Granulox® (topical haemoglobin spray): a review of the scientific and clinical data

Philip Davies, Senior Global Medical Affairs Manager (Medical and Economic Affairs Department), Mölnlycke Health Care

Mölnlycke®

CONTENTS

Declaration of interest

This white paper has been written by Philip Davies, an employee of Mölnlycke Health Care. It has not been subject to double-blind peer review.

About the author

Philip Davies has more than 30 years of experience of working in healthcare-related industries. During that time, he has authored and contributed to numerous peer-reviewed journal articles and conference presentations (oral and poster) relating to wound care and other areas of healthcare. Philip was awarded a BSc (Hons) Medical Cell Biology and Biochemistry by the University of Liverpool (United Kingdom) in 1989.

www.molnlycke.com
Mölnlycke Health Care AB, Box 13080, GamlestadsvägenSE-402 52 Göteborg, Sweden. Phone + 46 31 722 30 00.

Document reference: GMAS-2019-062-01

ABSTRACT

Background

Oxygen is an important requirement for wound healing pathways. In a chronic, non-healing wound, the wound bed is persistently hypoxic, therefore supplying additional oxygen may help promote healing. Topical oxygen therapies (TOT) deliver oxygen directly to the wound tissue to facilitate the healing process and can help to reverse localised hypoxia within a wound. There are several types of TOT products available. One TOT product, Granulox®, delivers haemoglobin in spray form to the wound bed, where it binds environmental oxygen which can then diffuse into the wound bed tissue. Increased levels of oxygen in the hypoxic wound bed tissue help to promote wound healing.

Aims

A literature review was undertaken to identify and summarise scientific and clinical research data relating to the use of Granulox as an integral component of wound management regimes.

Methods

The MEDLINE (National Library of Medicine, Bethesda, United States of America) and EMBASE (Elsevier BV, Amsterdam, Netherlands) bibliographic databases were searched. In addition, abstract books and proceedings documents relating to national and international conferences were scanned in order to identify presentations (oral, e-poster, poster) of relevance to the review.

Results

The literature review identified thirty nine peer-reviewed journal articles and nine conference presentations that made specific reference to the use of Granulox, and included two systematic reviews / meta-analyses, one randomised controlled trial (RCT), four interventional clinical studies (plus two health economic study based on the findings of two interventional clinical studies), fourteen observational clinical studies, sixteen case study / case study series, one pre-clinical study and seven expert reviews. The wound types referred to in the identified references were burns, foot ulcers, leg ulcers, pressure ulcers, surgical and traumatic wounds, and were predominantly chronic, non-healing wounds.

Conclusion

The research data referred to in this review strongly indicate that the inclusion of Granulox in wound care regimes facilitates the significant reduction of wound size or complete wound closure of chronic, non-healing wounds. Granulox is reported to be safe and easy to use, and offers a cost-effective adjunctive therapy to standard wound care treatment.

BACKGROUND

Role of oxygen in wound healing

Oxygen is critically important for wound healing processes, e.g. angiogenesis, revascularisation, synthesis of connective tissue, and resistance to infection. Typically, wounds are hypoxic at their centre, with an increasing oxygen gradient towards the intact tissue[1]. Hypoxia may be due to increased demand, as a result of the high metabolic activity of a healing wound, but may also be affected by the partial oxygen pressure of the surrounding tissue and circulating blood supply, e.g. injured microcirculation, diffusive constraints due to oedema, poor blood circulation (peripheral arterial disease (PAD)), or oxygen consumption by bacterial biofilm. Although, initially, hypoxia acts as a signal to stimulate the wound healing process, prolonged hypoxia is detrimental to healing progression[2 3]. Chronic wounds have been shown to have a sustained oxygen deficit at the wound bed, with a concomitant detrimental effect on wound healing[4]. The delivery of oxygen, either intrinsically from the blood supply, or extrinsically via oxygen therapy, to a chronic wound is therefore a vital therapy to facilitate wound healing progression.

Key points

- Oxygen is an important requirement for wound healing pathways.
- The wound bed of a chronic, non-healing wound is persistently hypoxic.
- Initially, hypoxia acts as a signal to stimulate the wound healing process; however, persistent hypoxia is detrimental to healing progression.
- Supplying additional oxygen to the chronic wounds may help promote healing.

Topical oxygen therapy

The first topical oxygen therapy (TOT), hypobaric oxygen therapy (HBOT) was first used in the field of wound care in the 1960s, but today HBOT is not widely available[3]. However, there are portable TOT products that can be used to administer oxygen to wounds, either topically over the injured tissue or by continuous or pressurised delivery systems[2 3 4]. This topical approach aims to generate an increase in oxygen at the wound site, facilitating the reversal of localised hypoxia, but unlike systemic oxygen therapy, e.g. HBOT, topical oxygen does not rely on the vascular system to deliver the oxygen to the wound site. TOT, as an adjuvant to standard wound care, provides a positive option to augment the management of chronic, non-healing wounds.

Key points

- TOT delivers oxygen directly to the wound tissue to facilitate the healing process.
- Topical oxygen can help to reverse localised hypoxia within a wound.
- Several types of TOT products are available.

Granulox (topical haemoglobin spray)

Granulox is a topical haemoglobin spray which improves the oxygen supply to chronic wounds through simplified diffusion, thereby supporting wound healing. When Granulox is applied to the wound bed, the haemoglobin binds oxygen from the surrounding air and transports it to the wound bed where it diffuses into the cells. As stipulated in the instructions for use supplied with the product, Granulox is indicated for the treatment of chronic wounds such as venous, arterial, and mixed leg ulcers, diabetic foot ulcers, pressure ulcers and the secondary healing of surgical wounds. It can also be used on sloughy and infected wounds.

Key points

- Granulox is a topical haemoglobin spray.
- Granulox helps improve the oxygen supply to chronic wounds to promote wound healing.

AIMS

When making decisions about clinical interventions, it is common practice to consider the relative weight of the available research data, according to the type and quality of studies from which they originate. In this so-called hierarchy of clinical evidence (Figure 1), randomised controlled trials (RCTs) and systematic reviews are considered to be the 'gold standards' for judging the benefits of interventions.[5,6]

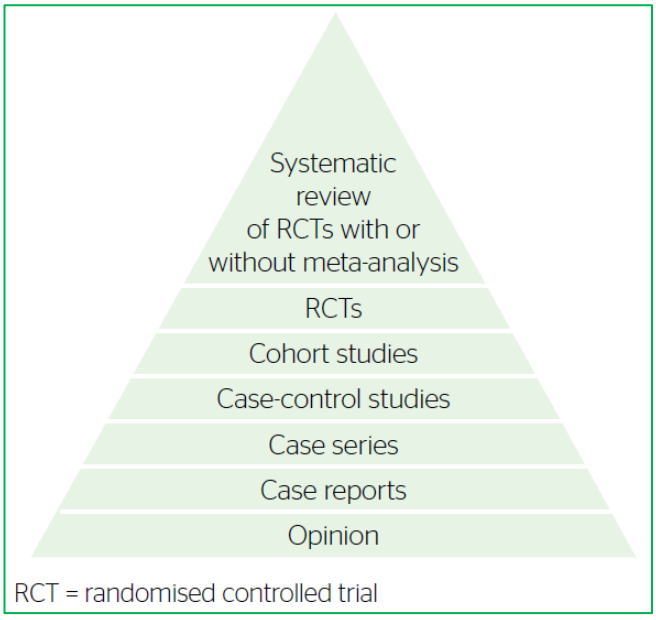


Figure 1. Hierarchy of clinical evidence (adapted from Akobeng, 2005[6])

While the conventional approach to evidence-based medicine is to use data from RCTs, many practitioners question their relevance in the field of wound area. Practice-based medicine is favoured and allows flexibility as the choice of intervention is based on the individual patient.[7,8,9,10,11] While this does not mean that all research data are equally valid, it does signify that all available evidence should be considered and evaluated.

