Granulox - Scientific Literature Collection

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Overview:

This document contains a list of clinical trials, clinical case study reports and pilot studies relating to Granulox – cited in PubMed. The document also contains non-PubMed publications (e.g. poster presentations from key wound care conferences). There are also relevant research publications and reviews which underpin the scientific knowledge base of oxygen’s role in wound healing. The intention is to maintain and add material to this list as they are published and where related research has been cited.

- PubMed Granulox references
  - Clinical trial publications and controlled cohort studies (5 references)
  - Case reports & Pilot studies (12 references)
  - Review articles (3 references)

- Other (non-PubMed) Granulox references
  - Consensus recommendation (2 references)
  - Pilot study (1 reference)
  - Review articles (1 reference)
  - Product Evaluation (1 reference)
  - Conference Posters (32 references)

- Science Base: non-Granulox references
  - Role of oxygen in wound healing (11 references)
  - Facilitated diffusion by haemoglobin (4 references)
PubMed – Granulox clinical trial studies


Abstract

OBJECTIVE: To investigate wound healing after application of adjunctive topical haemoglobin spray in patients with chronic wounds.

METHOD: Consecutive patients with a diversity of chronic wounds (defined as <40% reduction in wound size within 4 weeks) were treated with standard wound care plus haemoglobin spray and evaluated over a 26-week period. Results were compared with a retrospective cohort of 50 consecutive patients treated with standard wound care alone.

RESULTS: We evaluated 50 patients for a 26-week evaluation period, during which 45/50 patients (90%) treated with haemoglobin spray were completely healed compared with 19/50 retrospective control patients (38%) (p<0.001). Mean time to complete wound healing was 6.6 weeks (range: 3-22) in the haemoglobin spray group compared with 11.4 weeks (range: 3-25) in the control group (p=0.01). Cox proportional hazards analysis model adjusting for baseline wound size and months wound present also yielded significant treatment effects. Exudate, slough and pain levels were all reduced to a greater extent versus control group.

CONCLUSION: Haemoglobin spray resulted in a higher number of healed wounds and a faster rate of healing, as well as a positive impact on other wound parameters. These results are in accordance with other published data and supports the adjunctive use of haemoglobin spray in patients with a wide variety of chronic wounds of all sizes and origins.


PURPOSE: Chronic leg ulcers can be a challenge to treat and long-term therapy a significant cost factor in western public health budgets. Objective wound assessment assays enabling selection of appropriate wound therapy regimes would be desirable. Oxygenation status in ulcer tissue has obtained increased attention as a relevant factor in wound healing. To increase oxygenation in wounds, a topical hemoglobin spray was developed. Although favorable results have been noted, the link between clinical efficacy and the mode of action has not been demonstrated. The aims were to determine if changes in tissue oxygenation can be measured after topical application of hemoglobin on chronic wounds and to evaluate the findings in terms of therapy strategies.

PROCEDURES: Photoacoustic imaging was used to measure the local oxygen saturation (StO2) in leg ulcers before and after hemoglobin spray treatment. Sclerosis of the leg ulcers was histopathologically graded and the change in wound size was documented in a follow-up examination.

RESULTS: Measuring 49 patients, an increase in StO2 after topical hemoglobin application from on average 66.1 to 71 % (p = 0.017) after 20 min was observed. Depending on the increase in StO2 (>10 % or <10 %) patients were stratified into a Responder and a Non-Responder group. Wound size significantly decreased in the Responder Group (p = 0.001), while no significant difference in the Non-Responder group (p = 0.950) was noted.
CONCLUSION: Our findings suggest that the likelihood of wound healing under conservative therapy can be predicted by measuring changes in StO2 after topical hemoglobin application. This assay may reduce treatment time and costs by avoiding ineffective conservative long-term therapy.

TRIAL REGISTRATION: German Clinical Trials Register: DRKS00005993.


Introduction: Hemoglobin spray (Granulox®) comprises purified hemoglobin and is a novel approach for increasing oxygen availability in the wound bed in diabetic foot ulcer patients. Its mode of action is to bind oxygen from the atmosphere and diffuse it into the wound bed to accelerate wound healing in slow-healing wounds. Patients and methods: Wound healing outcomes that is, wound size, pain, percentage of slough, and exudate levels, were compared retrospectively to a similar cohort of patients treated over the same period the previous year. The same inclusion and exclusion criteria applied to both groups.

Results: All 20 (100%) hemoglobin spray-treated patients and 15 (75%) control patients experienced some wound healing by week 4, with 5 (25%) and 1 (5%), respectively, achieving complete wound closure. At week 4, mean wound size reduction was 63% in the hemoglobin spray group versus 26% for controls, increasing to 95% reduction at week 28 in the hemoglobin spray group versus 63% for controls (p < 0.05 at all timepoints). Hemoglobin spray was associated with substantially lower pain scores using a 10-cm visual analogue scale, with 19/19 patients (100%) being pain-free from week 12 onwards, compared to 6/18 patients (33%) in the control group. At week 28, 2/18 patients (11%) in the control group still had pain. Both groups had similar baseline slough levels, but hemoglobin spray-treated wounds had slough completely eliminated after 4 weeks versus 10% mean reduction in the control group (p < 0.001). Hemoglobin spray was associated with markedly reduced exudate levels; within 4 weeks, no patients had high exudate levels in the hemoglobin spray group versus 5 in the control group.

Conclusion: Standard wound care plus hemoglobin spray results in improvements in wound closure, wound size reduction, pain, slough, and exudate levels compared to control patients for chronic diabetic foot ulcer treatment.


Background: Improvement of oxygenation is getting increasing attention as an important aspect in modern wound care. The aim of such complementary wound care approaches is to improve and accelerate wound healing.

Patients and Methods: A solution comprising purified haemoglobin was added to the standard wound care procedure of patients with venous leg ulcers and compared to a second group without addition of the haemoglobin treatment. In each group, 36 patients were included. The duration of treatment was 13 weeks. Primary end point was the reduction of wound size or wound closing.

Results: In the group treated with the additional haemoglobin solution, an average of 53% of wound size reduction was obtained. No statistically significant reduction was observed in the second control group.

Conclusion: The addition of haemoglobin solution in the wound care procedure for venous leg ulcers suggests a significant improvement of wound healing in comparison to a control group.

Background: A new technological approach for supplying hypoxic chronic wounds with oxygen is a moist wound treatment with aqueous solutions containing tissue compatible oxygen binders. This facilitates diffusion of oxygen, necessary for the healing process, from the surroundings (room air through an open-porous wound padding) into the ulcerous tissue. A product that is still in development is a spray which contains haemoglobin obtained from domestic pigs. Clinical investigations (a clinical trial, treatment observations and single patient uses) are presented, which were performed to create clinical data regarding efficiency and safety of this product. All data have demonstrated that the application of the haemoglobin spray promoted wound healing in all analyzed cases.

Results: Data from a clinical study in Mexico and subsequent therapy observations revealed that in 39 out of 42 patients (93%) the treated wounds were healed. Nine patients from a series of therapy observations in Monterrey (Mexico) showed similar outcomes. All treated wounds were closed. Single patient uses carried out in Witten (Germany; 6 wounds from 8 (75%)) and Prague (Czech Republic; 5 wounds from 5 (100%) were healed) further support these results.

Conclusions: The application of haemoglobin spray can promote healing of chronic wounds. Within the framework of the clinical investigation, the treatment observations, and the individual healing experiments the haemoglobin spray was applied more than 2,000 times onto chronic wounds of 82 patients. In all cases, the spray was well tolerated and there were no adverse event that might have been an adverse reaction to the haemoglobin spray.

**PubMed – Granulox case reports & pilot studies**


**Abstract**- A recent multi-centre observational evaluation investigated the effect of a topical haemoglobin spray (Granulox, Infirst), used as an adjunct to standard care, on wound size reduction in 17 patients (4 females/13 males) with 20 chronic diabetic foot ulcers (DFUs) over a 4-week period. In 14 of the 18 wounds that completed the evaluation (one patient dropped out due to an infection) there was a mean reduction of 53.8% (range: 11.9-100%). The product was acceptable to both patients and clinicians, who all found it easy to use. This article describes the outcomes for the remaining 13 patients (with 15 wounds) who continued using the spray after the 4-week evaluation ended. (Data are not available for two patients and the one patient who healed during the 4-week evaluation.) By 12 weeks, three wounds (20%) had healed, eight (53%) were progressing towards healing, three (20%) increased in size and one (7%) was slow healing.


**Abstract**- Painful acute cysts in the natal cleft or lower back, known as pilonidal sinus disease, are a severe burden to many younger patients. Although surgical intervention is the preferred first line treatment, postsurgical wound healing disturbances are frequently reported due to infection or other complications. Different treatment options of pilonidal cysts have been discussed in the literature, however, no standardised guideline for the postsurgical wound treatment is available. After surgery, a common recommended treatment to patients is rinsing the wound with clean water and dressing with a sterile compress. We present a case series of seven patients with wounds healing by secondary intention after surgical intervention of a pilonidal cyst. The average age of the patients...
was 40 years old. Of the seven patients, three had developed a wound healing disturbance, one wound had started to develop a fibrin coating and three were in a good condition. The applied wound care regimens comprised appropriate mechanical or autolytic debridement, rinsing with an antimicrobial solution, haemoglobin application, and primary and secondary dressings. In all seven cases a complete wound closure was achieved within an average of 76 days with six out of seven wounds achieving wound closure within 23-98 days. Aesthetic appearance was deemed excellent in five out of seven cases excellent and acceptable in one. Treatment of one case with a sustained healing disturbance did result in wound closure but with a poor aesthetic outcome and an extensive cicatrisation of the new tissue. Based on these results we recommend that to avoid healing disturbances of wounds healing by secondary intention after surgical pilonidal cyst intervention, an adequate wound care regime comprising appropriate wound debridement, rinsing, topically applied haemoglobin and adequate wound dressing is recommendable as early as possible after surgery.


Aim: The aim of this multi-centre observational evaluation was to assess the percentage reduction in wound area of non-healing diabetic foot ulcers (DFUs), treated with Granulox haemoglobin spray over a 4-week period. Secondary outcome parameters—for example, adverse events, patient acceptability and ease of use—were also recorded.

Method: After a run-in-period (2 weeks for existing patients and 4 weeks for new patients) to determine if the wounds were non-healing despite receiving local best practice, patients whose foot ulcers had decreased in size by < 20% were then entered into the evaluation. A sample of 17 patients (4 females and 13 males), comprising 4 with type 1 and 13 with type 2 diabetes, with a total of 20 DFUs, met the inclusion criteria. These data were collected from six sites across the UK.

Results: There was an overall positive reduction in size in 14 of the wounds, equating to a mean reduction of 53.8% (standard deviation (SD): 26.6; range: 11.9–100%). One participant, with two ulcers, had to be withdrawn due to infection. All clinicians and participants found the product easy to use.

Conclusion: The addition of a topical oxygenation therapy in this cohort of non-healing DFUs showed reduction in wound surface area and progression to healing. The product was also found to be acceptable and very easy to use by both participants and clinicians.


AIM: This evaluation aimed to determine whether the use of a haemoglobin spray solution expedited sloughy wound healing.

METHOD: A descriptive evaluation was undertaken within a community setting exploring 25 patients presenting with sloughy healing and non-healing wounds, and the effects of 8topically administered haemoglobin treatments over a 4-week period. Standard wound cleansing and dressing management were continued, with no changes to pre-evaluation regimens, and care being provided by the patients themselves or by a carer. Data were collected weekly with regard to primary outcomes of slough reduction, wound surface area reduction, patient ease of use (self-care), and overall product experience.

RESULTS: At 4 weeks, all wounds demonstrated positive measured endpoints of slough elimination and continued wound-size reduction. Patients and carers found the product easy to use (self-caring) with an overall positive wound care experience.

CONCLUSION: The administration of a haemoglobin spray solution on patients presenting with sloughy wounds resulted in positive healing outcomes of slough elimination and wound reduction alongside positive self-care
and product satisfaction. Continued evaluation is recommended to build upon the evidence of this form of treatment.


Abstract: The development and subsequent deterioration of diabetic foot ulceration (DFU) is a common occurrence across all healthcare divides, concerning all patient groups, age, gender and social environments. It increases demand on clinical resources and creates unnecessary hardship for patients. Chronic DFU is challenging to prevent and notoriously difficult to manage owing to the complex nature of the patient and the disease itself. The improvement of oxygenation to many chronic wound groups is gaining momentum across wound care; particularly in those wounds such as DFU that present with circulatory, oxygen-deficient scenarios.

METHOD: A descriptive evaluation was undertaken in an acute clinical setting where a spray solution containing purified haemoglobin was used in a cohort of 20 patients who presented with chronic (>12 weeks) DFU. Standard wound care was undertaken by 18 health professionals with no changes to products, devices or practice before evaluation. All wounds received the addition of the product on eight set occasions over a 4-week period and the resulting data correlated in regards to the set outcomes of wound surface area reduction, ease of use, adverse events and patient acceptability.

RESULTS: At 4 weeks all wounds had demonstrated positive wound reduction, there were no adverse events, all patients and clinicians found the product acceptable and easy to use. Interestingly, although not a set outcome, all wounds commenced the evaluation with wound-bed slough present and at 4 weeks 100% were deemed slough free. At a further 4-week review no patients wounds had regressed.

