every 2 days).

If a wound was infected, the peri-wound skin was protected, where applicable, with a zinc cream.

Fig 2. Wound healing per wound type, comparing results at day 0 and day 42



LU=leg ulcer; DFU=diabetic foot ulcer; PU=pressure ulcer; VLU=venous leg ulcer

Treatment was according to wound phase. For instance, highly exuding wounds received an absorbent dressing; deep wounds were treated with a wound filler (such as an alginate) and covered with a secondary dressing (such as a foam).

Follow up study

On completion of the study, the wound healing clinics kept AM as part of their treatment protocol. A further study was conducted between June 2009 and October 2010 at the same four wound healing clinics, using the same methodology and the same wound types as the present cohort study. Data were selected from 1158 patients, treated with AM, with various wound types, to assess the effectiveness of AM treatment and confirm its safety.

Results

All patients that were included (n=73) completed the study, and no adverse events were recorded. The mean age of participants was 68.8 years (SD±7.97) (range: 9–95 years). 35 were female. The duration of wounds before the start of this treatment ranged from 0.5 months to 221 months. Prior to entry into the study, the cleansing regimen for wounds was just PHMB. The same moist wound healing dressings were used. Table 1 shows patient characteristics, concomitant diseases, wound types and wound locations.

In 90% of cases, standard AM rinsing solution was used. The median treatment period was 46.04 days (range: 3–197 days). At 42 days, 33% (n=24) of included wounds had healed, 58% (n=42) had improved (with at least a 20% reduction in wound area), 3% (n=2) remained stagnant and 7% (n=5)

had deteriorated. All of the wounds that remained stagnant or deteriorated had issues with microcirculation, or an arterial component. Results are given at 42 days as this is the time by which wounds of the included categories might be expected to improve or heal.^{2,5,9} There were no differences in healing rates between treatment centres. For details of wound healing results by wound type, see Fig 2.

At the beginning of the study (day 0) peri-wound skin inflammation was present in all of the included wounds, with a mean score of 3.6 (SD±3.12) on the four-point scale. By the end of the study (day 42), this had resolved in 60% (n=44), with a mean score of 1 (SD±1.02); was minimal in 33% (n=23), with a mean score of 1.7 (SD±1.14); and was moderate in 7% (n=6), with a mean score of 2.8 (SD±2.62).

Clinicians and patients both noted a reduction of offensive odour within 10 minutes of applying AM. On day 0, very offensive odour was present in 36% (n=26) with a mean score of 4.6 (SD±4.32) on the five-point scale used. By the second dressing change, the odour score had reduced to a mean of 2.1 (SD±2.02) in 18 of these patients (25% of the total) and in the remaining 8 patients (11%) odour scores were moderate, with a mean of 3.2 (SD±3.18). At the end of the study, offensive odour had been resolved in all cases, with a mean score of 1.2 (SD±0.96). No significant differences were found between the scores given by clinicians and patients.

Results concerning the impact of wound odour on quality of life were positive, with patients reporting an improvement in their everyday quality of life as a result of odour reduction. At day 0, the mean score was 4.2 (±3.8), whereas by day 42 this had reduced to 1.8 (±1.6).

On day 0, 42% of patients (n=31) had wounds with symptoms and signs of critical colonisation and/or infection. Infection was confirmed in 12 cases (16% of the total) by wound swab. One patient received systemic antibiotics. Local wound treatment with AM was sufficient for the other patients.

Clinicians reported that handling AM during dressing changes was easy. The majority (84.2%) scored its clinical efficacy as 'very good' and stated that they would recommend AM for wound cleansing.

AM was successfully applied in combination with various dressings, including absorbent pads, alginates, Hydrofiber, hydrocolloid, collagen, foam, films and superabsorbent dressings.

Follow up study results

The follow up study found similar cleansing efficacy. Of the 33% (n=386) of patients that had wounds with symptoms and signs of critical colonisation and/or infection at day 0, 28% (n=108) had resolved within 14 days of AM treatment, which is in line with the results of the cohort study. Eradication of infection was confirmed by comparing wound cul-

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tures taken on days 0 and 14, together with the clinical picture of symptoms and signs. No adverse events were reported when performing wound cleansing and/or wound disinfection with AM, which suggests that it is safe to use in various wound types.