With this in mind, this document considers scientific and clinical data from across the entire evidence hierarchy. It is not a systematic review but aims, instead, to summarise the available evidence.

Key points

- Evidence-based practice should reflect all types of evidence.
- This document aims to summarise all the evidence generated from clinical and scientific studies relating to the use of Granulox.

METHODS

An extensive literature search was undertaken to identify published articles citing scientific and clinical data in relation to the use of Granulox. Electronic searches of bibliographic databases MEDLINE (National Library of Medicine, Bethesda, United States of America) and EMBASE (Elsevier BV, Amsterdam, Netherlands) and specialist websites – Cochrane Library, World Wide Wounds – were performed to identify published articles of relevance. The search ranged from January 2010 to October 2020, covering the period when Granulox was developed and has been subsequently marketed. The following search terms were used: 'Granulox' OR 'haemoglobin spray' OR 'topical haemoglobin'. In addition, abstract books and proceedings documents from national and international conferences of relevance to wound care held since 2010 (Box 1) were scanned to identify relevant presentations:

Box 1. Wound care conferences

- World Union of Wound Healing Societies (WUWHS) Congress
- Symposium on Advanced Wound Care (SAWC)
- Wound Ostomy and Continence Nurses (WOCN) Society Conference
- Association of Perioperative Registered Nurses (AORN) Conference
- European Wound Management Association (EWMA) Conference
- European Tissue Repair Society (ETRS) Meeting
- European Burns Association (EBA) Congress
- Wounds UK Conference
- Conference Nationale des Plies et Cicatrisations
- Simposio Nacional Ulceras por Presion y Heridas Cronicas
- Associazione Italiana Ulcere Cutanea Conference

Key points

- Bibliographic databases were searched for relevant research articles.
  Abstract books and proceedings documents from specialist conferences were scanned to identify relevant presentations (oral, e-poster, poster).

RESULTS

The literature search identified thirty nine peer-reviewed journal articles and nine conference presentations that make specific reference to the use of Granulox (Table 1).

Table 1. Literature search results

Type	Number
Evidence communication type	
Peer-reviewed articles	39
Conference presentations (oral, e-poster, poster)	9
*Wound types referred to in evidence communications**	
Burn	8
Foot ulcer	19
Leg ulcer	22
Pressure ulcer	10
Surgical wound	14
Traumatic wound	12
Study types referred to in evidence communications[+]	
Meta-analysis / systematic review	2
Randomised controlled trial (RCT)	1
Interventional clinical studies (including 2 economic studies based on results of clinical studies)	6
Observational clinical studies	14
Case study series / case study	16
Pre-clinical study (*in vitro* / *in vivo*)	1
Expert opinion (narrative review / commentary / survey / audit)	7

*Numbers of wound types are greater than the numbers of evidence communication types as some communications refer to multiple wounds types

[+]Numbers of evidence communication types are greater than the numbers of study types as the details of one RCT have been published in two journal articles

Meta-analyses and systematic reviews

The literature search identified one systematic review and one meta-analysis. In the systematic review, Hu et al[12] reviewed two RCTs, three historical controlled studies, and 14 case series studies, and concluded that topical haemoglobin (Granulox) promoted the healing of several wound types (burn, leg ulcer, foot ulcer, pressure ulcer, surgical or traumatic wound), and was especially efficacious in chronic, non-healing wounds. In addition, the ability of Granulox to eliminate slough and relieve pain indicated the potential for a new generation of debridement technology. Its ease of use was considered to support patient self-management, with the associated benefit of reduced health-care costs.

Elg & Hunt[13] performed a meta-analysis of three published studies[16 17 20] to determine the relative healing benefit of Granulox across three wound types: diabetic foot ulcer, chronic wounds and sloughy wounds (the latter two types included burns, foot ulcers, leg ulcers, pressure ulcers, surgical wounds and traumatic wounds). In each study, Granulox plus standard care was associated with a significantly higher chance of healing for each wound type compared with standard care alone.

Table 2. Meta-analyses and systematic reviews

Reference	Design methodology	Main outcome measures	Main results
Hu et al, 2020[12]	Literature search (PubMed, Embase, Scopus, CENTRAL, CINAHL, and Web of science databases) Twenty studies met the eligibility criteria: 1 animal model study and 19 clinical studies.	Efficacy, scope, adverse reactions and required precautions of local haemoglobin therapy	Pre-clinical and clinical studies have demonstrated that topical haemoglobin therapy can promote the healing of various types of wounds, especially those that are chronic and non-healing Topical haemoglobin therapy can substantially reduce the quantity of slough in a variety of wounds and can relieve pain Topical haemoglobin therapy is simple to use and not limited by equipment and the therapeutic setting, which is conducive to patient self-management of the wound and has superior economic cost-effectiveness
Elg & Hunt, 2018[13]	Meta-analysis of three published studies (Hunt & Elg, 2016[20], Hunt & Elg, 2017[17], and Hunt et al, 2018[16]) to determine the relative healing benefit of Granulox across different wound types (diabetic foot ulcer, chronic and sloughy) Each wound type with >10 patients in both the Intervention (Granulox + standard care) and Control (standard care alone) groups (n = 257; 73% of patients) was evaluated	Reduction in wound size or wound closing over a 26-week treatment period	The use of Granulox is associated with a significantly higher chance of healing in each wound type: Cox proportional hazards log-rank regressions - Traumatic wound: 1.55 (1.23 - 1.96, n=110, p<0.001) Diabetic foot ulcer: 2.39 (1.52 - 3.75, n=60, p=0.01) Venous leg ulcer: 4.98 (1.69 - 14.7, n=33, p=0.04) Burn: 1.82 (1.11 - 2.99, n=30, p=0.02) Post-surgical wound: 2.75 (1.53 - 4.96, n=24, p=0.001)

Randomised controlled trials

The literature search identified one RCT that assessed the introduction of Granulox into the standard wound care regimen (nanofibre dressing, gauze fixation and short-stretch compression bandaging), as compared to standard care alone, in the treatment of chronic venous leg ulcers[14 15]. After 13 weeks of treatment, those wounds treated with the additional Granulox demonstrated an average 53% reduction in wound size, as compared to a slight increase in wound size in the control group.