CONCLUSION: The incorporation of a haemoglobin spray solution within this cohort of DFU resulted in a positive improvement in wound healing and slough elimination. Further work in this area is recommended to increase the evidence.


Abstract: A published evaluation (Tickle, 2015) of the use of a topical haemoglobin spray plus standard care in 18 patients with pressure ulcers showed that, following 4 weeks of treatment, the wound size reduced in 17 wounds and there was a progression toward healing in all 18. All but one of the wounds were over 2 months in duration at baseline. This article reports the results of the healing rates at 3 months of the 11 patients who continued to be treated with the haemoglobin spray. Nine of the 11 wounds healed, and 2 reduced in size by week 12 (i.e. 1 wound reduced from 30 cm² at baseline to 7 cm², while the other reduced from 6 cm² to 4 cm²). Of the 10 patients who were experiencing wound pain at baseline, 9 were pain free by week 8. Rapid elimination of slough was observed in all patients. The 82% healing rate achieved at 3 months and the fact that most patients continued to receive the same standard care as they had in the 4 weeks before recruitment into the evaluation increases the likelihood that the clinical outcomes observed here can be attributed to the haemoglobin spray. Topical haemoglobin shows promise in terms of its ability to accelerate healing in chronic pressure ulcers.


Abstract: The effect of pressure ulcers on patient quality of life have been recognised as a real problem for many years, and the need for robust and effective management of pressure ulcers is now a prominent national health-care issue. Myriad different interventions exist for the treatment of pressure ulcers, including clinically effective dressings and pressure-relieving devices, yet many pressure ulcers still do not heal and often become
a chronic wound. This is the second of a series of articles (Norris, 2014) discussing the clinical evaluation of a topical oxygen therapy in practice. It describes a small evaluation involving 18 patients with pressure ulcers. The study set out to determine the effect of a topical oxygen therapy on wound size. The therapy comprises a canister that sprays pure haemoglobin in a water solution into or onto the wound. The haemoglobin spray needs to be used at least once every 3 days, does not require training on its use and can be used in any care setting. Overall, results identified wound healing progression in all 18 wounds and wound size reduction in 17 of the 18 wounds.


Abstract- Acute wounds will generally heal independently of any interventions, whereas chronic wounds are chronic for a reason and are unlikely to successfully heal without intervention. In the treatment of venous leg ulcers, the gold standard will always be compression therapy. However, many wounds still do not heal despite best practice. Therefore, the use of adjunct therapies alongside standard care become the priority for healing. This article describes a small evaluation, involving 17 patients with chronic venous leg ulcers, which set out to determine the effect of a topical oxygen therapy on wound size. The therapy comprises a canister that sprays pure haemoglobin in a water solution into the wound. The haemoglobin spray needs to be used at least once every 3 days, and no training is required on its use. Results showed the device helped promote wound healing in 14 out of 17 wounds treated for more than 2 weeks. These patients had previously been shown to be non-healing during a 4-week run-in period where they received standard care, including compression therapy.


Background: Although the underlying primary cause of chronic wounds may vary, a common aetiology of this is a hypoxic or ischemic status of the affected tissue of the lower extremities. In particular, for rare diseases associated with disturbed blood flow a correlation between cause and effect is often diagnosed inappropriately. As a consequence, chronic wounds may develop and persist for years.

Main Observations: We present a case of a patient with chronic venous insufficiency due to an occlusion of the inferior caval vein. Initially, a Budd-Chiari syndrome was diagnosed which is a thrombotic obstruction of the hepatic venous outflow. In addition, the patient developed an obstruction of the inferior caval vein and subsequently a chronic venous insufficiency. As a consequence, chronic leg ulcers developed with a history of more than 7 years. Various wound care approaches were performed without success in wound closure. Finally, a combination of compression therapy and topical application of a haemoglobin solution successfully led to fast and persistent wound closure.

Conclusions: Chronic ulcers of the lower limb such as venous leg ulcers, even for patients with rare disorders like Budd-Chiari syndrome, are associated with oxygen supply disturbances resulting in a hypoxic status of the affected tissue. Therefore, an adequate oxygen supply to chronic wounds plays a pivotal role in successful wound healing. Compression therapy in combination with enhancement of the local oxygen supply by topically applied haemoglobin showed marked improvement of wound healing in the presented patient.


Background - A new healing procedure has been developed on the basis of the successful treatment of therapy-resistant hypoxic (and practically anoxic) leg ulcerations located within a heavy dermatoliposclerosis.
The procedure involves an initial intra-ulceral application of haemoglobin followed by the intermittent administration of normobaric oxygen via inhalation. Haemoglobin is capable of externally supplying the granulating wound bed with oxygen at low partial pressure in a physiological manner, like a micro lung, so that oxidative stress can be avoided. A long-term daily administration of oxygen from within - including the peri-ulceral skin - is achieved by intermittent normobaric oxygen inhalation (INBOI) regularly throughout the day in the form of 1-hour sessions.

**Observations:** Using this combined healing treatment during haemoglobin applications the ulcerations healed within about 1 month, and subsequently with INBOI therapy within further approx. 4 months the peri-ulceral skin regenerat ed as far as the oxygenation status was concerned: The peri-ulceral transcutaneous oxygen partial pressure (tcPO(2)) of zero (measured during breathing of normal air) rose to a satisfactory value of approx. 35 mmHg. After 28 months of treatment, the completely hypoxic and degenerated skin on the leg had practically returned to normal with a PO(2) of 45 mmHg. Furthermore, the skin dermatoliposclerosis regressed. The skin regeneration was long-lasting, which was probably related to cellular tissue regeneration with an increase in the capillary density, whereby it had to be maintained by regular oxygen inhalation (INBOI maintaining treatment). By unintended intra-individual therapy variations it is evidenced that local hypoxia was the reason for skin degeneration: 3 x 1 h oxygen inhalation were sufficient for the healing treatment; 2 x 1 h sufficed for maintenance, whereas 2 x 0.5 h did not.

**Conclusions:** The new procedure carries practically no risks, is simple, cheap and effective. Whereas the application of haemoglobin requires professional supervision, the oxygen inhalation can be carried out at home following initial guidance and monitoring by a physician. Using this novel method, the therapy-resistant ulceration could be closed within 5 months, during which daily outpatient care was only necessary for 1 month. The successful outcome of the treatment in terms of improvement of oxygen supply can monitored at any time using peri-ulceral tcPO(2) measurements, whereby, due to the inhomogeneity of the values, measurements at a minimum of two locations at the wound edge are strongly recommended and more measurements at more skin locations would be preferable. Besides its use in the healing of ulcers, the new procedure is also suitable for the prevention of ulceration development (prophylactic INBOI treatment) in skin rendered susceptible due to the presence of hypoxia. Here, peri-ulceral transcutaneous oxygen partial pressures of below 10 mmHg should be considered as being critical and an indication for a prophylactic oxygen inhalation treatment. The new procedure may also be suitable even before the peri-ulceral oxygen partial pressure falls below 10 mmHg. Four measures for rehabilitation, conservation, and prevention with regard to a healed chronic wound are proposed.


**Objective:** To evaluate the effect of topical haemoglobin spray on treatment response and wound-closure rates in patients with chronic venous leg ulcers.

**Method:** A linear regression model was used to forecast healing outcomes over a 12-month period. Simulated data were taken from normal distributions based on post-hoc analysis of a 72-patient study in non-healing and worsening wounds (36 patients receiving standard care and 36 receiving standard care plus topical haemoglobin spray). Using a simulated 25,000 'patients' from each group, the proportion of wound closure over time was projected.

**Results:** Simulation results predicted a 55% wound closure rate at six months in the haemoglobin group, compared with 4% in the standard care group. Over a 12-month simulation period, a 43% overall reduction in wound burden was predicted. With the haemoglobin spray, 85% of wounds were expected to heal in 12 months, compared with 13% in the standard care group.

**Conclusion:** Topical haemoglobin spray promises a more effective treatment for chronic venous leg ulcers than standard care alone in wounds that are non-healing or worsening. Further research is required to validate these predictions and to identify achievable outcomes in other chronic wound types.

**Objective:** To use a non-invasive measurement of oxygen saturation in chronic leg ulcers after the application of a topical haemoglobin spray to investigate if photoacoustic tomography is able to measure the oxygen saturation and if the stimulated oxygen increase can be demonstrated.

**Method:** We measured the oxygen saturation of the ulcer tissue in five patients with chronic leg ulcers before application and 5 and 20 minutes after application of the haemoglobin spray, using photoacoustic tomography as a new method to assess oxygenation in real-time.

**Results:** The average oxygen saturation showed a significant increase from 56.4% before to 69% (p=0.042) after 5 minutes and 78.8% (p=0.043) 20 minutes after the topical haemoglobin application.

**Conclusion:** The oxygenation status of chronic, hard-to-heal wounds is gaining increasing interest in modern wound therapy. Topical haemoglobin spray is a new and effective method to increase the oxygenation in the ulcer tissue, but until now the link between clinical results and the mode of action was unclear. We were able to show for the first time that the use of a topical haemoglobin spray leads to an increase in oxygen saturation in vivo using photoacoustic tomography.

**Declaration of interest:** Joachim Dissemond received financial support from the company SastoMed for several scientific projects as well as for lectures and as an advisor. The haemoglobin spray was provided by SastoMed GmbH (Georgsmarienhütte, Germany).

**PubMed – Granulox review articles**


**Abstract**

Wound management is a major burden on today’s healthcare provider, both clinically with regard to available resources and financially. Most importantly, it has a significant impact on the patient’s quality of life and experience. Within the field of wound care these pressures, alongside an ageing population, multiple comorbidities, disease processes and negative lifestyle choices, increase incidences of reduced skin integrity and challenging wounds. In an attempt to meet these challenges alternative, innovative therapies are being explored to support the wound healing process. Wound care experts are now exploring the scientific, biological aspects of wound healing at a cellular level. They are taking wound care back to basics with the identification of elements that, if introduced as an 'adjunct' or as a stand-alone device alongside gold-standard regimens, can positively impact the static or problematic wounds that pose the most challenges to clinicians on a daily basis. This article explores the phenomenon of oxygen, its place in tissue formation and the effect of depletion on the wound healing process and highlights ways in which patients may receive benefit from non-invasive intervention to improve wound care outcomes.


**Abstract** - 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.


Abstract - Postoperative infection and the presence of osteosynthetic material in human body pose a major problem for patients and operators. Previously, it was considered that osteosynthetic material must be removed, and only then the expected full infection recovery could occur. However, removal of osteosynthetic material in unhealed fractures complicates bone fracture healing, as well as infection recovery. Nowadays, it is indicated to place an external bone fixator and in case of soft tissue recovery access to reosteosynthesis. The negative pressure wound therapy has brought new opportunities for treatment of this type of infections without the need of osteosynthetic material removal. Direct and indirect effects of negative pressure wound therapy create optimal healing conditions. Local use of new materials, transforming powder (Altrazeal) and topical haemoglobin spray (Granulox), provide and improve physiological conditions for appropriate and safe healing.

4. Prof. Dr. Dr. von Eiff W. Focusing on Quality, Well-Being of Patients, and Costs. HCM. 2013 Nov; 4th vol.: 38-41.

Summary and Recommendations: The superiority of combination therapy with topical haemoglobin in wound care, especially for therapy refractory wounds, leads to the recommendation to spread the application of this procedure. Unfortunately it must be noted that independent practitioners are unsure whether the statutory health insurance providers absorb the costs of such services. Here the following must be noted: Granulox, the product underlying the combination therapy, is not a drug that must be separately approved to be included into the catalogue. Rather, it is a wound dressing that requires no specific approval since pursuant to § 31 I 1 of the German Social Code it must be reimbursed by the statutory health insurance.

Other (non-PubMed) Granulox references


Abstract

Aim Diabetic foot ulcers (DFU) do not respond well to treatment and cause substantial costs. The topical hemoglobin contact spray Granulox* when applied in addition to the standard wound care regimen results in an acceleration of wound healing and an improvement in wound closure even in stalling wounds. Aim of this study is to analyse the impact of a topical hemoglobin contact spray on cost from the perspective of the German statutory health insurance.

Methods Based on clinical trial data a 28-week Markov model was programmed covering the following model states: “Stalled Wound Healing”, “Normal Wound Healing”, “Infected Wound”,
“Amputation”, “Ceased”, “Healed”. Analysis of incremental differences were performed and tested for robustness with a sensitivity analysis.

**Results** Patients with standard wound care regimen caused average total costs during 28 weeks of 1737 €, patients with adjunct topical hemoglobin contact spray resulted in a total of 1027 €. Costs for nursing and dressing changes represented the major cost factor with an average of 806 € in standard wound care regimen and 474 € when topical hemoglobin contact spray was added. The cost decrease of 709 € was confirmed when varying assumptions in the sensitivity analysis.

**Conclusion** When applying the topical hemoglobin contact spray Granulox® in addition to standard wound care regimen of diabetic foot ulcer in Germany a substantial cost reduction could be achieved from the perspective of the German statutory health insurance.


This supplement highlights the clinical and cost impact of using Granulox, through case studies, an example of best practice and an examination of the cost data. The real-life examples from clinics in the UK illustrate the role Granulox can play in reducing wound-related pain and slough, improving healing and reducing costs (Hunt, 2015).