Discussion

The results of our study indicate that AM reduces signs of infection and peri-wound skin inflammation and that it supports wound cleansing.⁹ Using the wet-to-dry phase with AM and absorbent dressings, there was a shift from chronic inflammation to proliferation, which shows that stagnating wounds moved on to granulation and epithelialisation. This suggests a reduction of proinflammatory cells, such as MMPs.¹⁵

The wounds that remained stagnant and/or deteriorated all had reduced microcirculation or an arterial component, which might explain their lack of response to treatment.^{15,16} AM's wound cleansing and disinfection efficacy was nonetheless demonstrated for various wound types.

It is thought that a major factor enhancing inflammation in stagnating wounds is an imbalance of oxidants and antioxidants.^{15,16,19} The stagnating wound microenvironment induces oxidative stress.^{15,16} Following wounding, leukocytes, such as neutrophils, release various ROS into the wound environment, such as superoxide anions, hydroxyl radicals, singlet oxygen and hydrogen peroxide.^{15,16} Endothelial cells and fibroblasts — in particular senescent fibroblasts, which are prominent in stagnating wounds — are also a potential source of ROS.¹⁹ The redox activity of AM's singlet oxygen may help to restore the balance of oxidants and antioxidants.^{10,11,15}

The effect of this product on wound odour reduction and its compatibility with dressings such as algi-

nates, Hydrofiber and foams, warrants further investigation of singlet oxygen in the treatment of chronic wounds. Offensive odour can be a big problem in oncology wounds^{20,21} and current strategies to reduce it involve the use of topical antimicrobials (such as metronidazole, cadexomer iodine and polihexanide) together with reducing the amount of dead tissue.²²⁻²⁴ These approaches are not always effective and can cause complications such as bleeding.^{25,26} Wound odour may be attributed to the size or irregular shape of the wound, the liquefaction of dead tissue or the management of exudate.²⁶ The current management options are not sufficient, as they do not stay activated long enough, are too toxic to be used on large surfaces, or they do not penetrate far enough, to anaerobic bacteria located beneath the surface.²⁶ Here, the application of AM has shown its potential. Especially as it may be combined with various dressings and it is appropriate for use on fragile tissues.

Limitations

As with many new commercially available cleansing products, direct comparative data on the use of AM is not yet available. Because there is no comparison or control group, cause and effect relationships cannot be inferred from the present study. However, before the study treatment was initiated, all of the included patients had previously been treated, unsuccessfully, with other therapeutic modalities, which may be considered as a historical control.

Conclusion

AM demonstrated effective wound cleansing, removing debris and slough from the wound bed. The product was easy to apply and can be safely used in both hospital and community settings. AM showed good tolerability and high levels of user satisfaction and patient comfort. ■

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Role of oxygen in wound healing: a review of evidence

- **Objective:** To review the evidence regarding the influence of oxygen as an intrinsic factor on cutaneous wound healing.
- **Method:** A literature search was performed using Ovid and the Cochrane Database with the search terms: 'Wound healing', 'Oxygen', 'Collagen', 'Angiogenesis', 'Inflammation' and 'Surgical Site Infection'. Human and animal studies were included if relevant and examined for methodological quality.
- **Results:** There are no meta-analyses of the use of oxygen in wound healing and only two randomised controlled trials (RCTs). Studies vary in methodological quality. The majority of the data comes from animal models. In total 1568 studies on wound healing and oxygen were found.
- **Conclusion:** Oxygen is vital throughout wound healing, especially in the inflammatory and proliferative phases. Research suggests that patient supplementation with oxygen could enhance bacterial killing and angiogenesis, reduce surgical site infection rates and increase wound tensile strength, facilitating improved healing.
- **Conflict of interest:** None.

oxygen; wound healing; inflammation; collagen; surgical site infection

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Following injury, wound perfusion and oxygenation are critical for acute inflammation and optimal wound healing. They can be compromised by many factors, both local (such as disrupted local vasculature following wounding, or relative hypoxia due to the increased oxygen demands of normal healing) and systemic (for instance, pre-existing co-morbidities, which can affect the oxygen and nutrient supply to injured tissues).¹ Tissue hypoxia (defined as oxygen levels below 30mmHg) can impact greatly on all phases of the wound healing process.²