Table 3. Randomised controlled trials

Reference	Design methodology	Main outcome measures	Main results
Arenbergerova et al, 2013[14,15] #	Venous leg ulcers (duration > 8 weeks) Intervention (n=36): Granulox plus standard care (short-stretch compression bandaging, nanofibre dressing with gauze fixation). Control (n=36): Sham treatment (physiological saline spray) plus standard care (short-stretch compression bandaging, nanofibre dressing with gauze fixation) Treatment duration: 13 weeks	Reduction in wound size or wound closure	Mean reduction in wound surface area in the Intervention group: 53%,(p<0.0001) vs mean increase in wound surface area in the Control group: 21%

#Study data used to forecast healing outcomes in Arenberger et al, 2015[28] (Observational clinical study)

Interventional clinical studies

The literature search identified four interventional clinical studies[16 17 18 19]. The studies assessed the effectiveness of Granulox when added to the standard wound care procedure in the treatment of sloughy[16], chronic[18 19] or hard-to-heal[17] wounds (burn, foot ulcer, leg ulcer, pressure ulcer, surgical wound, traumatic wound), as compared to a retrospective control of standard care alone. Each study reported significant wound size reduction, with >75% of wounds completely healed in the intervention group, as compared to the control group. In addition, all four of the studies observed that wounds treated with Granulox had reduced levels of slough, wound exudate, and pain.

Elg & Bothma[20] used real-life data from one of the interventional clinical studies[17] to demonstrate the cost-effectiveness of including Granulox in the standard care treatment regimen for hard-to-heal wounds (pressure ulcers, leg ulcers, diabetic foot ulcers, burns, surgical and traumatic wounds), as compared to standard care alone in a retrospective control. Dressing costs for the intervention group were £6953, with 874 cumulative weeks healed, as compared to £9547 and 278 cumulative weeks healed for the control group.

Brüggenjürgen et al[21], using real life data from another of the interventional clinical studies[19] in a Markov model, demonstrated a potential 40% reduction in overall wound care costs when Granulox was included in the treatment regimen for diabetic foot ulcers.

Table 4. Interventional clinical studies (economic studies, based on results of interventional clinical studies, are highlighted in grey)

Reference	Design methodology	Main outcome measures	Main results
Hunt et al, 2018[16]	Sloughy wounds (burn, foot ulcer, leg ulcer, pressure ulcer, surgical wound, traumatic wound) Intervention group: Granulox plus standard care, applied twice weekly. (n=100) Retrospective control group: Standard care. Twice weekly dressing changes (n=100) Treatment duration: 26 weeks	Wound healing over a 26-week treatment period	Wounds completely healed at 26 weeks: 94% Intervention group vs 63% Control group Mean wound size reduction: 98% Intervention group vs Control group 74% (p=0.002) Mean slough coverage of wound: 1% Intervention group vs 29% Control group (p<0.001)

Hunt & Elg, 2017[17]	Hard-to heal wounds (e.g. pressure ulcer, leg ulcer, diabetic foot ulcer, burn, surgical and traumatic) Intervention group: Granulox plus standard care (pre-evaluation dressing) applied twice weekly (n=50) Retrospective control group: Standard care. Twice weekly dressing changes (n=50) Treatment duration: 26 weeks	Wound healing over a 26-week treatment period	Wounds healed at 26 weeks: 90% (45 / 50) Intervention vs 38% (19 / 50) Control (p<0.001) Mean time to complete wound healing: 6.6 weeks (range 3-22-weeks) Intervention vs 11.4 weeks Control (range 3-25-weeks), (p=0.01)
Elg & Bothma, 2019[20]	A micro-costing analysis of wound dressing costs for the treatment of hard-to heal wounds (e.g. pressure ulcer, leg ulcer, diabetic foot ulcer, burns, surgical and traumatic), based on data from a real-life study (Hunt & Elg, 2017)[17] Prospective intervention group (n=50) received Granulox plus standard care and retrospective control group (n=50) received standard care alone	Cost-effectiveness and break-even analysis of Granulox as an adjunct therapy over a 26-week treatment period	Total dressing costs at 26 weeks: Intervention group - £6953 with 874 cumulative weeks healed vs control group £9547 with 278 cumulative weeks healed Incremental cost-effectiveness ratio (ICER) for Granulox, i.e. the incremental cost / additional week healed: negative (dominant) Total treatment costs per week were lower from week six onwards, with break-even estimated to be at week 10.2
Hunt, 2017[18]	Diabetic foot ulcer (duration >20 weeks) Intervention group: Granulox plus standard wound care (pre-evaluation dressing) applied twice weekly (n=20) Retrospective control group: Standard wound care (n=20) Treatment duration: 28 weeks	Wound closure after 28 weeks	Number of wounds completely healed at 28 weeks: 15 (Intervention group) vs 8 (Control group) (p=0.04) At 28 weeks, wounds in the Intervention group were reduced in size by 95% vs a 63% reduction in wound size in the Control group (p=0.02)
Hunt & Elg, 2016[19]	Chronic diabetic foot ulcer Intervention group (n=20): Granulox plus standard care (pre-evaluation dressing type with off-loading if required) applied twice weekly Retrospective control group (n=20): Standard care. Twice weekly dressing changes Treatment duration: 28 weeks	Reduction in wound size or wound closure over a 28-week treatment period	Reduction in wound size at 28 weeks: 95% (Intervention group) vs 63% (Control) (p=0.02)
Brüggenjürgen et al, 2018[21]	Chronic diabetic foot ulcer Analysis of the impact of topical haemoglobin contact spray on cost 28-week Markov model was programmed using data from a published real-life study (Hunt & Elg, 2016[19])	Total costs (dressing change related costs, therapeutic nursing care costs, potential antibiotic therapy, Granulox spray costs) over the period of 28 weeks for each treatment group	Total predicted average costs: Standard wound care plus Granulox = €1027 Standard wound care alone = €1737 Equivalent to 40% cost reduction

Observational clinical studies

The literature search identified fourteen observational studies. Two of the articles[22] [23] were not published in an English- speaking journal so no details of the studies are presented or discussed in this review. In a simulated study, Arenberger et al[24], using data from a RCT (Table 3)[14] [15], performed a post-hoc analysis with 25,000 simulated patients over a projected 12-month period, that forecast a more effective therapy when Granulox was included into a standard care treatment schedule for chronic venous leg ulcers than standard care alone, especially in non-healing or worsening wounds. This prediction is corroborated in eight of the studies[25] [26] [27] [28] [29] [30] [31] [32] that involved a variety of wound types (diabetic foot ulcer[25] [26] [27], leg ulcer[28] [29] [32], burn[28] [29], traumatic wound[28] [29],

surgical wound[28 29], pressure ulcer[30 31]), many being chronic or non-healing. All of the studies reported a positive reduction in wound size following treatment with Granulox and standard wound care management, with four of the studies[26 28 29 31] reporting significant numbers of healed wounds. In two of these studies[28 29], the wounds (leg ulcer, burn, surgical and traumatic wounds) at presentation were covered with slough (ranging from 10 – 100% of the wound bed), which can negatively impact on wound healing progression. Following treatment with Granulox, (3-weeks[28] and 5-weeks[29]), all wounds were slough-free. Petri et al[33 34], identified increased local oxygen saturation (StO_2) in chronic leg ulcer wound tissue following treatment with Granulox. Interestingly, increases in StO_2 varied between wounds, with those having an increase in StO_2 of greater than 10% exhibiting a significant decrease in wound size[33]. Granulox was reported as an easy-to-use product [27 28 29 35] , an especially important consideration in the concept of self-care, that helps patients engage with their healthcare needs, but also facilitates the reduction of the ever-escalating costs to the healthcare provider.