**Abstract:** Diabetic foot ulceration (DFU) is a particularly challenging wound group in today’s healthcare arena, occurring across primary and secondary care settings, resulting in physical, psychological and financial burden to the patient and healthcare provider. According to Edmonds (2007), the most common occurrences that clinicians and patients experience are infection, tissue trauma and deterioration, amputation and resulting disability. Clinicians, healthcare stakeholders and industry, alongside patient focus groups, are constantly seeking new ways of preventing, managing and improving DFU outcomes through exploring new and exciting innovations, such as topical oxygenation therapy as an adjunct to standard care (Norris, 2014; Bateman, 2015; Tickle, 2015). This paper will discuss the positive outcomes of wound healing, pain reduction, slough reduction and exudate levels within an acute setting of 20 patients who presented with chronic DFU who received topical haemoglobin therapy via a spray device, compared with a similar group who only received standard care alone by the same clinical teams in the same ward environment.

**Key Opinion Leaders, Consensus Recommendation**

3. **Expert consensus on practical aspects of wound therapy with hemoglobin spray**

**ABSTRACT**

In the course of physiological wound healing, molecular oxygen (O2) is required in almost every process. However, oxygen supply – especially in chronic wounds – is often limited and usually treatment of the underlying disease is not sufficient to meet the tissue’s oxygen need. Therefore, additional oxygen supply within the framework of phase-specific wound treatment might be essential. Different options for topical oxygen supply are currently available. In 2012, haemoglobin spray was introduced onto the market, representing an easily and location-independently applicable approach which can simply be implemented into
standard wound care and even handled by the patient himself. Based on the physiological concept of facilitated diffusion, haemoglobin transports oxygen from the ambient air to the wound bed, bypassing the diffusion barrier of wound exudate. At present, it represents the only topical option for supplying oxygen directly to the affected tissue. The efficacy of hemoglobin spray has already been demonstrated in clinical studies and case reports with a significant improvement of healing especially in hard-to-heal wounds without improvement after four weeks of standard treatment. However, a practical-oriented clinical algorithm is not available to date. Therefore, based on published evidence and clinical experience, the advantages and disadvantages of hemoglobin spray usage were discussed in an interdisciplinary panel of experts from D.A.CH. region. According to the experts, hemoglobin spray is a potent product usable for the improvement of oxygen supply in acute and chronic wounds without wound size reduction by $\geq 40\%$ after four weeks of standard treatment. The advantage of hemoglobin spray comprises the ease of use without side effects and the distinct medical-economic benefit due to the often seen significantly shortened healing period when applied in accordance with the outlined recommendations.

**Wounds UK -**

4. **Appropriate use of topical haemoglobin in chronic wound management: consensus recommendations**
   **Wounds UK, 11/05/15**
   Paul Chadwick, Joanne McCardle, Luxmi Mohamud, Joy Tickle, Kath Vowden, Peter Vowden.

Oxygen has a crucial role in wound healing; 97% of chronic, non-healing wounds have been shown to have low oxygen levels (Hauser, 1987). Topical oxygen therapy has been shown to be effective in treating non-healing wounds, but is still underutilised. A working group of key opinion leaders met in February 2015 to determine the potential role of topical haemoglobin in non-healing wounds and to develop a clear decision-making pathway for clinical practice, as well as sharing practical tips for use. The group’s consensus recommendations on appropriate use are presented here.

**Pilot study**

5. **Pilot study: haemoglobin spray in the treatment of chronic diabetic foot ulcers**
   Chadwick, Paul; Wounds UK; Nov2014, Vol. 10 Issue 4, p76

**Abstract -** Wounds cannot heal without oxygen. In fact, healing wounds demand more oxygen than healthy tissues yet chronic wounds are often at least partly due to vascular insufficiency. A novel spray aims to make use of haemoglobin, the transport molecule for oxygen in the bloodstream, to bind atmospheric oxygen and deliver it to the hypoxic wound bed. The product, Granulox® (Infirst Healthcare), may be of particular interest in patients with impaired levels of tissue perfusion/oxygenation, which may be impeding wound healing.

**Review article**

I. **Gottrup F, Dissemond J, Baines et al. Use of oxygen therapies in wound healing, with special focus on topical and hyperbaric oxygen treatment. J Wound Care, 2017; 26(5), Suppl, S1–S42.**

The overall aim of this document is to highlight the present knowledge with regard to the use of oxygen therapies in the care and treatment of wounds of different aetiologies, which fail to progress through an orderly and timely sequence of repair. In this document, these types of wounds are defined as ‘non-healing’. Excluded from this document are animal and cellular models, acute wounds, such as surgical/trauma wounds and burns. The distribution of supplementary systemic oxygen at barometric pressure in connection with surgery is not covered by this document. We provide an overview of the treatment options, as well as assessments of the best available evidence on their respective results. In addition the document will go into detail with specific aspects and current discussions regarding the use of oxygen in wound healing including:
• The role of oxygen and hypoxia in the wound healing process
• Patient perspectives of oxygen treatment
• Cost-effectiveness aspects of oxygen therapies
• What remains controversial with suggestions for future actions.


Abstract: Adequate oxygen supply is mandatory for every wound healing and wound healing is generally associated with a greatly increased oxygen demand. This increased oxygen demand is caused by the variety of biochemical and cellular processes in the different phases of wound healing. At present, in Germany several options of local oxygen therapy of chronic wounds are available: 1. transporting oxygen in wounds by oxygen transporter (example Granulox®), 2. Treatment with a slight oxygen overpressure (Example OxyCare®), 3. treatment with continuous oxygenation without overpressure (Example Natrox®), 4. oxygen-releasing dressings (Example Oxyzyme®). All methods assume that the wounds were carefully cleaned and debrided before treatment. Exclusively Granulox® takes claim for itself that it enables the oxygen to pass the remaining liquid barrier on the wounds and increases oxygen supply on the level of the cells. Although all the other methods increase the local concentration of oxygen, they do not give any explanation how this oxygen reaches the cells.

KEYWORDS Oxygen therapy, Granulox®, Oxycare®, Natrox®, Oxyzyme®

Product Evaluation

Wounds UK

Topical oxygen-haemoglobin use on sloughy wounds: positive patient outcomes and the promotion of self-care. SHARON DAWN HUNT

Sloughy wounds are challenging because they are time consuming to manage, often require specialist input for slough removal, and have a significant effect on quality of life.

Method: A descriptive evaluation was undertaken within a community setting, exploring 100 patients who presented with sloughy wounds and the effects of twice-weekly, topically administered haemoglobin therapy over a 4-week period. Normal standard wound cleansing and dressing regimens were continued, with wound care being provided by the cohort group independently or with supervision and support from a designated carer. Data were collected weekly in relation to primary outcomes of slough reduction, wound surface area reduction, patient ease of self-care use, and overall product experience.

Results: At 4 weeks, all wounds had demonstrated positive measured endpoints of slough elimination (100%) and continued wound size reduction (99%), with 100% of patients and carers finding the product easy to use and having an overall positive wound care experience.

Conclusion: The administration of a haemoglobin spray solution in patients presenting with sloughy wounds resulted in slough elimination and wound reduction, along with positive self-care and product satisfaction.
**Conference Poster**

**ISPOR 2017, Glasgow**

**WOUND MANAGEMENT IN DIABETIC FOOT ULCER (DFU) – INCREMENTAL COST-ANALYSIS OF TREATING DIABETIC NEUROPATHIC FOOT LESIONS WITH ADJUNCT HEMOGLOBIN CONTACT SPRAY* IN GERMANY**

**Aim:** The aim of this study is to analyse the impact of a topical hemoglobin contact spray on cost from the perspective of the German statutory health insurance.

**Methods:** Design: Incremental cost analysis using a Markov model. Data Sources: Cohorts of 40 patients with topical hemoglobin contact spray who presented with chronic DFU in an acute clinical setting were compared with a cohort of 20 patients selected from the same period the year prior using the same protocol, retrospectively, from the same clinic (Control) (Hunt et al. 2016)

**Conclusion:** When applying the topical hemoglobin contact spray Granulox® in addition to standard wound care regimen of diabetic foot ulcer in Germany a substantial cost reduction could be achieved from the perspective of the German statutory health insurance.

**Harrogate November 2017**

**Clinical Effectiveness Of Haemoglobin Spray As Adjunct Therapy -Meta-analysis By Wound Type Across Three Real World, Retrospective Cohort Controlled Evaluations.** S. Hunt and F. Elg

**Aim:** The vast majority of wounds with healing complications have low levels of oxygen availability in the wound bed. Correspondingly, facilitated diffusion using haemoglobin is a promising approach to increase oxygen availability but so far no attempt has been made to assess the relative benefit achievable between wound types.

**Method:** Wound types were extracted from three very similar 6-month controlled evaluations of haemoglobin spray compared with standard care alone

**Results:** Kaplan-Meier time-to-wound healing was significantly better across each wound type, with weekly chance of healing more than 2x greater with haemoglobin spray in each wound type (p<0.01). Results were confirmed in Cox proportional hazards log-rank regressions for baseline covariates for each of the five wound types (p<0.02).

**Conclusion:** Adoption of haemoglobin spray in the regular treatment of trauma, DFU, Burn, VLU, or post-surgical wounds with delayed or complicated healing is expected to realise substantial healing benefits to patients. Further research should evaluate further wound types and patient sub-populations where no significant benefit is expected, and clarify cost-effectiveness as a means to facilitate appropriate pricing.

**The Scientific Meeting of Thai Enterostomal Therapy Society 2017**

**Using of Hemoglobin spray to treat complex chronic ulcers to accelerate wound healing and save treatment cost- 10 case studies.** Somboon Jermsujarit, Apirat Saengpethsong et al.

**Background:** Chronic wounds can be defined as wounds with a slow healing tendency, they are also referred to as hard-to-heal or difficult-to-heal wounds, affect patient quality of life, length of hospital stay and treatment cost. Considerably increasing of chronic wounds cause family, social burden and challenging in healthcare system in fact, the importance of oxygen in the process of successful healing is currently scientific opinion that has been long-recognized. However, in chronic wounds, inadequate supply of oxygen to the tissue is often caused by the underlying diseases like chronic venous insufficiency or diabetes. Granulox® (Hemoglobin Spray) is an innovative medical device for treating of chronic wounds by improving the oxygen supply through
simplified diffusion and in this way Granulox® will help to promote and accelerate wound healing for chronic wounds.

**Objective:** To evaluate the effect of Hemoglobin spray to accelerate wound healing and save treatment cost

**Method:** Spray with Granulox® cover with foam dressing every 2 days

**Conclusion:** Complex chronic ulcers is difficult to heal, treatment with Granulox® and foam dressing can accelerate the healing time and save treatment cost

**EWMA 2017**

[EP132] THE USE OF TOPICAL PORCINE HAEMOGLOBIN IN CHRONIC WOUNDS. Liezl Naude

**Aim:** To evaluate the effect of using a topical porcine haemoglobin spray on chronic wounds as adjunctive therapy.

**Method:** 30 cases were evaluated in an Advanced Wound Management Centre in Pretoria, South Africa. The topical Haemoglobin was applied after 2-4 weeks of standard wound care to facilitate faster wound healing. Topical Haemoglobin was applied as adjunctive therapy together with standard care by following the Wound Bed Preparation Guideline in treating also the underlying causes such as vascular insufficiency, infection and pressure.

- Wounds were soaked for 15-20 minutes with an anti-biofilm gel or irrigation solution which was then removed with saline
- After wound cleansing the topical haemoglobin spray was applied per manufactures guideline directly on the wound
- Secondary dressing was applied as required permitting that the dressing was a permeable dressing.
- Gold standard treatment was still applied i.e. offloading for diabetic ulcers and pressure ulcers and compression bandaging for venous ulcers
- Wounds were treated every 3-4 days.

**Results /Discussion:** All wounds showed a significant decrease in size within the first 2 weeks of treatment. Overall 50%-70% faster healing rate when compared to just standard care. Patients also experienced a significant improvement in quality of life with a 95% decrease in pain after 1 week. All cases showed a reduction of slough and fibrin as well as an improvement in the quality of granulation tissue.

**Conclusion:** The use of topical porcine haemoglobin as an adjunctive therapy when treating chronic wounds demonstrates shorter healing times with less complications. Patients are experiencing improved quality of life within the first week of application especially with a significant reduction in pain levels and increased mobility.

[EP292] CLINICAL EFFECTIVENESS OF HAEMOGLOBIN SPRAY AS ADJUNCT THERAPY - META-ANALYSIS BY WOUND TYPE ACROSS THREE REAL WORLD, RETROSPECTIVE COHORT CONTROLLED EVALUATIONS. Fredrik Elg, Sharon Dawn Hunt

**Aim:** The vast majority of wounds with healing complications have low levels of oxygen availability in the wound bed. Correspondingly, facilitated diffusion using haemoglobin is a promising approach to increase oxygen availability but so far no attempt has been made to assess the relative benefit achievable between wound types.