Since the 1960s, oxygen and reactive oxygen species (ROS) have been studied to discern the roles they play in the different phases of wound healing. Early research by Hunt and colleagues³ recognised that oxygen was vital both for granulation tissue formation (through aerobic cell respiration) and as a cofactor during the hydroxylation of proline and lysine during collagen synthesis. The same team went on to show that the tensile strength of experimental wounds was directly proportional to the partial pressure of atmospheric oxygen.⁴

A clinical guideline has been published by the National Institute of Health and Clinical Excellence (NICE) to address the issue of surgical site infections (SSIs).⁵ With their considerable morbidity and mortality, SSIs are a major economic cost to the NHS. They increase the burden of wound management, sometimes causing further complications (that can require additional surgeries) and they have a huge impact on quality of life.

In 1984, Knighton et al.⁶ showed that in an animal model, higher inspired concentrations of oxygen

reduced the extent of infection following intradermal bacterial inoculation. In the early respiratory burst of the inflammatory phase, oxygen is a crucial substrate for the production of ROS by neutrophils,¹ whereas in the later proliferative phase of wound healing, the absence of oxygen plays a role in angiogenesis — hypoxia initiates neovascularisation and the induction of vascular endothelial growth factor (VEGF).⁷

This review examines the evidence of oxygen's influence on wound healing since these early experiments, and aims to give a balanced view of both hypoxia and hyperoxia throughout the different phases of wound healing.

Oxygen and inflammation

Neutrophils are active in the early inflammatory phase of healing.⁸ They produce ROS, which destroy micro-organisms in a process named the 'respiratory burst'.⁹ ROS are especially important during the inflammatory phase of wound healing.¹

An *in vitro* experiment by Allen et al. showed the concentration of atmospheric oxygen to be directly proportional to neutrophil oxygen consumption during the respiratory burst.¹⁰ Temperature, pH and glucose concentration were all tightly controlled, although the experiment was not blinded and gave no data of inferential statistics. The researchers found no quantitative differences between neutrophils isolated from serum and those isolated from wounds, which enhanced the experiment's external validity. Interestingly, neutrophil oxygen consumption failed to plateau, which suggests that it may be possible to enhance neutrophils' antibacterial activity, using high concentrations of inspired oxygen, clinically.

In vivo human evidence comes from a study of 130 surgical patients, in whom the rate of SSIs (classified as infection in the wound, up to 30 days postoperatively) had a statistically significant, inversely proportional relationship with subcutaneous wound oxygen tension ($p < 0.03$).¹¹ Due to the variety of cases, the external validity of this result was high, but reliability was limited as there was no control over the use of supplemental oxygen, prophylactic antibiotics or fluids given post-operatively. However, despite these methodological flaws, this result is hard to ignore.

Further clinical evidence comes from two double-blind randomised controlled trials (RCTs).^{12,13} In the first of these studies, by Greif et al., 500 patients were given either 30% or 80% oxygen (via mask) intra-operatively and for two hours post-operatively. SSI rates (classified as wound infections in the first 15 days post surgery) were found to be significantly lower in the 80% oxygen group ($p < 0.01$). The original study design aimed to collect data on 1000 patients, but the trial was stopped early due to the marked statistical difference between groups and the ethical implications of not offering all patients the best treatment.¹²

The second study, by Belda et al.,¹³ had similar

results in 300 colorectal patients. SSI rates were statistically significantly reduced, from 24.4% in the 30% group to 14.9% in the 80% group ($p = 0.04$). This is remarkably similar to Greif et al.'s results, which is surprising given that the predicted SSI rates in Belda's study were nearly double those expected in Greif's. Belda's study differed further, as oxygen was inhaled for an extra 4 hours postoperatively, and there was no mention that patients were always adequately oxygenated, determined using pulse oximetry in the UK, which is recommended in the NICE SSI guideline.⁵ We do not know the extent to which the 15-day cut off reduced the reported incidence of SSIs compared with a 30-day cut off (as seen in previous research).⁹ Additionally, it remains unclear how a postoperative FiO_2 of 0.8 was achieved in Belda's study, as even using a re-breathing mask, the maximum possible FiO_2 is 0.6.