Table 5. Observational clinical studies

Reference	Design methodology	Main outcome measures	Main results
Petri et al, 2018[33]	Chronic venous leg ulcer (n=39), mixed leg ulcer (n=5), pyoderma gangrenosum or necrobiosis lipoidica (n=5). (Median wound duration: 27 months, range 2-126 months) Local oxygen saturation (StO_2) of each wound measured three times: 1. Five minutes prior to Granulox application. 2. Five minutes after Granulox application. 3. Twenty minutes after Granulox application Standard wound care received by all patients Follow-up assessment at 3-4 months	Tissue oxygenation levels Wound size reduction	After Granulox application, StO_2 increased within the wound on average from 66.1% to 71 % (p=0.017) after 20 minutes Patients divided into: StO_2 increase >10%: Responder StO_2 increase <10%: Non-Responder Wound size at follow-up significantly decreased in the Responder Group (p=0.001); no significant difference in the Non-Responder group (p=0.950)
Haycocks et al, 2016[25]	Non-healing diabetic foot ulcer (<20% reduction in wound size following a period of standard care (2 weeks - existing patients, or 4 weeks - new patients) (n=17) Granulox plus standard care (dressings used included adhesive, non-adhesive foams, hydrofiber, superabsorbents, antimicrobials) Treatment duration: 4 weeks	Percentage wound size reduction over the 4-week treatment period	Fourteen ulcers had reduction in wound size Mean percentage reduction in wound size: 53.8% (SD 26.6, range 11.9 - 100%)
Hunt, 2016[35]	Traumatic wound (n=20) Self-care of wounds using Granulox plus patient's normal dressing regimen, twice weekly Treatment duration: 4 weeks	Patient ease of (self-care) use of Granulox Overall product experience	100% (n=20) of self-harm behaviour patients were able to apply Granulox therapy independently 85% (n=17) said Granulox was easy to use and 15% (n=3) found it manageable 90% (n=18) found the experience excellent and 10% (n=2) deemed it good
Hunt et al, 2016[26]	Chronic diabetic foot ulcer (n=13, 15 wounds) Continuation of Haycocks et al, 2016 [25] Granulox plus standard care Treatment duration: Up to 12 weeks	Progression towards healing	After 12 weeks of treatment: - 3 wounds (20%) healed - 8 wounds (53%) had progressed towards healing - 1 wound (7%) was healing slowly - 3 wounds (20%) increased in size
Marinovic et al, 2016[22]	Traumatic and surgical wound	This article is not in English - English abstract contains no relevant information	

Petri, 2016[34]	Chronic leg ulcer (n=5) (duration > 8-weeks) Local oxygen saturation (StO_2) of wound measured three times: - Prior to application of Granulox - Five minutes after Granulox application - Twenty minutes after Granulox application	Oxygen saturation	After Granulox application, average StO_2 significantly increased within the wound: - Before Granulox application: StO_2 = 56.4%. - Five minutes after application: StO_2 = 69 % (p=0.042) - Twenty minutes after application: StO_2 = 78.8% (p=0.043)
Arenberger et al, 2015[24]	Venous leg ulcer (n=72) Linear regression model 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) (Arenbergerova et al, 2013)[14 15]	Proportion of wound closure over time (using 25,000 simulated patients for each group)	Predicted wound closure rates at 6 months: 55% (Intervention group) vs 4% (Control group) Predicted wound closure rate at 12 months: 85% (Intervention group) vs 13% (Control group)
Bateman, 2015[27]	Chronic diabetic foot ulcer (n=20) (duration >12 weeks) Twice weekly applications of Granulox, plus standard wound dressing management as received prior to study. Standard care included foam dressings, retention bandage, and the continuation of off-loading boots and shoes Treatment duration: 4 weeks	Wound size reduction Ease of use	After 4 weeks: - All wounds demonstrated positive wound size reduction - All patients and clinicians rated Granulox easy to use
Bateman, 2015[28]	Sloughy wounds (leg ulcer, burn, traumatic wound, surgical wound) (n=25) Granulox applied twice weekly, plus standard wound cleansing and previous dressing management Treatment duration: 4 weeks with 5-week follow-up	Slough reduction Wound surface area reduction Patient ease of self-care use Overall product experience	After 3 weeks of treatment, all wounds were 100% slough-free (6 Granulox applications) After 4 weeks of treatment and 5-week follow-up period, 76% (n=19) wounds had completely healed 100% of patients / carers found Granulox easy to use 100% patients / carers had a positive wound care experience
Hunt, 2015[29]	Sloughy wounds (burn, leg ulcer, surgical wound, traumatic wound) (n=100) Granulox applied twice weekly alongside normal cleansing and dressing regimen (dressings included soft silicone foam, hydrofiber, compression therapy and retention bandages) Treatment duration: 4 weeks with 5-week follow-up	Slough reduction Wound surface area reduction Patient ease of self-care use Overall product experience	After 4 weeks of treatment: 96% wounds were slough-free (100% at week 5) All wounds reduced in size; 80% had completely healed at the end of the follow-up period 100% patients / carers found Granulox easy to use 100% patients / carers had a positive wound care experience
Tickle, 2015[30]	Pressure ulcers (category 2, 3 and 4) (n=18) Granulox, applied at each dressing change, plus standard care (dressings included adhesive foam, alginate, hydrofiber and hydrogel) Treatment duration: 4 weeks	Wound size reduction	After 4 weeks of treatment: - Wound healing progression observed in all 18 wounds (100%) - Wound size reduction recorded in 17 wounds (94%)

Tickle & Bateman, 2015[31]	Pressure ulcer (category 2-4) (n=11) Granulox plus standard care (dressings included adhesive foam, alginate, hydrofiber and hydrogel) as performed in the original study (Tickle, 2015[30]) Treatment duration: 12 weeks	Wound healing / wound size reduction	After 12 weeks of treatment: - Nine wounds had healed (82%). - Two wounds had reduced in size (77% and 33% reductions)
Marinović et al, 2014[23]	Traumatic wound	This article is not in English - English abstract contains no relevant information	
Norris, 2014[32]	Venous leg ulcer (n=17) (average duration – 41months (range 6-120 months) Inclusion to trial if <40% size reduction after 4-week run-in period with standard care Granulox applied at each dressing change (median - twice a week, (range: daily - 3 times / week). Standard care as per run-in period. Compression therapy if required Treatment duration: 4 weeks	Wound size reduction	After 4 weeks, all patients who completed the study (n=14) showed a reduction in wound area Percentage wound reduction ranged from 15.5% to 96%, with a median reduction of 68%