**Method:** Meta-analysis across data from three 6-month controlled evaluations in n=2x100, n=2x50, and n=2x20 patients where haemoglobin spray was compared with standard care alone in wounds with healing complications in matched real world cohorts using similar designs. Results were evaluated for clinically meaningful impact over time, on Slough, Pain, Wound size reduction, and Wound persistency, for each wound type with ten or more patients in either group; Trauma (n=110), DFU (n=60), VLU (n=33), Burn (n=30), Post-surgery (n=24). Proportions of haemoglobin treatment vs standard care alone was about half (38-55%) across wound types.

**Results / Discussion:** Slough was significantly lower in all five wound types from week 2 onwards (53-88% greater reduction, p<0.01). Similarly, average reported pain scores were significantly lower.
within two weeks (p<0.01), with 49-78% greater reduction (p<0.01). Wound-size reduction was consistently accelerated with at least 38% greater mean size reduction across wound types by Week 8 (p<0.01). ANCOVA of baseline attributes across each group showed robustness to baseline covariates; wound size, persistency, and patient age (p<0.01). Kaplan-Meier time-to-wound healing was significantly better across each wound type, with weekly chance of healing more than 2x greater with haemoglobin in each wound type (p<0.01). Results were confirmed in Cox proportional hazards log-rank regressions for baseline covariates (p<0.02).

**Conclusion:** Adoption of haemoglobin spray in the regular treatment of trauma, DFU, Burn, VLU, or post-surgical wounds with delayed or complicated healing is expected to realise substantial healing benefits to patients. Further research should evaluate further wound types and patient subpopulations where no significant benefit is expected.

**[EP311] THE EFFICACY OF A HAEMOGLOBIN OXYGEN SPRAY ON BIOFILMS.** Steven Percival, Sonya Taylor, Lousie Suleman

**Aim:** Oxygen therapies have shown encouraging results in aiding wound closure in hard-to-heal wounds. The use of haemoglobin to deliver oxygen to the wound and aid wound healing has also been explored, however the effects on wound biofilm has not. It was therefore the aim of this study to assess the efficacy of a haemoglobin spray*1 on biofilms.

**Method:** Biofilms were formed using various models*2 whereby biofilms were grown on filters and in glass chamber slides. Staphylococcus aureus, Pseudomonas aeruginosa or Candida albicans were grown in Tryptone Soya Broth (TSB) overnight at 37°C before being diluted for biofilm growth. Biofilms were grown for 48 hours in all models. Biofilms were treated with the haemoglobin spray*1 for 15 minutes, 30 minutes, 1 hour, 3 hours and 24 hours. Total Viable Counts (TVC) were taken. Biofilms in the glass chamber slides were stained using a bacterial viability kit*3 before treatment and live confocal imaging.

**Results / Discussion:** Bacterial enumeration showed a 5-to-6-log reduction in all biofilm models after 24-hours exposure with the haemoglobin spray*1. Confocal imaging of 48-hour biofilm treated with the haemoglobin spray showed detachment of microorganisms from the surface and the death of cells within microcolonies.

**Conclusion:** This study demonstrated the effectiveness of a haemoglobin spray*1 on biofilms established in a variety of laboratory models. Therefore, the use of the haemoglobin spray*1 to treat chronic wounds could be used as part of a wound care and anti-biofilm strategy.

**Harrogate November 2016**

**Real world, retrospective cohort controlled, evaluation of relative effectiveness of topical haemoglobin spray as adjunct therapy in chronic diabetic foot ulcers – results after 12 weeks follow-up.** Sharon Dawn Hunt, Fredrik Elg

**Aim:** A controlled study with two cohorts was undertaken in an acute clinical setting in North East England where a spray solution containing haemoglobin (Granulox®, infirst Healthcare) was used in 20 patients with chronic (>12 weeks) DFU and compared with 20 patients selected from the same period the year prior using the same protocol, retrospectively, from the same clinic (Control). Results were evaluated in regards to set outcomes of standard wound evaluation metrics including wound surface area (Length*Width*π/4), resource utilisation, and adverse events, as well as ease of use, and patient acceptability. Wound healing at 12 weeks was set as primary outcome.

**Results:** At the primary endpoint at 12 weeks, mean wound size reduction for patients that completed the evaluation was -89%, vs -37% in the Control (p<0.01), and 9/19 (47%) had healed vs 2/19 (11%) in the Control (p<0.05). A significant difference vs Control was also observed well before 12 weeks. Secondary outcome evaluation demonstrated that all wounds commenced the evaluation with wound-bed slough present.
use analysis suggested a -49% reduction in overall number of dressing changes required and total cost of care savings of -65% (£1,927 cost /pt, excluding the cost of haemoglobin spray) over the 12-week observation period vs Control; driven by lower dressing costs (-67%, -£80/pt), lower nursing costs (-51%, -£1,043/pt), fewer unplanned surgical interventions for amputation and debridement (-100%, -£804/pt, of which -£423 due to one amputation at £8,450).

Discussion: The incorporation of a haemoglobin spray solution within DFU treatment is likely to result in significantly better outcomes, with results in this study suggesting a doubling of the average wound healing rate, more than twice as many wounds healed within three months, and significant quality of life benefits gained from reduced pain and rapid wound slough elimination vs the control cohort. Future research should aim to assess the effectiveness of haemoglobin spray across a broader set of chronic wounds and clarify the extent to which these benefits are sustained longer-term, over six months – which indeed is what we are working on.

Conclusion: The incorporation of a haemoglobin spray solution within DFU treatment is likely to result in significantly better outcomes and substantial cost savings.

A real world, retrospective cohort controlled, evaluation of clinical effectiveness of haemoglobin spray as adjunct therapy in chronic wounds – interim results at 12 weeks Sharon Dawn Hunt, Fredrik Elg

Aim: A controlled evaluation with two cohorts was undertaken in a primary care clinic, where a haemoglobin spray (Granulox®, infirst Healthcare) was used in a cohort of 50 patients with chronic wounds demonstrating <40% wound size reduction over the preceding 4 weeks of standard care and compared with a cohort of 50 patients selected from the same period the year prior using the same protocol, retrospectively, from the same clinic (Control). Results were evaluated on standard wound evaluation metrics including wound surface area reduction, wound tissue type (i.e. sloughy), pain (0-10), exudate, resource utilisation, and adverse events, as well as ease of use, and patient acceptability. Wound healing at 12 weeks was set as primary (interim) outcome as part of an ongoing 6-month evaluation study.

Results: At the 12-week primary endpoint mean wound size reduction was -92%, vs -41% in the Control (p<0.01), and 40/50 (80%) wounds had healed vs 11/40 (28%) in the Control (p<0.01). A significant difference vs Control was also observed before 12 weeks. At 4 weeks 47/50 (94%) wounds in the haemoglobin spray group had demonstrated positive wound size reduction vs 20/49 (41%) in the control (p<0.05) and 16 had healed vs 5 in the Control (p<0.01). At 8 weeks the mean size reduction was more than 4 times greater in the haemoglobin group; at -87% vs -14% (p<0.01) and 5 times more wounds closed 40/50 (80%) vs 7/49 (14%) (p<0.01). Secondary outcome evaluation showed mean pain score reductions significantly greater from week one (p<0.01), despite being higher at baseline in the haemoglobin group. Also slough and exudate levels saw significantly faster improvements vs Control within as little as one week, with slough reduced by -25% vs -4% (p<0.01), and the patients with high exudate reduced from 26 to 4 vs no change in the Control (20 wounds) (p<0.01). At 4 weeks 100% of patients in the haemoglobin spray group were slough free vs 10/49 (20%) in the Control (p<0.01). At the 8-week review no patients’ wounds had regressed in the haemoglobin spray group while 33/49 patients in the Control remained sloughy (p<0.01). Resource use analysis suggested -48% reduction in number of dressing changes, and total cost of care savings of - 55% (£1,118 cost /pt, excluding the cost of haemoglobin spray and not considering additional self-care benefits realised) over the 12-week observation period vs Control; driven by lower dressing costs (-47%, -£61/pt), lower nursing costs (-45%, -£707/pt), and fewer unplanned surgical interventions (-100%, -£350/pt). All costs based on NHS tariff prices if available. Six patients died in the Control group and one in the Haemoglobin spray group, unrelated to their wounds. There were no other adverse events in the haemoglobin spray group while there were 16 in the Control (p<0.01); eight surgeries, and eight infections requiring antibiotics. Patients and clinicians alike found the haemoglobin spray product acceptable and easy to use. The primary endpoint results were also robust in light of covariance (ANCOVA) to account for variations in baseline values, with the effect of haemoglobin spray on wound size reduction at 12 weeks p<0.01 also when controlling for baseline wound size (p=0.59) and prior wound
persistence (p=0.10). Analysis for the secondary endpoints similarly showed robust results regardless of baseline variations (p<0.05). No adjustments for multiple analysis was made for reported p-values.

**Conclusion:** Adoption of haemoglobin spray in the treatment of chronic wounds is expected to realise substantial healing benefits to patients.

**Haemoglobin spray in sloughy wounds - A real world, 200-patient, retrospective cohort controlled, evaluation of clinical effectiveness – interim results at 12 weeks.** Sharon Dawn Hunt, Fredrik Elg

**Aim:** A controlled evaluation with two cohorts was undertaken in a primary care clinic where a haemoglobin spray (Granulox®, infirst Healthcare) was used in a cohort of 100 patients presenting with sloughy wounds (at least 10% slough coverage), with patients recruited in May through July 2015 and compared with a cohort of 100 patients selected from the same period the year prior using the same protocol, retrospectively, from the same clinic (Control). No changes to care practices or dressings were made unless medically required, i.e. due to changes in exudate levels or wound size. Results were evaluated on standard wound evaluation metrics including wound surface area reduction, resource utilisation, and adverse events, as well as ease of use, and patient acceptability. Wound healing at 12 weeks was set as primary (interim) outcome as part of an ongoing 6-month evaluation study.

**Results:** At the 12-week primary endpoint mean wound size reduction was -96%, vs -57% in the Control (p<0.01), and 83/100 (83%) wounds had healed vs 47/96 (49%) in the Control (p<0.01). A significant difference vs Control was also observed before 12weeks. Resource use analysis over the 12-follow-up, showed -47% fewer dressing changes, and total cost of care savings of -53% (-£707 cost /pt, excluding the cost of haemoglobin spray and not considering additional self-care benefits realised) vs Control; driven by lower dressing costs (-59%, -£73/pt), lower nursing costs (-47%, -£485/pt), and fewer unplanned surgical interventions (1 vs 14, -£142/pt). The primary endpoint results were also robust in light of covariance (ANCOVA) to account for variations in baseline values, with the effect of haemoglobin spray on wound size reduction at 12 weeks p<0.01 also when controlling for baseline wound size (p=0.26), prior wound persistence (p=0.02), and patient age (p=0.03). No adjustments for multiple analysis was made for reported p-values.

**Discussion:** The haemoglobin spray treatment group had substantially improved healing outcomes in sloughy wounds vs the retrospective control cohort, with 40% percentage points greater average healing speed and significantly more wounds healed by week 12. These healing benefits also translated into improved quality of life through reduced pain and exudate and substantial total cost of care savings of more than 50%. Longer-term savings are likely to be substantially higher and future research should aim to assess the effectiveness of haemoglobin spray when used in sloughy wounds over the longer-term, over six months – an evaluation already in progress and for which this evaluation reports the half-way outcome.

**Conclusion:** Adoption of haemoglobin spray in the treatment of sloughy wounds is expected to realise substantial healing benefits to patients.

**EWMA 2016**

I. **[EP181] Implementation of haemoglobin spray in the treatment of patients with infected wounds.** Nesat Mustafi & Peter Engels

**Aim:** Infection or at least critical colonisation of wounds frequently becomes a critical factor for impaired wound healing and the development of further infection-related complications. Therefore an integrated treatment regime is important to reduce bacterial load while stimulating wound healing in parallel. Here we summarize 12 case reports of a successful treatment of infected wounds by using a treatment regime combining infection control, haemoglobin spray as topical oxygen carrier and further modern wound care modalities.
Method: In all cases wounds were thoroughly debrided, prior to further treatment. In different settings haemoglobin spray was applied prior to covering the wound with an appropriate non-occlusive wound dressing.

Results / Discussion: The presented 12 cases of infected or colonised wound were effectively treated by debridement and antimicrobial treatment in conjunction with haemoglobin spray, and an appropriate wound dressing. The results demonstrate that the use of haemoglobin spray in the treatment regime of infected or colonised wounds has no negative impact on wound healing but resulted in an enhanced wound healing. A prerequisite of successful treatment is a thorough debridement and cleansing. Haemoglobin spray was applied evenly to initiate granulation by providing additional oxygen to the wound as one of the key factors for successful wound healing.

Conclusion: Haemoglobin spray might be an adjunctive therapy option for infected or colonised wounds to accelerate wound healing and improve skin integrity.


Aim: Patients with diabetes frequently develop chronic wounds with a common problem in of insufficient supply of nutrients and oxygen to the affected tissue. Several approaches are available to provide additional oxygen topically to the wound. One of the most recent developments is to facilitate oxygen diffusion at the wound by applying purified haemoglobin. Aim was to implement haemoglobin application in the treatment of severe wounds. Here we present 15 cases of patients with diabetes mellitus presenting either severe acute (trauma) or chronic wounds, all treated at a wound care centre in Mexico.