Interestingly, a more recent clinical study from Denmark has refuted these findings.¹⁴ This large, double blinded RCT found no statistically significant difference in SSI rates between patients inhaling 0.8 FiO_2 and those inhaling 0.3 FiO_2 during abdominal operations and for two hours post-operatively ($p = 0.64$). However, it is possible that the trial was

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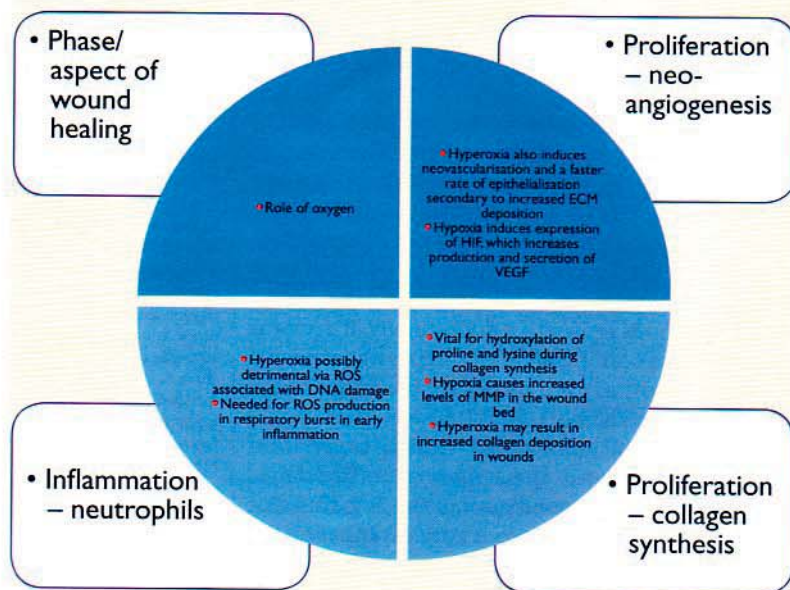
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Figure 1. The role of oxygen in wound healing



ROS=reactive oxygen species; ECM=Extracellular matrix; HIF= hypoxia-inducible factor; VEGF=vascular endothelial growth factor; MMP=matrix metalloproteinase

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underpowered to find a small statistically significant risk reduction. This study suggested that a short duration high FiO₂ is not detrimental to respiratory function, an adverse effect that was previously considered following sub-group analysis in Greif et al.'s study.¹²

Further research is needed to determine if excessive oxygen causes uncontrolled release of ROS. A study of hyperbaric oxygen in the treatment of a variety of chronic wounds,¹⁵ found concomitant antioxidant and hyperbaric therapy to increase the percentage of healing wounds compared with placebo. However, it also showed that cells in an environment with high levels of ROS become sensitised to oxidants, with less oxidative damage to DNA over time. It is unknown if high levels of ROS in acute wounds inflict the same level of DNA damage and whether or not supplementation with normobaric oxygen might be harmful.

Further evidence is needed to elicit which FiO₂ is most beneficial to wound healing, and the duration for which supplemental oxygen should be inspired for maximum benefit.

Oxygen and angiogenesis

In the early 1980s, research on neo-angiogenesis highlighted the importance of hypoxia and a wound-tissue hypoxic gradient.^{16,17} It is now understood that hypoxia promotes angiogenesis via hypoxia-inducible factor 1 (HIF-1) and dependent expression of pro-angiogenic growth factors such as VEGF.¹⁸

Paradoxically, a more recent study has found

wound hypoxia to be detrimental throughout all the phases of wound healing, including angiogenesis, while hyperoxia seems to confer benefit.¹⁹ This animal study by Hopf et al. examined the effects of hypoxia and hyperoxia on neovascularisation in gel plugs implanted under the skin of mice. They found significant increases in angiogenesis in hyperoxic wounds (p<0.05) while observing a significant decrease of angiogenesis in hypoxic wounds (p=0.001). Reliability was low, however, as hypoxic wounds were also treated with VEGF, impregnated into the implanted gel. It is also of note that all significant results came from wounds that were treated with hyperbaric (2.0, 2.5 and 3.0 ATA) and not normobaric 100% oxygen.