Case studies and case study series

The literature search identified two case studies and fourteen case study series. The wound types referred to in the evidence communications include leg ulcers[36 37 38 39 40 41 42 43 44 45], surgical wounds[36 38 40 41 46 47], pressure ulcers[39 42 46], foot ulcers[37 40 41 42 47 48 49 50], burn wounds[47] and traumatic wounds[47 51]. All the wounds were chronic. The wounds were all treated using Granulox plus standard wound care regimes, including compression therapy if required[36 37 38 39 43 44 45]. Wound size reduction was reported in all sixteen studies following the introduction of Granulox therapy, and in nine of the studies, complete wound closure was recorded[36 38 39 41 43 45 46 50 51], with three studies reporting no recurrence of the wounds[36 43 45]. The inclusion of Granulox into the treatment regime was reported to help avoid amputation surgery[37 41], reduce slough, wound exudate and pain[48], and improve quality of life for the patient[45]. In addition, Granulox was shown to be a cost-effective treatment, with >50%[41] reduction in dressing related costs, and >30%[38] and >70%[42] reductions in overall costs reported in two other studies, when compared to standard care alone.

Table 6. Case studies and case study series

Reference	Wound type	Treatment regime	Main observations
Loh et al, 2020[36]	Leg ulcer (n=3) Surgical wound (n=2)	Case 1: Granulox plus Mepilex® Ag (silver-containing foam dressing with soft silicone wound contact surface) and 4-layer compression bandage every 3 days Case 2: Weekly Granulox plus Mepilex Ag and 2-layer compression system Cases 3 -5: treatment regime not stated	Introductory review of existing clinical evidence suggests that Granulox aids with both wound healing and symptom relief in chronic wounds Case 1: Leg ulcer healed after 4 weeks Case 2: Mixed arterial-venous leg and foot ulcers healed after 5 weeks Case 3: Amputation wound healed after 16 weeks of treatment Case 4: Leg ulcer healed after 3 weeks Case 5: Amputation wound healed after 15 weeks Granulox treatment hastened wound healing time with a lower recurrence rate

Winaikosol et al, 2020[51]	Radiation ulcer (n=1)	Granulox in combination with hyperbaric oxygen therapy (30 sessions)	Gradual progress towards healing with achievement of good granulating base. Wounds closed after 2 months using small split thickness skin graft
Lee et al, 2019[46]	Pressure ulcer (n=2) Surgical wound (n=1)	Granulox plus standard wound care	Case 1: wound healed after 2 months Case 2: wound almost healed after 1 month Case 3: wound healed after 2 months
Wilasrusmee, 2019[37]	Diabetic foot ulcer (DFU) (n=1) (duration >1month) Chronic venous leg ulcer (VLU) (n=1) (duration >1year)	Case 1 (DFU): Granudacyn® (hypochlorous acid-containing wound cleanser) and Granulox (no other details specified) Case 2: Granudacyn® Gel (hypochlorous acid) for 3 weeks followed by Granulox for 3 weeks, plus standard care including compression	Case 1: wounds almost healed 2 months after treatment. Below knee amputation avoided Case 2: ulcer decreased in size; increase in granulation tissue in the wound bed
Wongprachum, 2019[48]	Diabetic foot ulcer (n=3) (duration >6 weeks)	Granulox plus standard wound care	Improved wound closure and wound size reduction, as well as reduced levels of pain, slough, and exudate levels
Grzegorz, 2018[38]	Leg ulcer (n=1) Surgical wound (n=2)	Following cleansing and debridement, Granulox was applied to the wound bed every 2 days at dressing change (non-adherent, silver-containing contact layer plus an absorbent dressing). Case 1 and 3: Temporary negative pressure wound therapy (NPWT) was applied from day 7 to day 14 Case 2 and 3: Compression therapy was applied	After 49 days of treatment, Case 1 & 2 wounds were almost healed; Case 3 had complete wound closure Cost analysis: Old treatment (simple gauze) - €1500 New treatment (advanced dressings plus NPWT) - €740 New treatment plus Granulox - €500 (Case 1 - €574, Case 2 - €541, Case 3 - €457)
Hong et al, 2018[49]	Foot ulcer (n=3)	Granulox plus antimicrobial hydrofiber dressing applied twice a week for 4 weeks	Case 1 and 2: Significant wound healing with complete epithelialisation after 3 weeks Case 3: Increased epithelialisation of wound edges after 3 weeks
Fletcher et al, 2017[39]	Leg ulcer (n=4) Pressure ulcer (n=4)	Brief overview of Granulox and the significance of oxygen in wound healing All cases: Granulox plus standard wound care. Cases 7 and 8 (described in greater detail): Granulox plus a foam dressing, and compression therapy	Cases 1-6: Condition of the wound improved in all cases. Cases 1 & 2: wounds healed after 2 and 3 months, respectively Cases 7 & 8: After 5 months of treatment, the wounds exhibited significant wound healing, with new epithelial tissue present
Jermsujarit et al, 2017[47]	Burn (n=1) Foot ulcer (n=4) Surgical wound (amputation due to osteomyelitis) (n=3) Traumatic wound (n=2)	Granulox applied to wound and covered with a foam dressing every 2 days	All 10 non-healing wounds exhibited significant reduction in size >50% treatment cost saving presented for three of the case studies
Laeuchli, 2015[40]	Hard to heal wounds (leg ulcer, foot ulcer, surgical wound) >6 months prior to treatment (n=13)	Granulox plus standard care for 12 weeks	Granulox facilitated healing progress, with a reduction in wound size in 10/13 wounds
Lopez et al, 2015[41]	Chronic wounds: surgical wound, diabetic foot ulcer, venous leg ulcer (n=15; 19 wounds)	Granulox application and dressing changes (standard care) 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 (1 patient therapy ongoing) Six cases of amputation were prevented

Mohamud, 2015[42]	Non-healing wounds: Foot ulcer (n=1) Leg ulcer (n=1) Pressure ulcer (n=1)	Granulox plus standard wound care (secondary dressing: hydropolymer foam)	Case 1; reduction in wound size Case 2: reduction in wound size by 80% with 100% granulation tissue after 4 weeks Case 3: reduction in wound size and condition of wound bed tissue improved after 4 weeks Total costs for Granulox plus dressings were reduced by 91%, 71% and 97% for cases 1, 2 and 3, respectively, as compared to costs prior to Granulox treatment
Mustafi & Engels, 2015[43]	Non-healing leg ulcer (n=2)	Ulcers on both legs had thin layer of Granulox applied and dressed with a polyurethane foam plus gauze. High compression therapy was performed. Left leg received skin graft. Treatment with Granulox plus a non-adhesive foam dressing and gauze was continued for both ulcers	Wound closure of infected chronic venous leg ulcers was achieved within less than 4 weeks No ulcer recurrence at 4-week follow-up
Paraschiv, 2015[44]	Venous leg ulcer (n=12)	Initial treatment with a DACC-foam dressing to remove infection, followed by Granulox plus foam dressings (DACC and silicone), and compression therapy (compliant patients)	All wounds exhibited healing
Babadagi-Hardt et al, 2014[45]	Venous leg ulcer (n=1)	Granulox applied as a thin layer to the wound bed (2-3 second spray >> 500µl/10cm^2) three times/week, following mechanical cleansing Initial 8 weeks of treatment: activated charcoal dressing with silver (primary dressing) plus super absorbent dressing, fixed with gauze bandage. Daily compression therapy After 8 weeks: absorbent silicone foam dressing (primary dressing) fixed with gauze bandage. Compression therapy	Complete wound closure after 16 weeks of treatment, with no recurrence at 2-month follow-up Significant improvement in patient quality of life
Chadwick, 2014[50]	Diabetic foot ulcer (n=4)	Daily Granulox application plus standard care (e.g. off-loading, infection management)	Two ulcers completely healed after 10 weeks (n=1) and 12 weeks (n=1) of treatment One ulcer exhibited 20% wound size reduction after 2 weeks of treatment Condition of one ulcer improved, but subsequently deteriorated and became infected following a missed treatment