Method: All cases selected were treated at the same wound care centre. All patients suffer from diabetes mellitus. Wounds were debrided, and rinsed with an antimicrobial electrolysed acid solution prior to the administration of the haemoglobin spray. A sterile paraffin gauze served as dressing. Frequency of dressing changes were initially three times per week or twice per and later reduced to once weekly.

Results/Discussion: For all wounds, wound closure or an enhanced healing process could be achieved. Of the 15 patients, 14 achieved wound closure, in one case wound healing was not completed while therapy is still ongoing. In 6 cases amputation was prevented. No adverse events related to the treatment with the haemoglobin spray were reported.

Conclusion: Haemoglobin spray might be an adjunctive therapy option for acute and chronic wounds to accelerate wound healing even for acute wounds.

III. [EP 185] Post-surgical wound management of patients with pilonidal cysts by using a haemoglobin spray. Nesat Mustafi, Peter Engels,

Aim: Painful acute cysts in the natal cleft or lower back, known as pilonidal sinus disease, is a severe burden to many patients. Although surgical intervention is the preferred first line treatment, post-surgical wound healing disturbances are frequently reported due to wound infection or other complications. Aim of the study was to develop a simple wound care regime comprising appropriate debridement, rinsing with an antimicrobial solution, haemoglobin application, and dressing with polyurethane foam to prevent healing disturbances. Here we present four cases of pilonidal cyst using the proposed wound care protocol after surgical intervention.

Method: Wounds were debrided and rinsed with an antimicrobial solution. After application of the haemoglobin solution a polyurethane foam dressing was applied. Frequency of dressing changes were initially two or three times per week and later reduced to once weekly.

Results& Discussion: Of the four wounds presented to the wound care unit, one had already developed a sustained wound healing disturbance due to wound infection, one had started to develop fibrin coating while two wounds were in a good condition. Three of four wounds showed wound closure within 70-98 days. Two cases revealed excellent aesthetic result of the wound closure while two showed only moderate or poor results. It is remarkable that best asthetic results have been achieved in those wounds that received adequate statement at an early stage.
Conclusions: To avoid healing disturbances and achieve an enhanced wound healing and reduced scar formation after pilonidal cyst surgery, an adequate wound care regime comprising appropriate wound debridement, rinsing, topical application of haemoglobin solution and adequate wound dressing is recommended.

IV. [EP 238] MEASUREMENT OF O2 ABSORPTION CAPACITY OF CHRONIC ULCERS AFTER TOPICAL APPLICATION OF HAEMOGLOBIN USING PHOTOACOUSTIC TOMOGRAPHY
Petri Maximilian, Julia Leyh, Jose Jithin, Ingo Stoffels, Joachim Klode, Joachim Dissemond, Andrea Schulz, Dirk Schadendorf

Aim: Objective parameters enabling an early decision on surgical or conservative treatment of patients with chronic ulcers are lacking. Topical haemoglobin spray is a new method which promotes improved oxygenation in chronic wounds. We will examine whether topical applications of haemoglobin really lead to an increase in tissue oxygenation and whether a statement can be made on the wound healing process based on the change in oxygen saturation.

Method: 48 patients with hard-to-treat ulcers from a wound outpatient department of a university skin clinic participated in this study. We used photoacoustic tomography as a new non-invasive method for measuring oxygen saturation in tissue. A measurement was carried out before application and 5 and 20 minutes after topical application of haemoglobin. The wound size was also recorded at the time of measurement as well as at a later follow-up appointment.

Results / Discussion: There was an increase in oxygen saturation from 66.1% to 69.1% (p=0.063) after 5 minutes and 71% (p=0.017) 20 minutes after application of haemoglobin. Patients were also grouped into “Responders” (>10% increase in oxygen saturation) and “Non-Responders” (<10% increase in oxygen saturation). At the follow-up examination, Non-Responders showed no significant change in wound size (p=0.929), whilst a significant healing trend could be measured with Responders (p=0.005).

Conclusion: The study demonstrated for the first time that local application of haemoglobin causes a significant increase in tissue oxygenation. An increase in oxygen saturation of >10% after application of haemoglobin also seems to present an objective surrogate parameter for conservative wound treatment. Thanks to screening, ulcer patients could receive adequate treatment more quickly in future.


Aim: This poster highlights the benefits of using a topical Haemoglobin spray therapy within DFU patients to review outcomes in regards to wound surface area reduction, patient acceptability and ease of use, no adverse events.

Method: A single acute center descriptive evaluation of 20 patients was undertaken to explore the efficacy defined within set primary outcomes; % reduction in wound surface area after four weeks treatment with Granulox and secondary outcomes of; patient acceptability, adverse events and ease of use. Inclusion criteria included those aged over 18 years, a (SINBAD) score maximum of 2 and diabetic foot ulcer located below the ankle. Exclusion criteria related to patients with infected ulcers, receiving systemic antibiotic therapy and corticosteroids, pregnant or actively lactating, that had a ABPI <0.5mmHg or toe pressure <70mmHg or HBA1c >10% or 86mmol/l and a SINBAD of >3.

Results /Discussion: At four weeks all wounds demonstrated positive wound reduction, no adverse events, all patients and clinicians found the product acceptable and easy to use. Interestingly, all wounds had levels of slough present at onset of treatment and were all slough free at end of the four week period. At a further four week follow up period none of the DFU had regressed.

VI. [EP 719] Benefits of utilising Topical Haemoglobin Spray on 100 sloughy wounds within a community setting. Sharon Hunt
Aim: This evaluation explores the positive impact upon sloughy wounds across all areas of wound pathology inclusive of healing, slow healing and non-healing wounds, with the innovative utilisation of a topical haemoglobin spray.

Method: A descriptive evaluation was undertaken within a community setting exploring 100 patients that presented with sloughy healing, slow healing and non-healing wounds, and the effects of eight topically administered haemoglobin treatments over a four week period. Standard wound cleansing and dressing management was continued with no changes to pre evaluation regimens with care being provided by the cohort group independently or carer.

Results / Discussion: At four weeks all wounds had demonstrated positive measured endpoints of slough elimination, continued wound size reduction with patients and carers finding the product easy to use (self-caring) with an overall positive wound care experience. At a further four week follow up period all 80 patients who had gone onto full healing within the evaluation and follow up period had no regression of wounds, 20 patients who did not fully heal were those of venous leg ulceration and vascular disease who went onto surgical intervention who also had no regression.

Conclusion: The administration of a haemoglobin spray solution within this reasonably large cohort of patients presenting with sloughy wounds resulted in positive healing outcomes of slough elimination and wound reduction alongside positive self-care and product satisfaction. Continued evaluation and data collection is recommended to build upon the evidence.


Aim: We present a patient with chronic wound of donor site in the lower leg. Two months after surgical treatment of harvesting partial thickness of skin graft according to Blair, there is a skin and partially showed subcutaneous tissue defect with purulent secretion.

Method: We performed wide debridement and lavage of the wound. We applied daily topically hemoglobin spray with a gauze as a secondary dressing four days a week and over the weekend we applied alginate silver dressing.

Results / Discussion: After admittance in the surgical practice, debridement was performed. We have removed cellular debris and traces of fibrin deposits. Tissue sample for microbiological diagnostics were taken. We applied topically hemoglobin spray on the wound with gauze as a secondary dressing. To the following control patient came after four days, wound contraction was present, with appearance of healthy granulations. The edges of wound began the epithelialization. We applied alginate silver dressing. Next control after four days showed further epithelialization and wound healing. The surrounding skin had proper colour and was euthermic. Control laboratory tests were within reference range. We continued with combination dressing using topic haemoglobin and alginate dressing. Medical examination after one month showed a properly healed wound.

Conclusion: Using topical hemoglobin spray and alginate silver dressing we increased oxygenation of tissue in the wound and controlled infection. This stimulated the creation of a "healthy" granulation tissue and allowed the epithelialization from the wound edges. The increased amount of oxygen and silver in the wound must have played a significant role in wound healing.

VIII. [EP 780] Comparison between Hospitals & Home Care Services in treating VLU using the same methods. Florin Paraschiv

Aim: Evaluate the efficacy of the VLU treatment in Hospitals vs Home Care Services

Method: There were evaluated 16 cases of Venous Leg Ulcers (10 in Hospital + 6 in Home care), infected, with fibrin and necrosis, for patients with the ages between 60-90 years old, with several co-morbidities. The dressings were changed every 2-3 even 4 days. The approaches were similar, the only difference was the debridement procedure and the prophylaxis on the infection more favorable conditions in Hospital. The protocols were almost similar, topical and systemic. Remove infection with (DACC) and wound antiseptics,
debridement (surgical & autolytic), management exudate dressings, compression therapy, wound healing accelerators and pain relievers.

**Results:** The DACC product was an excellent autolytic wound debrider in both battle fronts, quick and efficient, in the hospital was applied surgical debridement some cases. The DACC antimicrobial dressings were assisted by antibiotic and local wound antiseptics therapies in order to accelerate the infection removing process. PEMF mobile devices were applied for pain relief and hemoglobin spray to decrease the hypoxia.

**Conclusion:** There is not a notable difference concerning the healing term, as regarding the costs for sure the Hospital is the choice but for the patient comfort there is clear advantage in the H.C. services. In conclusion the mentioned products are able to treat in a professional and efficient approach the VLU both in Hospitals and Home Care

IX.  **[EP 801] Diabetic Foot Ulcer treated with combined and accessible technologies.** Florin Paraschiv

Aim: Using accessible and effective methods and dressings to close DFU.

Method: There were evaluated 4 cases of DFU, infected, with fibrin and necrosis. The patients ages between 53-87 years old, with different co-morbidities. Dressings were changed each 1-3 days, hard cleaned with a terile soap and disinfecting with biological wound antiseptic, before applying the DACC dressing, covered by foams and super absorbers as secondary dressings. After removing the infection there was applied hemoglobin spray in order to decrease the cellular hypoxia phenomenon and accelerate the healing process.

**Results / Discussion:** The first challenge was to remove the infection and keep the prophylaxis. The mixed antimicrobial procedures with local biological wound disinfectant, sterile soap and DACC helped to remove the infection. The debridement option was the autolytic one, being in home care. For pain therapy it was used PEMF technology, mobile devices, stimulating the production of collagen, reducing inflammation and repairing the damaged tissues.

**Conclusion:** This experience generated a functional kit for the DFU’s healing, proved in the real field. The patients were treated successfully in home-care services and self-care also, in short time between 55 – 120 days, with no complications, using different and complementary technologies, with synergies discovered in practice. The efficacy and cost effectiveness of the treatments were appreciated by the professionals and patients at the same time.

X.  **[EP 860] THE USE OF A NOVEL HAEMOGLOBIN SPRAY TO PROMOTE HEALING IN CHRONIC WOUNDS WHILST REDUCING TREATMENT COSTS.** Eleanor Wakenshaw

Aim: To use a novel product to assess if introducing oxygen to chronic wounds by topical application of a haemoglobin spray could stimulate wound healing.

**Method:** Ten patients with wounds of different aetiologies were treated with the haemoglobin spray for 8 weeks. Photographs and data were obtained at beginning and end of study. Product was applied twice weekly.

**Results / Discussion:** 8 patients finished the evaluation, 2 patients were not included as they did not follow the treatment care plan. Of those who finished the evaluation: 1 healed, 5 progressed towards healing, 2 became infected.

**Conclusion:** 1) The results from this small cohort showed progress towards wound healing in all patients. If replicated in the wider population of patients with chronic wounds this could impact patient outcomes in this difficult to heal group. 2) As a surrogate endpoint, a reduction in pain resulting in the perception of their overall health being improved. This was unexpected and if confirmed in other studies could see a reduction in analgesics used in the management of complex wounds. 3) Due to the simplicity of applying the treatment, patients who are able can apply the treatment themselves at home. This empowers patients to actively take part in their own self-management. 4) With more patients being managed at or near home this product has advantages over others which require a healthcare professional for every visit. Reducing nursing time would have a major financial benefit for the NHS.
EWMA 2015

I. [EP020] TREATMENT OF CHRONICAL LOWER LEG ULCERS WITH TOPICAL HEMOGLOBIN SPRAY
Danijela Semenic, Adrijana Debelak, Irena Jovisic, Janja Nikolic, Dragica Maja Smrke
Slovenia, University Medical Center Ljubljana; Department of Surgical Infections

Aim: Primary diseases such as peripheral arterial occlusive disease, chronic venous insufficiency, diabetic foot syndrome may lead to a long term reduction in oxygen supply to the tissue. Partial pressure of oxygen in tissue is reduced, owing to capillary degeneration, which leads to consequent necrosis and chronic wounds formation. The healing of chronic wound is accompanied by increased energy metabolism of the skin. It requires more oxygen than normal metabolism of healthy skin. Even if sufficient amount of oxygen is available in the air, it cannot cross the bottom of the wound due to the diffusion barrier. We tested if oxygen from the air can be available for cellular activity and healing through topical application of haemoglobin spray on the wound bed.

Method: In a pilot study we treated 10 patients with chronic lower leg ulcers of different etiology, without systemic or local signs of inflammation. After flushing the wounds with local antiseptic solution, topical haemoglobin spray was used and covered with non-occlusive silicon-polyurethane modern dressing. We applied haemoglobin spray every 2-3 days for 16 weeks.