Studying this same effect, Sander et al. examined acute wounds in rats treated with hyperbaric oxygen, finding that neovascularisation occurred statistically significantly earlier (p<0.05) compared with control animals, with faster rates of epithelialisation and wound closure.²⁰ This blinded study used an *in vivo* photographic method to measure vascularisation and would have been affected by hydration, cutaneous temperature and oxygenation of the blood, which reduces its reproducibility and the reliability of measurements. A method for overcoming such physiological variability and accurately measuring vascularity, is histological analysis of wound tissue. This has been used successfully in other studies.¹⁹

VEGF expression has previously been linked to ROS.⁷ More recent work in patients with chronic wounds has shown that VEGF-β is significantly up-regulated by treatment with hyperbaric oxygen therapy (p<0.05).²¹ VEGF-β appears to be regulated by ROS, as when patients are treated with α-lipoic acid (LA) at the same time, which acts as a biological antioxidant, scavenging ROS,¹⁵ this result is reversed. It is unknown if this work translates to acute wounds.

A study by Trabold and colleagues has shown that VEGF synthesis is stimulated by increasing lactate levels in wounds, compared with control (p<0.05).²² This study was not without its limitations — it used an animal model, all the wounds were incisional, and lactate production was artificial (from an implanted Polyglactin 910 woven mesh). We do not know if the levels of lactate in these experimental wounds match those seen clinically, which affects the external validity of the study. Nonetheless, this finding, thought to be independent of hypoxia,¹⁹ highlights that there are other mechanisms of action within wounds, stimulating VEGF expression.

Oxygen and collagen

It has long been known that molecular oxygen is necessary for the hydroxylation of proline and lysine during collagen synthesis and that without it only proto-collagen, a functionally deficient variant of collagen, is produced.³

This theory has been corroborated by evidence from Kan and colleagues,²³ who examined human fibroblasts in hypoxic wound conditions. They found a reduced amount of collagen in these wounds, which may be explained by a statistically significant increase ($p < 0.001$) in matrix metalloproteinase-1 (MMP-1). This study was carried out *in vitro* on a small number of fibroblast populations. *In vivo* clinical data is limited, most likely due to the ethical considerations of enforcing hypoxic wound conditions in humans. This evidence suggests a possible new role of oxygen as an inhibitor of MMPs and hence, as a promoter of granulation tissue formation.

Oxygen supplementation has been examined with regard to the amount of collagen deposited in wounds. An *in vivo* study that used a rat model²⁴ showed that, compared with control, four weeks of hyperbaric oxygen therapy significantly increased fibroblast infiltration and collagen deposition in porous polyethylene blocks implanted beneath the skin ($p < 0.05$). However, it is possible that this finding stems from a type 1 statistical error, as it was revealed by a sub-group analysis.

Human studies are less conclusive; Nakada and colleagues found that, in conjunction with basic

fibroblast growth factor (bFGF), hyperbaric oxygen therapy increased the amount of collagen in healed wounds ($p < 0.001$).²⁵ While this result is significant, it should be noted that the study was a case series, with no blinding of investigators or participants and no control groups. Without a control, we do not know if the result is due to hyperbaric oxygen alone, bFGF alone, or a combination of the two, although it seems unlikely that the result is solely due to hyperbaric oxygen, as seven of the patients had previously received hyperbaric oxygen therapy with no clinical improvement in their ulcers.

A double blinded RCT by Stotts and colleagues examined the effect of hydration on collagen formation in expanded polytetrafluoroethylene (ePTFE) tubes implanted into the upper arms of elderly, nursing home residents.²⁶ Patient hydration is known to augment subcutaneous tissue oxygen levels by increasing tissue perfusion.²⁷ However, Stotts' study found no significant differences between the treatment and control groups in either collagen levels ($p = 0.84$) or subcutaneous tissue oxygen levels ($p = 0.13$), indicating that in this elderly population there were other intrinsic factors controlling tissue oxygenation and subsequent collagen production.