Pre-clinical studies

The literature search identified one pre-clinical study. Holzer et al[52], determined the inhalation risk of using Granulox to the user, bystander or the patient. Granulox spray was shown to pose no danger from inhalation, as no nanoparticles or dust were created during its application.

Table 7. Pre-clinical studies

Reference	Design methodology	Main outcome measures	Main results
Holzer et al, 2019[52]	Laser scattered light photometer and scanning mobility particle sizer (SMPS) used to measure risk of product inhalation (Granulox) by the patient and bystander Spectrometer used at 5 different distances to determine product particle size and product concentration	Total particle concentrations and particle size fractions	No nanoparticles or dust were created during the application of the Granulox spray The use of the Granulox spray poses no danger from inhalation for the user, a bystander, or the patient

Expert comment

The literature search identified seven review articles[2 3 4 52 53 54 55]. All the articles discuss the positive use of Granulox as a topical oxygen therapy for the treatment of chronic, non-healing wounds. A common recommendation supported the initiation of Granulox treatment, if after 4 weeks of standard care, the wound failed to demonstrate healing[2 52 53 54 55]. Three reviews[3 52 54] discussed the acceptability and ease of use of Granulox, and the lack of side-effects, and two of these reviews[3 54] also considered the cost-effectiveness of including Granulox into a wound care management regimen as compared to standard care alone.

Table 8. Expert comment

Reference	Design methodology	Key points
Kröger et al, 2020[53]	Narrative review of the publicly available *in vitro* and *in vivo* clinical data relating to Granulox	Summarises the pre-clinical and clinical data relating to the use of Granulox on venous leg ulcers, diabetic foot ulcers and pressure ulcers; also discusses the safety and economic benefits of Granulox. The findings highlight the acceptability and ease of use of Granulox
Chadwick et al, 2019[2]	Expert panel proceedings, focusing on the role, evidence base and practicalities of using topical oxygen therapies (including Granulox) in the management of diabetic foot ulcers	Recommends that topical oxygen therapy (Granulox) should be used as an adjunct to best practice and considered after 4 weeks of standard care if the wound appears to be non-healing. Early initiation should be considered if the patient has peripheral arterial disease (PAD), ulcer pain, a non-healing amputation wound or following debridement
Stang, 2018[54]	Expert panel consensus guidelines on the use of Granulox in the treatment of diabetic foot ulcers and how it 'fits' with standard wound care. Discusses the identification of appropriate patients and recommendations for the use of Granulox in different health care settings	Recommends that, after 4 weeks of standard care in patients with non-healing wounds, Granulox treatment should be considered. Patients at risk of delayed healing should be considered for Granulox treatment at an earlier time Document also presents a 'traffic light' system to help clinicians decide when and how to initiate Granulox treatment
Gottrup et al, 2017[3]	Narrative review of the published evidence for Granulox as a topical oxygen therapy, considering outcomes, cost-efficiencies, and the patient perspective of treatment	Key findings of the review: - Granulox evidence (1 RCT, 1 controlled open label study, 3 controlled cohort studies included) graded 1B with a positive effect statistically shown - In excess of 50,000 Granulox treatments in more than 20 countries with no relevant side effects; a clear positive benefit risk value identified - Granulox therapy has a high level of patient acceptance and is easy to use by the patients themselves - Granulox has a relatively low cost of application
Strohal, 2016[55]	Interdisciplinary expert panel proceedings, discussing the advantages and disadvantages of haemoglobin spray usage	Evidence base on topical haemoglobin is positive; Granulox is an adjunct therapy to best practice wound management Granulox promotes healing by improving the supply of oxygen to non-healing (≥40%) acute and chronic wounds (after 4 weeks of standard wound care) The advantages of Granulox listed as: simple application (can be performed by patient), few side-effects, health-economic effect

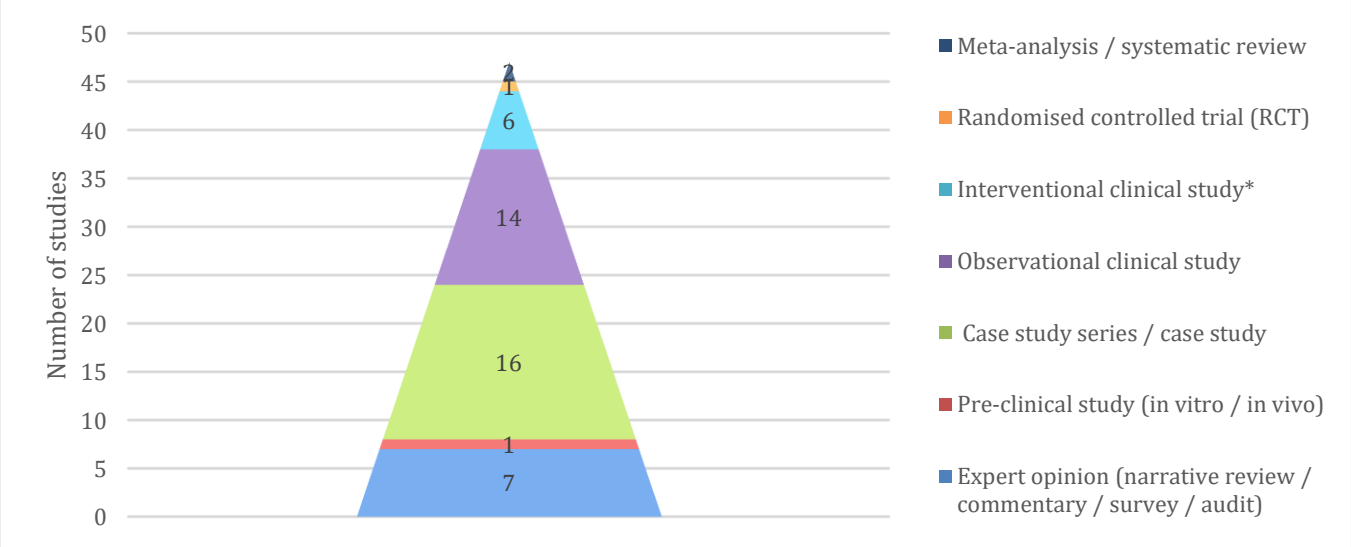
Dissemond et al, 2015[4]	Narrative review, focussing on topical oxygen therapeutic approaches for chronic wounds and their impact on healing. Includes an overview of published clinical data relating to Granulox	Results to date for Granulox suggest a potent adjunctive effect of haemoglobin on the healing process in different types of chronic wounds
Dissemond et al, 2014[56]	Narrative review, focussing on aspects of non-interventional, topical wound treatments for daily practice	Granulox is named as one of a number of wound (kick) starter products intended to alter the wound milieu or wound surface of chronic wounds which despite optimal care, remain hard-to-heal

Key points

- Treatment of chronic, hard-to-heal wounds with Granulox, in combination with standard care, facilitates a significant reduction of wound size or complete wound closure.
- Granulox is a safe, easy to use product.
- Granulox is a cost-effective adjunctive therapy to standard wound care treatment.