Results/Discussion: Surface area of ulcers as well as secretion rate had diminished and epithelisation of wound edges and scar formation was noted.

Conclusion: Cells need at least 20mmHg of oxygen partial pressure to survive, wound closure/granulation/epithelisation require a minimum of 40mm Hg. Consequently in the case of hypoxia, stagnation of the wound healing is present. Use of natural oxygen transporter – haemoglobin as a topical application in a form of a spray can be helpful for wound healing.

Ray Norris, Joy Tickle

Aim: This pilot study aims to investigate the effect a topical haemoglobin spray in reducing the size of chronic venous leg ulcers (VLUs).

Method: Patients whose VLU wounds were non-healing after 4 weeks of standard care (decreased wound size <40%) were treated with the haemoglobin spray at each dressing change in addition to standard care for 4 weeks. The spray is designed to deliver oxygen to wounds through facilitated diffusion. Standard care comprised compression therapy and wound dressings. Wound size, number of dressing changes, wound-bed characteristics, exudate level and patient-reported pain were recorded during the treatment period.

Results/Discussion: Seventeen patients were recruited. Three were withdrawn and data from 14 patients were analysed. Seventeen wounds were assessed; the average baseline wound duration was 41 months (range 6–120). The average wound area decreased from 52.5 cm2 (range 11.25–130.5) before treatment to 45.29 cm2 after treatment, with an average reduction of 7.21 cm2 (range 15.5–96%; median 68%). All participants showed a reduced wound area after the 4-week treatment period, with a reduction of slough and increase in granulation and epithelial tissue, and most reported reduced pain.

Conclusion: Fourteen of the 17 patients were progressing towards healing, despite the relatively short treatment period of 4 weeks. The results support those of two earlier randomised studies on the efficacy of haemoglobin spray on chronic wounds.

III. [EP177] TREATMENT OF INFECTED CHRONIC LEG ULCERS COMBINING INFECTION CONTROL, SURGICAL MODALITIES, HEMOGLOBIN SPRAY, WOUND DRESSING, AND
COMPRESSION THERAPY
Peter Engels, Nesat Mustafi

Aim: Venous leg ulcers are the most common form of leg ulcers. In addition, bacterial burden becomes often a critical factor in impaired wound healing of chronic wounds and the development of infection-related complications. Therefore an in integrated treatment regime is important to reduce bacterial load and stimulate wound healing. Here we report two case reports with a successful treatment of infected chronic leg ulcers by using a treatment regime combining infection control, surgical modalities (skin graft), a topical oxygen carrier (haemoglobin), antimicrobial polyurethane foam, and compression therapy.

Method: Antiseptic treatment and mechanical wound debridement or cleansing, wounds were rinsed and incubated with an antiseptic solution to reduce bacterial load. Debridement was performed by using a sharp spoon to remove necrotic tissue and fibrinous coating. Subsequently, wounds were rinsed with antiseptic solution, followed by a rinsing with isotonic saline solution. Thereafter, a thin layer of haemoglobin spray was applied on to the wound area. As wound dressing served specific polyurethane foam which contains a non-ionic surfactant. Compression therapy was performed by using medium stretch bandages.

Results/Discussion: The presented treatment regime revealed that it was possible to reduce the bacterial load while stimulating wound healing processes successfully. A prerequisite for such treatment is a thoroughly cleansing of the wound and debridement of the biofilm. During initial treatment bacterial load of MRSA and Pseudomonas colonisation was reduced. It was the basis for the next step of pre-conditioning the wounds prior to a skin grafting. Even after the mesh graft transplantation, the same treatment regime was applied to the wound. As result in both cases more than 99% of the mesh skin graft was adhered. A coordinated therapy regime using appropriate antiseptics, skin graft, haemoglobin spray and secondary wound dressing was successful to achieve a wound closure of infected chronic venous leg ulcers within less than 4 weeks.

Conclusion: In the presented cases, skin graft transplantation in conjunction with haemoglobin spray, an antimicrobial polyurethane foam and compression bandaging, showed convincing results regarding fast healing of infected venous leg ulcers compared to the previous dressing plus compression strategy.

Nesat Mustafi & Peter Engels

Aim: Burns affect the integrity of the skin and can ultimately result in skin scarring. Current therapeutic goals of wound treatment focus on the reduction of scar formation and severity. However, scar formation itself varies from patient to patient and within an individual based on the location of the wound. Therefore, the preparation of customized treatments for individual patients represents an important therapeutic goal in the fields of burns and wound healing. The objective of this study has been to evaluate the usefulness of haemoglobin spray in the treatment of burns and its impact on scar formation.

Method: Burn wounds were mechanically debrided or cleansed. After rinsing with an antimicrobial solution, a thin layer of haemoglobin spray was applied onto the wound area. Hydro polymer foams served as secondary wound dressing.

Results / Discussion: Burn wounds from ten different patients are shown and treatment results are highlighted. The wound severities range from grade 1 to grade 2B. In particular, for grade 2 wounds the scar formation was an important aspect of the evaluation. In all cases, we observed a fast healing of the burns. In addition, skin integrity and scar formation seemed to be improved.

Conclusion: Haemoglobin spray might be an adjunctive therapy option for severe burns (2A & B) to accelerate wound healing and improve skin integrity.

V. [EP251] COMPLETE HEALING WITH HAEMOGLOBIN SPRAY IN 5/6 NON-HEALING DIABETIC FOOT ULCERS THAT FAILED STANDARD CARE
Mike Green, Birmingham, United Kingdom, Soho Road Health Centre
Aim: Foot ulcers are slow to heal and are frequently further delayed by diabetes. The aim of the study was to evaluate the usefulness of haemoglobin spray in the treatment of non-healing foot ulcers.

Method: Patients with non-healing ulcers which had failed to improve despite standard care, had their wounds sharp debrided and cleansed. After cleansing with saline, a thin layer of haemoglobin spray was applied onto the wound area. Hydro polymer foams were used as secondary wound dressing.

Results / Discussion: The wounds of 4 patients (6 wounds in total) used the spray during a 6 month period. 4 wounds healed and 1 showed significant improvement. 3 of the patients had peripheral vascular disease where the vascular surgeon was deemed them not suitable for surgery.

Conclusion: Haemoglobin spray might be an adjunctive therapy option for hard to heal ulcers to accelerate wound healing. Secondly all patients reported a reduction in wound pain levels.

VI. [EP417] FAST HEALING OF VLUS WITH INNOVATIVE AND COMBINED TECHNOLOGIES
Florin Paraschiv, Bucharest, Romania.

Aim: Remove the infection, relieving the pain and close in an accelerated way the VLUs.

Method: There were evaluated 12 cases of VLU, infected, with fibrine and necrosis, for patients with the ages between 50 - 90 years old, with different co-morbidities. The patients were dressed every 2-4 days, cleaned with a sterile soap before applying the DACC (antimicrobial and debridement), followed by the haemoglobin spray for granulation, and covered by foams as secondary dressings. For the compliant patients was applied the compression therapy.

Results/Discussion: The DACC removed successfully the infection, also did an autolytic debridement. DACC was used until the end of the treatment together with the granulation hemoglobin spray in order to eliminate the risk of reinfection, because of the protein excess of the spray. The pain was relieved by electromagnetic impulse in low frequency. Each time the compression therapy was used, resulted obvious improvement signs.

Conclusion: This experience generated a functional kit for the VLU’s healing, proved in the real field. The patients were treated successfully, in Hospitals, home-care services and self-care also, in short time between 25 – 90 days, with no complications, using different and complementary technologies, with synergies discovered in practice. The efficacy and cost effectiveness of the treatments were appreciated by the professionals and patients at the same time.

VII. [EP425] THE SYNERGY BETWEEN HEMOGLOBIN SPRAY AND DACC DRESSINGS
Robert Tudoriu, Bacau, Romania, Fan Life - Home Care Services

Aim: Accelerating the healing time of a pressure sore eliminating hypoxia.

Method: We observed 8 cases with pressure sores, women (46%) and men (54%) with the ages between 40-92 years, most of the patients were immobilized. The wounds were infected, with fibrine, slaugh, and necrosis. The dressings were changed between 1-3 days in Hospitals and home care services. The approach was: Autolytic debridement, removing the infection and generate the red granulation tissue with DACC dressings, eliminate hypoxia with the haemoglobin spray, remove pain/inflammation and stimulated producing of collagen with the electromagnetic device, keep moisture in the wound with hydrophilic dressings.

Results/Discussion: The wounds were stabilized by removing the infection with the DACC dressings; the granulation was stimulated with haemoglobin spray. DACC ribbon gauze was used during the complete treatment to eliminate the high risk of reinfection. The pain was relieved by electromagnetic impulse in low frequency.

Conclusion: We found a range of compatible AWC products, in order to heal pressure sores in a reasonable time with small costs and ergonomic way, with not too many technical skills or expensive medical equipment. The patients were happy regarding time of healing, costs and pain management. The synergy between the DACC dressings and the haemoglobin spray was proved in practice, giving the chance to use the hemoglobin in earlier stages of the wounds, and keeping the “peace” by physical hanging the potential harmful pathogens.
VIII. [EP430] ACCELERATE TREATMENT OF A VERY OLD AND INFECTED FISTULA
Mitu Roxana, Bucharest, Romania, Bio Hygiene-Home Care Services

Aim: Remove the infection and close in an accelerated way the deep and old fistula.
Method: Male, 52 years old, with an infected open fistula for more than 18 months, as a post-op infection with E. Coli and Staphylococcus aureus. The patient was dressed every 2-3 days, cleaned with a sterile soap before applying the DACC ribbon gauze, alginates for the exudate absorption. For the last dressing sessions was applied haemoglobin spray covered by a foam as a secondary dressing.
Results/Discussion: The fistula was closed after only 14 days. The DACC ribbon successfully removed the infection; it was used until the end of the treatment together with the granulation haemoglobin spray in order to eliminate the risk of reinfection. The bad smell disappeared after the first 3 dressing changes.
Conclusion: A very old open wound was closed in short time, the patient was dressed first by the nurse, and then he was able to dress the wound by himself, the protocol being accessible. The patient was pleased with the results from all points of view (efficacy and cost effectiveness).

IX. [EP441] THE USE OF GRANULOX TO HEAL A FOOT ULCER IN A HIGH RISK PATIENT WITH DIABETES: A CLINICAL CASE STUDY
Alexandra Whalley, UK, Bolton Diabetes Centre

Aim/Methods: Diabetic foot ulcers can be notoriously difficult to heal. Complications such as infection, osteomyelitis, peripheral vascular disease and co-morbidities can delay wound healing and increase the risk of amputation. This case study demonstrates how a haemoglobin spray* heals a wound on the foot of a transplant patient who has Type 2 diabetes, is extremely high risk with peripheral vascular disease, underlying osteomyelitis and multiple co-morbidities. Method: Mr E presented with an ulcer on the apex of his R/1st toe in March 2014. Initial assessment found no palpable foot pulses in the right leg, monophasic Doppler sounds and neuropathy. The wound was swabbed and the patient referred for x-ray and vascular opinion. Underlying osteomyelitis was diagnosed and the patient was deemed to be unsuitable for any vascular intervention unless the situation became critical. Mr E wished to commence conservative treatment and commenced on a 12 week course of antibiotics, offloading of the wound and best wound management. Despite this the wound failed to heal and the osteomyelitis persisted. Haemoglobin spray* was commenced July 2014.
Results/Discussion: Mr E underwent weekly applications of haemoglobin spray* on the wound bed in addition to his normal wound management. Following 8 applications, the wound healed and remains healed.
Conclusion: There is an increasing number of high risk patients where surgery is not appropriate and palliative wound care is the only option. This case study has demonstrated that haemoglobin spray* can be a very useful addition to the treatment of foot ulcers in very high risk patients with diabetes where healing may not otherwise have been achieved.

X. [EP443] USING HAEMOGLOBIN TO IMPROVE OXYGEN DIFFUSION IN COMPLEX CHRONIC ULCERS LEADS TO FASTER HEALING AND REDUCED COST OF DRESSING CHANGES AND NURSING CARE - 3 CASE STUDIES
Luxmi Mohamud,, London, UK, Guys and St Thomas Community Services; Dulwich Community Hospital

Aim: To evaluate the use of enhanced oxygen diffusion in wound healing through topical application of haemoglobin spray in the treatment of chronic wounds where standard care has failed.
Method: Three patients with non-healing ulcers which had failed to improve despite standard care had their wounds reviewed. After assessment, topical haemoglobin spray (Granulox) was added with a view to kick -start the healing process by improving the oxygen level in the wound bed of each wound. Hydro polymer foams were used as secondary wound dressing.
Results/Discussion: Patient 1: Leg ulcer intermittent for 8 years. Started on topical haemoglobin spray in August 2014 and in December wound bed appears healthier and patient only changing dressing every 3 days
instead of daily as per previous regimen. **Patient 2:** A lady with Spina Bifida acquired a stage 4 pressure ulcer in October’14 (18cmx10cm). After limited healing progress and daily dressing, topical haemoglobin spray was started in November’14 and within 4 weeks reduced by 80% in size with 100% granulation tissue and dressed only every 72 hours instead of daily. **Patient 3:** Diabetic foot ulcer for over 2 years. Dressing change on alternate days. Topical haemoglobin spray started to a wet, sloughy wound bed. After 2 weeks, wound bed appeared clean and granulating but still wet, after further 2 weeks of topical haemoglobin spray 2x weekly, wound bed healthier and reduced in size.