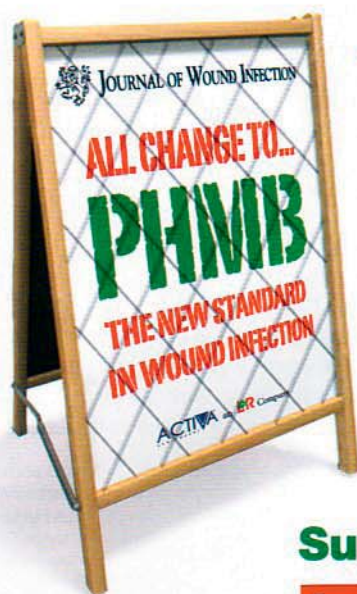
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Further research using a younger *in vitro* human model is needed to clarify the role of supplemental oxygen in collagen formation in healing wounds.

Methods to increase wound oxygenation

As well as supplemental oxygen breathed at normal pressure, there are many methods for increasing tissue oxygenation, some with limited validation. Routine patient management, including the optimisation of hydration status and temperature, has been shown to improve tissue oxygenation as measured by transcutaneous partial pressure of oxygen (TcPO₂).²⁸ In this study, patients were excluded if there was a known history of vascular disease but not if they had other risk factors, such as diabetes or current smoking.

Another interesting route to supplement oxygenation is through the administration of liposomal haemoglobin vesicles, as has been done in mice with critically ischaemic tissue.²⁹ Wound healing has been found to significantly improve in mice supplemented with vesicle solution. Haemoglobin vesicles have a half-life of approximately 72 hours and histological examinations of the major organs has shown no damage. Further work is needed for efficacy and safety to be established in human models.

Hyperbaric oxygen therapy uses 100% oxygen administered at pressures of 2.5 ATM for durations of around 90 minutes per day.² Its use to enhance chronic wound healing is limited by the availability of facilities and tough criteria for treatment, considering its cost. Research on hyperbaric oxygen has shown that the oxygen carrying potential of the blood surpasses that of the maximum level of saturated haemoglobin; it is unknown if the same results can be obtained with normobaric high concentration oxygen.²

Finally, an animal model using pigs has shown that topically applied oxygen increases partial pressures of oxygen in the wound bed.³⁰ This study's method was limited in terms of the mechanism used to supply the wound with oxygen and the maximum wound depth to which oxygen is able to

seep. At present, there are no valid clinical claims of its efficacy in wound healing, although more research may be expected.

Conclusion

Oxygen has a diverse and vital role in wound healing. Hyperoxia has been implicated in facilitating each phase of wound healing. It appears to be vital in the inflammatory phase, where increased pO₂ reduces wound infection rates via a neutrophil-ROS mechanism. Infection risk might, therefore, be minimised by ensuring that all surgical patients have supplemental oxygen delivered post-operatively. Given that body temperature and hydration status affect tissue oxygenation, these should also be closely monitored, with any deficits compensated for, to ensure optimal oxygenation.

Oxygen has a paradoxical role in angiogenesis, as the early growth of new vessels is stimulated by hypoxia. However, the later stages of angiogenesis are also stimulated by hyperoxia. By increasing the gradient between healthy tissue and the wound, angiogenesis is facilitated, with the benefits of hyperoxia passed onto the wound bed once a vascular network has been established, following stimulation by the steep oxygen gradient. This further suggests that optimal post-operative oxygen is important in facilitating enhanced wound healing.

We know that oxygen plays a role in collagen synthesis but unfortunately, there appears to be confounding evidence surrounding what this role is exactly. Hypoxia and hyperoxia may affect the aesthetic result of the wound and it is possible that oxygen supplementation may improve tensile strength.

More work is needed to fully quantify the effects of oxygen on wound healing and determine the length of time for which oxygen supplementation is beneficial. Research is also warranted into the effects of increasing ROS concentration, following either normobaric or hyperbaric oxygen therapy, which might also determine whether or not these therapies have any detrimental as well as beneficial effects. ■

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