CONCLUSION

The available evidence in the published literature related to Granulox strongly indicates that it is a safe, and both cost- and therapeutically- effective topical oxygen therapy for use on a range of chronic, hard-to-heal wounds. The use of Granulox is supported by scientific and clinical data generated from studies that span across the entire evidence hierarchy (Figure 2) However, although this evidence is compelling, the evidence is mostly generated from lower level non-randomised studies, often involving relatively low sample sizes. Moving forward, larger RCTs and interventional clinical studies, with larger sample sizes are warranted in order to fully elucidate the expected clinical and economic benefits of Granulox.



*includes 2 health economic studies based on results of clinical studies

Figure 2. Quantitative analysis of Granulox-related evidence

REFERENCES

[1] Bishop, A. Role of oxygen in wound healing. Journal of Wound Care 2008; 17(9): 399-402.
[2] Chadwick, P., Edmonds, M., Fox, A., Leigh, R., Stang, D., Vig, S. Expert panel report. The role of topical oxygen therapy in the management of diabetic foot ulcers. Diabetic Foot Journal: London, United Kingdom, 2019.
[3] Gottrup, F., Dissemond, J., Baines, C., Frykberg, R., Jensen, P., Kot, J., Kröger, K., Longobardi, P. Use of oxygen therapies in wound healing. Journal of Wound Care 2017; 26(5 Supplement): S1-S42.
[4] Dissemond, J., Kröger, K., Storck, M., Risse, A., Engels, P. Topical oxygen wound therapies for chronic wounds: a review. Journal of Wound Care 2015; 24(2): 53-63.
[5] Barton, S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. British Medical Journal 2000; 321(7256): 255-256.
[6] Akobeng, A.K. Understanding randomised controlled trials. Archives of Disease in Childhood 2005;90(8):840-844.
[7] Sacket, D.L., Rosenberg, W.M., Gray, J.A., Haynes, R.B., Richardson, W.S. Evidence-based medicine: what it is and what it isn't. British Medical Journal 1996; 312(7023): 71-72.
[8] Gottrup, F. Rapid response to Dressings for venous leg ulcers: systematic review and meta-analysis. British Medical Journal 2007; 335: 244.
[9] White, R., Jeffery, S. The evidence debate in wound care. Wounds UK 2010; 6(3): 10.
[10] White, R.., Maylor, M., Iverson, C. Evidence is 'in', ignorance is 'out': a dilemma for wound care products. Wounds UK 2010; 6(3): 114-116.
[11] Kaplan, B.J., Giesbrecht, G., Shannon, S., McLeod, K. Evaluating treatments in health care: the instability of a one-legged stool. BMC Medical Research Methodology 2011; 11: 65.
[12] Hu, J., Guo, S., Hu, H., Sun, J. Systematic review of the efficacy of topical haemoglobin therapy for wound healing. International Wound Journal 2020 doi:10.1111/iwj.13392 [Epub ahead of print].
[13] Elg, F., Hunt, S. Hemoglobin spray as adjunct therapy in complex wounds: Meta-analysis versus standard care alone in pooled data by wound type across three retrospective cohort controlled evaluation. SAGE Open Medicine 2018; 6: 1-9.
[14] Arenbergerova, M., Engels, P., Gkalpakiotis, S., Dubská, Z., Arenberger, P. Effect of topical haemoglobin on healing in patients with venous leg ulcers. European Wound Management Association Journal 2013; 13(2): 25-30.
[15] Arenbergerova, M., Engels, P., Gkalpakiotis, S., Dubská, Z., Arenberger, P. Effect of topical haemoglobin on healing in patients with venous leg ulcers. Der Hautarzt 2013; 64(3): 180-186.
[16] Hunt, S.D., Elg, F, Percival, S.L. Assessment of clinical effectiveness of haemoglobin spray as adjunctive therapy in the treatment of sloughy wounds. Journal of Wound Care. 2018; 27(4): 210-219.
[17] Hunt, S., Elg, F. The clinical effectiveness of haemoglobin spray as adjunctive therapy in the treatment of chronic wounds. Journal of Wound Care 2017; 26(9): 558-568.
[18] Hunt, S. Exploring the effectiveness of topical haemoglobin therapy in the acute care setting on diabetic foot ulceration. The Diabetic Foot Journal 2017; 20(3): 176-183.
[19] Hunt, S., Elg, F. Clinical effectiveness of hemoglobin spray (Granulox®) as adjunctive therapy in the treatment of chronic diabetic foot ulcers. Diabetic Foot & Ankle 2016; 7: 33101.
[20] Elg F, Bothma G. Cost-effectiveness of adjunct haemoglobin spray in the treatment of hard-to-heal wounds in a UK NHS primary care setting. Journal of Wound Care 2019; 28(12): 844-849.
[21] Brüggenjürgen, B., Hunt, S., Eberlein, T. Wound management in diabetic foot ulcer (DFU) - Incremental cost-analysis of treating diabetic neuropathic foot lesions with adjunct hemoglobin contact spray in Germany. Gesundheitsokonomie und Qualitatsmanagement 2018; 23(6): 320-327.
[22] Marinovic, M., Fumic, N., Laginja, S., Smokrovic, E., Bakota, B., Bekic, M., Čoklo, M. Application of topical hemoglobin spray in infected posttraumatic and postoperative wounds. Acta Medica Croatica 2016; 70(Supplement 1): 101-104.
[23] Marinović, M., Španjol, J., Fumić, N., Bakota, B., Pin, M., Čukelj, F. Use of new materials in the treatment of chronic post-traumatic wounds. Acta Medica Croatica 2014; 68(Supplement 1): 75-80.
[24] Arenberger, P., Elg, F, Petyt, J, Cutting, K. Expected outcomes from topical haemoglobin spray in non-healing and worsening venous leg ulcers. Journal of Wound Care 2015; 24(5): 228, 230-232, 236.
[25] Haycocks, S., McCardle, J., Findlow, A.H., Guttormsen, K. Evaluating the effect of a haemoglobin spray on size reduction in chronic DFUs. British Journal of Nursing 2016; 25(6 Supplement): S54- S62.
[26] Hunt, S., Haycocks, S., McCardle, J., Guttormsen, K. Evaluating the effect of a haemoglobin spray on size reduction in chronic DFUs: clinical outcomes at 12 weeks. British Journal of Nursing 2016; 25(12): S59-S64.
[27] Bateman, S.D. Topical haemoglobin spray for diabetic foot ulceration. British Journal of Nursing (Tissue Viability Supplement) 2015; 24(12): S24-S29.
[28] Bateman, S.D. Use of topical haemoglobin on sloughy wounds in the community setting. British Journal of Community Nursing 2015; 20(9): S32-S39.
[29] Hunt, S.D. Topical oxygen-haemoglobin use on sloughy wounds: Positive patient outcomes and the promotion of self-care. Wounds UK 2015; 11(4): 90-95.