**Conclusion:** Haemoglobin, when used as an adjunct therapy, has proved to be very effective in enhancing wound healing. Also it led to more cost effective way of managing long-term wounds, where nursing time was reduced by 2/3 and less dressing change being undertaken.

**XI. [EP451] HEALING A 14 YEAR-OLD LEG ULCER IN FOUR MONTHS WITH TOPIC HEMOGLOBIN**

Annemiek Mooij, Amsterdam, Netherlands, Slotervaartziekenhuis

**Abstract:** A 25-year-old woman, with a history of sickle cell disease, born in Brazil, suffered a leg ulcer since she was 12 years old. In Brazil she was always treated with silver sulfadiazine cream. She felt always sad, because of the wound she wasn’t able to work and to dress nice. In 2013 she came to the Netherlands after the doctors in Brasil suggested amputating her leg. When we started the treatment the ulcer was 20 cm by 10 cm, covered with a yellow-grey slough. The wound was treated with an alginate dressing and later on with a honey dressing. The edema was treated by compression. There was no effect. After a month we started treating the wound with topic haemoglobin. It was sprayed on the wound twice a week. In the following 4 months the wound healed, even though the patient suffered sickle cell crises 4 times. She was also admitted at the ICU. After 131 days the wound was almost closed, apart from a few very small defects. The patient was very happy and moved back to Brazil.

**XII. [EPS19] USE OF TOPICAL HAEMOGLOBIN IN POSTTRAUMATIC WOUND WITH EXPOSED HARDWARE**

Marin Marinovid, Josip Spanjol, Davor Primc, Stanislava Laginja, Nera Fumid, Bore Bakota, Branka Spehar, Eva Smokrovic, Aldo Ivancic. University Hospital Rijeka; Ogulin, Karlovac & Home Healthcare and Rehabilitation

**Aim:** We present a patient with chronic posttraumatic wound in the lower leg. The patient was injured in a road accident as a driver of a motor scooter. Immediately after trauma locking plate osteosyntesis was performed. Two months after surgical treatment, there is a skin and subcutaneous tissue defect in the surgery area with exposed hardware material.

**Method:** We performed wide debridement and lavage of the wound. Topically haemoglobin spray was applied with a gauze as a secondary dressing.

**Results/Discussion:** After admittance in the surgical practice, sharp debridement was performed by which we have removed cellular debris and traces of fibrin deposits. Abundant lavage with saline was done. Tissue sample for microbiological diagnostics were taken. We applied topically hemoglobin spray on the wound. We recommended, to the patient, daily application with prior toilette. To the following control patient came after seven days, when we spotted wound contractions, with the appearance of healthy granulation that filled the wound. The edges of wound began the epithelialization. During next seven days the whole defect is epithelialized. The surrounding skin had proper colour and was euthermic. Control laboratory tests were within reference range. Medical examination after two months showed properly healed wound.

**Conclusion:** Using topical haemoglobin spray we increased oxygenation of tissue in the wound. This stimulated the creation of a “healthy” granulation tissue that completely filled the defect and allowed the epithelialization from the wound edges. The increased amount of oxygen in the wound must have played a significant part in controlling bacterial colonization.
[EP520] IS AMPUTATION THE ONLY SOLUTION FOR THE DIABETIC FOOT?
Stanislava Laginja, Marin Marinovid, General Hospital of Ogulin & University Hospital Rijeka

Aim: Diabetes mellitus is one of the leading public health problems in the world. Diabetics have 20 fold risks for the amputation of lower extremities than a general population. Based on the epidemiological studies, it is estimated that 25 % of all patients with the diabetes acquire the diabetic foot with ulceration, and 5-15 % will undergo the amputation. Hyperbaric oxygen therapy (HBOT) has been promoted as an effective treatment for the diabetic foot wounds.

Method: We want to show the young man who is work-capable and who was supposed to undergo an amputation of the lower extremity. He was in the hyperbaric oxygen chamber twice. Despite the HBOT, the local state of our patients wound did not improve. On the contrary, it got worse so we decide to employ a local treatment.

Results/Discussion: Every day we did a tedious wound debridement, and we used the NPWT a few times. We continued the treatment with bioinclusive dressings and the topical haemoglobin. After applying the topical haemoglobin, we noticed that the wound began to heal much faster and that the pain was greatly reduced. But the most important thing was that our patient did not have to undergo the amputation that was proposed from the very beginning.

Conclusion: Despite the sophisticated treatments we developed, there are still lots of amputations of the lower extremities due to the diabetic foot. We should therefore use the modern techniques of treatment and all of our available funds for this cause, because most of the patients who undergo the amputation are young people who can still contribute a lot to our society.

Harrogate 2015

Using topical haemoglobin spray as an adjunct to standard care in non-healing complex wounds
Alexandra Whalley, Advanced Podiatrist, Bolton NHS Foundation Trust

Aim: To evaluate enhanced oxygen diffusion in wound healing through topical application of haemoglobin spray in the treatment of two non-healing wounds where standard care has failed.

Method: Two patients with non-healing ulcers which had failed to improve despite standard care had their wounds reviewed. After assessment, topical haemoglobin spray was added with a view to kick-starting the healing process by improving the oxygen level in the wound bed.

Results: At week 12, the wound had healed and remains stable.

Conclusion: Topical haemoglobin proved an effective adjunct to standard therapy in the management of non-healing diabetic foot ulcers, improving not only the clinical outcomes but also the quality of life issues affecting the individual patients.

Accelerate wound healing of acute and chronic wounds in patients with Diabetes: Experience from Mexico using supplementary haemoglobin spray. Obdulia Lopez Lopez, Peter Engels, Fredrik Elg

Introduction: Wounds normally heal in an orchestrated mode and the underlying complex processes take place in well-regulated and overlapping phases (haemostasis, inflammation, proliferation and remodelling) and most of these processes need a sustained amount of oxygen. Patients with diseases like diabetes, chronic venous insufficiency or arterial occlusive disorder frequently develop chronic wounds as one common problem in such patients is the insufficient supply of oxygen to the affected tissue. Consequently, one recent focus in the field of wound care relates to the increased demand of oxygen in every wound healing phase. In addition to the accurate management of the underlying disease, oxygen supply at the wound side should be considered as important part of modern wound management.

There are several approaches available to provide additional oxygen topically to the wound area. One of the most recent developments is to facilitate oxygen diffusion at the wound area by applying purified haemoglobin, leading to an increased oxygen availability in the wound bed.
**Method and summary of results:** In total 15 patients with 19 wounds were analysed, all patients provided written informed consents was obtained prior to the treatment. Average baseline wound size was 46 cm²/41 cm³, median 26.3 cm²/19 cm³ and average treatment period was 91 days (14 weeks), median was 87 days (12 weeks). Average of wound dressing changes was 16 (median 16), and 15 haemoglobin applications (median 14). Frequency of haemoglobin application and dressing changes were initially three times per week or twice per week during the first days or weeks, and later reduced to weekly. Of the 15 patients, 14 achieved wound closure, in one case wound healing was not completed while therapy is still ongoing. In 6 cases amputation was prevented. Average cost per patient and overall treatment was €197 (£141) corresponding to €9,30 (£6.70 per dressing change). No adverse events related to the treatment with the haemoglobin spray were reported.

**Discussion:** Early implementation of Graulox® in ulceration in diabetics may help prevent development of chronic wounds and / or amputation. Further studies are desirable to further evidence the beneficial effect of Granulox® in wounds at risk to develop a wound healing disturbance.

**Conclusions:** Recommendation: Haemoglobin spray is an effective adjunctive therapy option for acute and chronic wounds in patients with diabetes, based on excellent tolerability. In all cases, the haemoglobin spray was well tolerated and no adverse effects were reported. Effective facilitation of healing at all stages can be applied during all wound healing phases in combination with most of the wound rinsing solutions and dressings. Cost effective: Total costs for materials used per patients were €197 (£141), with a median of €132 (£95), or €9,30 (£6.70) per dressing change (€7.50/£5.40 median).

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**THE USE OF A NOVEL HAEMOGLOBIN SPRAY TO PROMOTE HEALING IN CHRONIC WOUNDS**

**Eleanor Wakenshaw, Tissue Viability Nurse, and Ruth Ropper, Lead Nurse Tissue Viability, NHS Lothian, Scotland**

**Background:** Chronic wounds present a huge burden to the NHS; these include pressure ulcers, leg ulcers and diabetic foot ulcers. Many intrinsic and extrinsic factors impact on wound healing. One of these is hypoxia, the lack of oxygen to the wound bed. This can lead to the wound entering a pro-inflammatory phase which delays the healing process. Research has shown that improving the oxygen available to the wound can stimulate wound healing but it has been difficult to achieve in practice. A novel product, Granulox®, offered the opportunity to assess if introducing oxygen to the wound by topical application of a haemoglobin spray could stimulate wound healing. Granulox® is an aqueous solution containing haemoglobin molecules which is delivered via a non-aerosol based spray. The haemoglobin molecule can bind oxygen from the atmosphere, transport it and then release it into the wound bed where oxygen levels are low. This increases tissue oxygen levels and stimulates the healing process The haemoglobin is not ‘used up’, so this step constantly repeats itself, allowing large quantities of oxygen to brought to the wound bed over a period of 72 hours.

**Method:** 10 patients with wounds, of different aetiologies, were treated with the Granulox® over a period of 8 - 15 weeks. Photographs and wound measurements were obtained at base line. Granulox® was applied and an appropriate secondary dressing used depending on exudate levels. The treatment was applied twice weekly. Further photographs and measurements were obtained at intervals of 2 weeks, 4 weeks and at the end of evaluation period.

**Results** Of the 10 patients who started the evaluation, 8 patients finished with 2 patients excluded from the results as they did not follow the treatment plan. Four patient examples are shown. Outcomes:

- 1 healed;
- 5 progressed towards healing;
- 2 became infected and stopped treatment.

An unexpected, but positive, result was that some patients showed a marked reduction in pain. For these patients this had become a chronic problem impacting on their quality of life.

**Discussion and Conclusions:** 75% of the patients in this small study showed significant progress towards wound healing with one person experiencing complete healing. Patients reported a reduction in pain resulting in the perception of their overall health being improved. Due to the simplicity of applying the Granulox® spray, several patients were able to apply the treatment themselves. This small study shows how a novel haemoglobin spray can significantly impact the lives of people living with chronic wounds including:

- Improving healing rates
- Supporting patient self management and empowering them to take control of their care.
• Reducing pain associated with chronic wounds. There is the potential to reduce long term costs to the healthcare system for wound treatments and possibly analgesics due to reduced pain.

**Recommendation:** Larger studies of patients with chronic wounds using Granulox®. This would confirm that patient outcomes around healing and quality of life could be significantly improved.

**Benefits Of Utilising Topical Haemoglobin Therapy On 100 Sloughy Wounds Within The Community Setting.** Sharon Dawn Hunt, Advanced Nurse Practitioner, South Tees NHS Foundation Trusts.

**Abstract:** Sloughy tissue containing viscous, malodourous, devitalized cells is renowned for being time consuming to manage, often needs specialist input within its removal and has a devastating effect upon patient’s daily activities as a consequence of maceration, malodours and pain.

**Method:** 100 sloughy wounds were administered a haemoglobin spray add-on therapy over a four week period. Normal standard wound cleansing and dressing regimens were continued as per pre-evaluation with wound care being provided independently or with supervision/support from a designated carer. Data was collected weekly in relation to primary outcomes of slough reduction; wound surface area reduction, patient ease of self-care use and overall product experience.

**Results:** At four weeks all wounds had demonstrated slough elimination (100%), continued wound size reduction (99%). 100% of patients and carers found Granulox® easy to use (self-caring) and had a positive wound care experience.

**Conclusion:** The administration of a haemoglobin spray to sloughy wounds resulted in positive healing outcomes of slough elimination and wound reduction alongside positive self-care and product and treatment satisfaction.

**Diabetic Foot Ulceration – Positive Outcomes Utilising Topical Haemoglobin Spray** Sharon Dawn Hunt, Advanced Nurse Practitioner, South Tees NHS Foundation Trusts.

**Abstract:** Diabetic foot ulceration (DFU) is common and notoriously difficult to manage, in a large part to poor oxygenation. An evaluation an acute clinical setting of Granulox® haemoglobin spray to improve wound oxygenation was conducted in a cohort of 20 patients with chronic (>12 weeks) DFU.

**Results:** Standard wound care was undertaken by 18 health professionals with no changes to products, devices or practice before evaluation. All wounds received the addition of the product on eight set occasions over a four-week period. At four weeks all wounds had demonstrated positive wound reduction, reduced pain, slough elimination, had no adverse events, and all patients and clinicians found the product acceptable and easy to use. At a further 4-week review no patients wounds had regressed.

**Conclusion:** The incorporation of a haemoglobin spray solution within this cohort of DFU resulted in a positive improvement in wound healing and slough elimination and is supportive of recent consensus guidelines suggesting Granulox® haemoglobin spray to be offered to DFU patients not substantially healed within 2-4 weeks of standard care alone.
Role of oxygen in wound healing


Wound repair is a quiescent mechanism to restore barriers in multicellular organisms upon injury. In chronic wounds, however, this program prematurely stalls. It is known that patterns of extracellular signals within the wound fluid are crucial to healing. Extracellular pH (pHe) is precisely regulated and potentially important in signaling within wounds due to its diverse cellular effects. Additionally, sufficient oxygenation is a prerequisite for cell proliferation and protein synthesis during tissue repair. It was, however, impossible to study these parameters in vivo due to the lack of imaging tools. Here, we present luminescent biocompatible sensor foils for dual imaging of pHe and oxygenation in vivo. To visualize pHe and oxygen, we used time-domain dual lifetime referencing (tdDLR) and luminescence lifetime imaging (LLI), respectively. With these dual sensors, we discovered centripetally increasing pHe-gradients on human chronic wound surfaces. In a therapeutic approach, we identify pHe-gradients as pivotal governors of cell proliferation and migration, and show that these pHe-gradients disrupt epidermal barrier repair, thus wound closure. Parallel oxygen imaging also revealed marked hypoxia, albeit with no correlating oxygen partial pressure (pO2)-gradient. This highlights the distinct role of pHe-gradients in perturbed healing. We also found that pHe-gradients on chronic wounds of humans are predominantly generated via centrifugally increasing pHe-regulatory Na+/H+-exchanger-1 (NHE1)-expression. We show that the modification of pHe on chronic wound surfaces poses a promising strategy to improve healing. The study has broad implications for cell science where spatial pHe-variations play key roles, e.g. in tumor growth. Furthermore, the novel dual sensors presented herein can be used to visualize pHe and oxygenation in various biomedical fields.


While the importance of oxygen to the wound healing process is well accepted, research and technological advances continue in this field and efforts are ongoing to further utilize oxygen as a therapeutic modality. In this paper, the authors briefly review the role of oxygen in wound healing and discuss the distinct mechanism of action as well as the advantages and disadvantages of the three major oxygen-based therapies currently in clinical use (Hyperbaric Oxygen and Topical Oxygen and Continuous Diffusion of Oxygen), as well as review the existing literature regarding these distinct therapeutic modalities.


Disturbances to healing observed under hypoxic conditions have given insights into the roles of oxygen. Wound hypoxia is more prevalent than generally appreciated, and occurs even in patients who are free of arterial occlusive disease. There is a strong scientific basis for oxygen treatment as prophylaxis against infection, to facilitate wound closure, and to prevent amputation in wounded patients. This article reviews extensive data from preclinical and human trials of supplemental inhaled oxygen, hyperbaric oxygen, and topical oxygen treatment. Oxygen supports biochemical metabolism and cellular function, and has roles in combating infection and facilitating the wound healing cascade.

Oxygen is a prerequisite for successful wound healing due to the increased demand for reparative processes such as cell proliferation, bacterial defence, angiogenesis and collagen synthesis. Even though the role of oxygen in wound healing is not yet completely understood, many experimental and clinical observations have shown wound healing to be impaired under hypoxia. This article provides an overview on the role of oxygen in wound healing and chronic wound pathogenesis, a brief insight into systemic and topical oxygen treatment, and a discussion of the role of wound tissue oximetry. Thus, the aim is to improve the understanding of the role of oxygen in wound healing and to advance our management of wound patients.


Topical oxygen therapy provides another tool in the armamentarium of clinicians treating refractory lower extremity wounds. Devices suitable for providing topical oxygen therapy in a clinical setting have recently become available. This article reviews the evidence to justify the use of this treatment modality, including in vitro, preclinical data, and clinical data. It also provides a protocol for how to administer topical oxygen therapy as well as guidance on patient selection and management to optimize outcomes. Randomized controlled trials are not yet reported and clearly necessary. The current body of evidence suggests that topical oxygen therapy may be considered as a second line of therapy for refractory wounds.


The state of wound oxygenation is a key determinant of healing outcomes. From a diagnostic standpoint, measurements of wound oxygenation are commonly used to guide treatment planning such as amputation decision. In preventive applications, optimizing wound perfusion and providing supplemental O(2) in the perioperative period reduces the incidence of postoperative infections. Correction of wound pO(2) may, by itself, trigger some healing responses. Importantly, approaches to correct wound pO(2) favorably influence outcomes of other therapies such as responsiveness to growth factors and acceptance of grafts. Chronic ischemic wounds are essentially hypoxic. Primarily based on the tumor literature, hypoxia is generally viewed as being angiogenic. This is true with the condition that hypoxia be acute and mild to modest in magnitude. Extreme near-anoxic hypoxia, as commonly noted in problem wounds, is not compatible with tissue repair. Adequate wound tissue oxygenation is required but may not be sufficient to favorably influence healing outcomes. Success in wound care may be improved by a personalized health care approach. The key lies in our ability to specifically identify the key limitations of a given wound and in developing a multifaceted strategy to specifically address those limitations. In considering approaches to oxygenate the wound tissue it is important to recognize that both too little as well as too much may impede the healing process. Oxygen dosing based on the specific need of a wound therefore seems prudent. Therapeutic approaches targeting the oxygen sensing and redox signaling pathways are promising.


Acute wounds are initially hypoxic. This state triggers the diffusion of oxygenated plasma from the surrounding intact tissue to the hypoxic area, and sets in train processes resulting in oxidative killing, angiogenesis and collagen synthesis.


Background: The presence of oxygen is necessary for normal wound healing. Oxygen has been given as a therapeutic modality to assist and speed wound healing.

Objective: The objective was to summarize the role of oxygen in wound healing.
**Materials and Methods:** A literature review of clinical and basic science studies regarding oxygen and wound healing was conducted.

**Results:** Hypoxia appears to jump start wound healing via hypoxia-inducible factor 1alpha and re-epithelialization. Nonetheless, oxygen is often required to start or sustain other wound healing processes.

**Conclusion:** Both the absence and the presence of oxygen have effects on wound healing; however, its role is not completely understood. Although hyperbaric oxygen and topical oxygen therapy have been described in aiding wound healing, case-controlled prospective studies are lacking and evidence for their efficacy is inconsistent. The authors have indicated no significant interest with commercial supporters.


We sought to review the role of oxygen in wound healing, with an emphasis on the role tissue oximetry has played in clinical advances in the care of patients with wounds. Oxygen is required for wound healing. Hypoxia sufficient to impair healing is common in wounds, frequently resulting from sympathetically induced vasoconstriction. Correction or prevention of vasoconstriction, as well as provision of increased inspired oxygen in well-perfused patients, has been shown in randomized, controlled clinical trials to improve wound outcomes. Our understanding of the role of oxygen in wound healing has been fueled by tissue oximetry. Advances in technology will lead to further advances in the management of patients with wounds.


This article provides an overview of the role of oxygen in wound healing. The understanding of this role has undergone a major evolution from its long-recognized importance as an essential factor for oxidative metabolism, to its recognition as an important cell signal interacting with growth factors and other signals to regulate signal transduction pathways. Our laboratory has been engaged in the study of animal models of skin ischemia to explore in vivo the impact of hypoxia as well as the use of oxygen as a therapeutic agent either alone or in combination with other agents such as growth factors. We have demonstrated a synergistic effect of systemic hyperbaric oxygen and growth factors that has been substantiated by Hunt’s group. Within the past 10 years research in the field of wound healing has given new insight into the mechanism of action of hypoxia and hyperoxia as modifiers of the normal time-course of wound healing. The article concludes with a discussion of why hypoxia and hyperoxia intercurrently play an important role in wound healing. Hypoxia-inducible factor 1 is crucial in that interplay.


Hypoxemia, caused by disrupted vasculature, is a key factor that limits wound healing. Correcting hypoxemia through the administration of supplemental oxygen (O(2)) can have significant beneficial impact on wound healing in the perioperative and outpatient settings. Beyond its role as a nutrient and antibiotic, O(2) may support vital processes such as angiogenesis, cell motility, and extracellular matrix formation. Recent discoveries highlight a novel aspect, addressing the role of O(2) in wound healing via the production of reactive oxygen species (ROS). Almost all wound-related cells possess specialized enzymes that generate ROS (including free radicals and H(2)O(2)) from O(2). Defect in these enzymes is associated with impaired healing. Low wound pO(2) is expected to compromise the function of these enzymes. At low concentrations, ROS serve as cellular messengers to support wound healing. The use of systemic hyperbaric O(2) therapy presents potential advantages, as well as risks. There is evidence to suspect that the use of pressure and systemic pure O(2) may not be essential in wound care. Elimination of these factors by using sub-pure systemic O(2) under normobaric conditions may significantly minimize the risk of O(2) toxicity. Furthermore, opportunities to treat dermal wounds using topical O(2) therapy warrant further investigation. Given that many growth factors require ROS for their function, it is reasonable to assume that approaches to correct wound pO(2) will serve as an effective adjunct in treating chronic wounds.
Facilitated diffusion by haemoglobin


Oxygen transport behavior in erythrocyte suspension or in hemoglobin solution was studied as a potential therapeutic model for the clinical treatment of blood loss, and this can also provide physiological data with which to evaluate blood substitutes. In the present project, we examined the in vitro kinetics of hemoglobin binding to and releasing oxygen, to provide detailed oxygen-flux measurements for unmodified hemoglobin solutions and erythrocyte suspensions in human, as well as other vertebrates. An in vitro method was used, based on a widely used artificial system, with the oxygen saturation level being detected in real time. Results from this study indicated that the kinetic curves of human erythrocyte suspensions and hemoglobin solutions were either S-shaped or hyperbolic, respectively. Based on these curves, the significance of T(50) emerged in our investigation, where T(50) is defined as the time needed for 50% hemoglobin to be saturated with oxygen, and reflects the efficiency with which hemoglobin carries oxygen. This parameter may be used to diagnose blood diseases, and could be a standard for evaluating blood substitutes. In this study, we also compared the T(50) of 4 species of vertebrates, and found that it shows a distinct efficiency of oxygen binding related to species, and potentially reveals the evolutionary function of hemoglobin and its possible adaptation to the environment.


Oxygen transport behavior of erythrocyte/extracellular hemoglobin mixtures flowing in microvessels was studied as a model of hemoglobin-based oxygen carrier (HBOC) performance. An experimental in vitro 25-microm-diameter capillary model was used to provide detailed oxygen flux measurements for hemoglobin solutions, erythrocyte suspensions, and erythrocyte/hemoglobin solution mixtures. The experimental apparatus includes computerized data acquisition and control coupled to a dual wavelength microspectrophotometer. This apparatus had been previously validated by good agreement of experimental measurements with predictive mathematical models of oxygen transport for either erythrocyte suspensions or hemoglobin solutions. The experimental methodology was extended to measurement of oxygen transport in erythrocyte/hemoglobin solutions. The hemoglobin solutions consisted of either purified or gluteraldehyde polymerized bovine hemoglobin. Dose-response plots were generated by varying the extracellular to intracellular hemoglobin ratio while holding the overall hemoglobin concentration constant. Measurements were also made on unmixed erythrocyte suspensions and hemoglobin solutions to generate limiting cases for comparison. Direct comparison of experimental results showed that both types of hemoglobin solutions were substantially more efficient than erythrocyte suspension in uptake and release of oxygen. Increased extracellular hemoglobin concentration increased oxygen transport efficiency for both uptake and release, even when total hemoglobin concentration was held constant. When only 10% of the total hemoglobin was extracellular, approximately half of the increased efficiency of pure hemoglobin solutions was reached. When 50% of the total hemoglobin was extracellular, the increased efficiency was virtually equal to that of pure hemoglobin solutions.


The basic equations for the simultaneous diffusion and chemical reactions of oxygen and hemoglobin in a film at steady state were solved assuming that the total oxygen flux was the sum of the flux by plain diffusion and that by diffusion of oxyhemoglobin. After collecting and scrutinizing the pertinent numerical data, particularly for the diffusion coefficients of oxygen and hemoglobin, numerical solutions were obtained by computer for a variety of conditions. It appeared that the gradients of oxygen and oxyhemoglobin across the slab were notably different from those stipulated for the attainment of chemical equilibrium. In particular we found that there must be a minute step in the oxygen gradient at the low pressure side with a slope equal to that at the high pressure side because of the boundary condition that the two surfaces must be impermeable for hemoglobin, and that the
saturation is higher at the low pressure side and lower at the high pressure side than at chemical equilibrium. When assuming mean values from available data for the diffusion coefficients of oxygen and hemoglobin we arrived at excellent agreement between the computed fluxes and those obtained experimentally by other authors. It is concluded that the facilitation of oxygen diffusion in the presence of hemoglobin can be described quantitatively when the chemical reactions are taken into account.


Summary: A study has been made of steady state diffusion of air at various pressures through hemoglobin solutions. Whereas nitrogen diffused in proportion to the pressure, the rate of oxygen transport was greatly enhanced and seemingly proceeded by means of two processes which are additive. One is a regular diffusion through the solvent (water), which is proportional to the pressure; the other is a specific transport mediated by the hemoglobin molecules. The rate of the latter is constant over a wide pressure range, and the process may at low tensions transport over eight times more oxygen than does straight diffusion. Preliminary studies have established that myoglobin and a few other pigments in vitro have the same property.
### Revision history:

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