Mölnlycke®

[30] Tickle, J. A topical haemoglobin spray for oxygenating pressure ulcers: a pilot study. British Journal of Community Nursing 2015; 20(3 Wound Care Supplement): S14-S18.
[31] Tickle, J., Bateman, S.D. Use of a topical haemoglobin spray for oxygenating pressure ulcers: healing outcomes. British Journal of Community Nursing 2015; 20(12 Wound Care Supplement): S14-S21.
[32] Norris, R. A topical haemoglobin spray for oxygenating chronic venous leg ulcers: a pilot study. British Journal of Nursing (Tissue Viability Supplement) 2014; 23(20): S48-S53.
[33] Petri, M., Stoffels, I., Griewank, K., Jose, J., Engels, P., Schulz, A., Pötzschke, H., Jansen, P., Schadendorf, D., Dissemond, J., Klode, J. Oxygenation status in chronic leg ulcer after topical hemoglobin application may act as a surrogate marker to find the best treatment strategy to avoid ineffective conservative long- term therapy. Molecular Imaging and Biology 2018; 20(1): 124-130.
[34] Petri, M., Stoffels, I., Jose, J., Leyh, J., Schulz, A., Dissemond, J., Schadendorf, D., Klode, J. Photoacoustic imaging of real-time oxygen changes in chronic leg ulcers after topical application of a haemoglobin spray: a pilot study. Journal of Wound Care 2016; 25(2): 87-91.
[35] Hunt, S. D. Self-care in the self-harm population: Positive patient outcomes utilising innovative topical haemoglobin therapy. Wounds UK 2016; 12(3): 76-82.
[36] Loh, C., Tan, Q.Y., Eng, D.L.K., Walsh, S.R., Chong, T.T., Tang, T.Y. Granulox - The use of topical hemoglobin to aid wound healing: A literature review and case series from Singapore. The International Journal of Lower Extremity Wounds 2020; doi: 10.1177/1534734620910318
[37] Wilasrusmee, C. Granulox: introduction and clinical experience. Oral presentation at European Wound Management Association conference, Gothenburg, Sweden, 2019.
[38] Grzegorz, K. Case reports of adjunct use of a topical haemoglobin spray - cost reduction via accelerated wound healing. Poster presentation at European Wound Management Association conference, Krakow, Poland, 2018.
[39] Fletcher, J, Percival, S., Macaskill, C., Sullivan, S., Laverty, T., Bojke, C. Oxygen wound therapy: the clinical and cost impact of using topical haemoglobin spray (Granulox®). Wounds UK: London, United Kingdom, 2017.
[40] Laeuchli, S. And finally it heals. Clinical experiences with hemoglobin in long-time persisting wounds. Oral presentation at European Wound Management Association conference, London, United Kingdom, 2015.
[41] Lopez, O., Engels, P., Elg, F. Accelerate wound healing of acute and chronic wounds in patients with Diabetes: Experience from Mexico using supplementary haemoglobin spray. Poster presentation at Wounds UK conference, Harrogate, United Kingdom, 2015.
[42] Mohamud, L. 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. Poster presentation at European Wound Management Association conference, London, United Kingdom, 2015.
[43] Mustafi, N., Engels, P. Granulox treatment in combination with skin graft & PolyMem – two case reports. E-poster presentation at European Wound Management Association conference, London, United Kingdom, 2015.
[44] Paraschiv, F. Fast healing of VLUs with innovative and combined technologies - venous leg ulcer. E-poster presentation at European Wound Management Association conference, London, United Kingdom, 2015.
[45] Babadagi-Hardt, Z., Engels, P., Kanya, S. Wound management with compression therapy and topical hemoglobin solution in a patient with Budd-Chiari syndrome. Journal of Dermatological Case Reports 2014;8(1): 20-23.
[46] Lee, C.Y., Jacon, V.A., Premchandran, N. Case series on the administration of topical oxygen therapy for wound care management in Malaysia. Wounds Asia 2019; 2(1): 50-52.
[47] Jermsujarit, S., Saengpethsong, A., Wongpromchai, M., Photipara, C., Wuthiprasert, P., Toboonmee, N., Kwanchainunthachart, V., Suwanmanee, S. Using of hemoglobin spray to treat complex chronic ulcers to accelerate wound healing and save treatment cost- 10 case studies. Poster presentation at Scientific Meeting of Thai Enterostomal Therapy Society Bangkok, Thailand, 2017.
[48] Wongprachum, B. Innovative topical haemoglobin spray helps drive the POIST concept in saving patients' limbs. Wounds Asia 2019; 2(1): 28-31.
[49] Hong, Q., Joethy, J., Choing, S. Efficacy of Granulox haemoglobin spray on diabetic foot wounds: an observational case series. Poster presentation at Plastic Aesthetic Surgery Meeting Singapore, 2018.
[50] Chadwick, P. Pilot study: haemoglobin spray in the treatment of chronic diabetic foot ulcers. Wounds UK 2014; 10(4): 76-80.
[51] Winaikosol, K, Punyawong, P., Jenwitheesuk, K., Surakunprapha, P., Mahakkanukrauh, A. Radiation ulcer treatment with hyperbaric oxygen therapy and haemoglobin spray: case report and literature review. Journal of Wound Care 2020;29(8):452-456.
[52] Holzer, J.C., Birngruber, T., Mautner, S., Graff, A., Kamolz, L.P. Topical application of haemoglobin: a safety study. Journal of Wound Care 2019; 28(3): 148-153.
[53] Kröger, K., Gäbel, G., Juntermanns, B. Assessment of acceptability and ease of use of haemoglobin spray (Granulox®) in the management of chronic wounds. Chronic Wound Care Management and Research 2020; 7: 1–10.

[54] Stang, D., Young, M., Wilson, D., Montgomery, S., Davidson, D. The role of topical oxygen therapy in the management of diabetic foot ulcer wounds in Scotland: round table recommendations. Diabetic Foot Journal 2018; 21(1): 56-61.
[55] Strohal, R., Gerber, V., Kröger, K., Kurz, P., Läuchli, S., Protz, K., Uttenweiler, S., Dissemond, J. Expert consensus on practical aspects of wound therapy with hemoglobin spray. Wundmanagement 2016; 5: 276–284.
[56] Dissemond, J., Augustin, M., Eming, S.A., Goerge, T., Horn, T., Karrer, S., Schumann, H., Stücker, M. Modern wound care- practical aspects of non-interventional topical treatment of patients with chronic wounds. Journal of the German Society of Dermatology 2014; 12(7): 541-554.