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Expert consensus on practical aspects of wound therapy with hemoglobin spray

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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, hemoglobin 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, hemoglobin 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 ≥ 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.

KEYWORDS

Wound healing, chronic wounds, hypoxia, oxygenation, hemoglobin

Introduction

Many processes in the human body, such as energy production, protein synthesis or defense against infection, function only with the participation of molecular oxygen (O_2). Therefore, an adequate supply of all tissues with oxygen is essential [11]. This also applies to physiological wound healing, since energy metabolism and thus demand for oxygen is significantly increased compared to intact skin [21, 46, 51]. Absorption of O_2, which is generally present in the form of covalently bonded homodimers as odorless and colorless gas at a concentration of 21 % in the air, into the body takes place via the lungs and to a very limited extent through the skin. The hemoglobin stored in the erythrocytes transports O_2 to the cells via the vascular system, with one capillary supplying several cells. The

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molecular O_2 that hemoglobin then releases in the capillaries reaches these cells by means of natural diffusion.

Importance of oxygen in wound healing

In the initial phase of healing (inflammatory phase) right after the wound occurs, cytokines and growth factors, among others things, are released, while neutrophils and macrophages migrate into the wound. There they release reactive oxygen species (ROS) as part of the so-called oxidative burst. This O_2-dependent process plays an important role in the defense against infection and leads to a 50- to 100-fold increase in the cells' need for molecular oxygen [2, 23, 48].

The subsequent proliferative phase is characterized by the formation of blood vessels, granulation and an extracellular matrix. This requires a lot of energy and therefore O_2 [24, 37, 40, 52]. At a later point in the wound healing process, epithelialization and maturation take place, reorganizing the new tissue. The O_2 concentration in the wound plays a major role here too, as many of the participating molecular metabolic processes are O_2-dependent. The activity of matrix metalloproteinase inhibitors (tissue inhibitors of metalloproteinases, TIMP) is essential in this phase. They regulate the matrix metalloproteinases (MMP), which ensure that damaged tissue is broken down at the start of the healing process.

In the granulation and epithelization phase, increased activity of these enzymes is undesirable as it can interfere with the formation of new tissue.

However, if the partial pressure of O_2 in the wound is too low, TIMP are inactive and the balance between MMP and TIMP is disturbed, delaying or even interrupting the wound healing process [42]. Cells perceive changes in O_2 partial pressure through an adaptive sensor system. This allows them to quickly adapt their normal level of activity (normoxia) to new circumstances [32, 36, 39]. Relative changes in oxygen concentration are thus detected via the hypoxia-inducible factor-1 (HIF-1) signaling pathway triggered by hypoxia, and cell metabolism is adjusted to the new value [32, 36].

Back in the 70s, Kivisaari et al. had already postulated that O_2 supply is one of the rate-determining steps in physiological wound healing [33]. They showed that a limited O_2 supply significantly slows the rate of healing.

Oxygen demand and supply in chronic wounds

According to Initiative Chronische Wunden e. V. (ICW e.V.), in addition to wounds with a delayed or stagnating healing process without healing after eight weeks, wounds with an underlying disease in need of treatment are also defined as chronic [16]. Common causes include diabetes mellitus, peripheral arterial occlusive disease (PAOD) or chronic venous insufficiency (CVI) [13, 14, 22, 25, 31, 35, 44]. Although its etiology is very different, the final pathophysiological phase of chronic wounds almost always includes chronic hypoxia [35, 49]. In patients with PAOD, for example, the hypoxia is often caused by arteriosclerotic vascular occlusions in the leg and pelvic arteries. The affected limbs suffer from an undersupply of blood and therefore O_2, resulting in the formation of necrosis and ulcers. Once so-called chronic critical ischemia develops, these wounds can no longer be expected to heal [12]. CVI, on the other hand, is characterized by chronic hypertension of upstream veins and venules. The resulting structural changes in the blood vessels, however, lead to a loss of capillaries and thus reduced capillary density. This, in turn, leads to microcirculatory disorders and, as a consequence, trophic skin changes or even venous leg ulcers [19, 30, 31, 54]. In the case of diabetic foot ulcers (DFU), polyneuropathy with macroangiopathy and functional microangiopathy are often responsible for lesion formation [38, 45]. In the course of tissue hypoxia, capillary density is reduced, the diffusion distance of O_2 increases and the necessary supply to the tissue is no longer given. However, since this is essential for physiological wound healing, hypoxia is now regarded as a ubiquitous, central factor in wound healing [35, 49].

The priority, in case of chronic wounds, is placed on treating the underlying disease, which is a prerequisite for healing. However, this does not always ensure sufficient supply of O_2 to the tissues. As part of phase-specific wound treatment according to the principles of physiological wound healing, which currently represent the standard for the treatment of chronic wounds, additional measures such as the incorporation of O_2 into the wound can be effective [12, 15, 26, 56].

Treatment options for the oxygenation of wounds

There are currently several wound treatment options for the application of O_2. Alongside systemic administration, which involves the supply of additional O_2 via the airways [7, 28], the following topical applications are available [17]:

1. Treatment with a slight overpressure,
2. continuous O_2 fumigation without overpressure,
3. O_2-releasing dressings and
4. O_2 transport via O_2 transporters.

For topical O_2 application with slight overpressure, small chambers or bags are used to fumigate the wound and the wound environment exclusively. Portable units, which generate a permanent stream of O_2 under normobaric conditions, allow the continuous oxygenation of wounds. In the case of O_2-releasing wound dressings, O_2 is either continuously released into the wound in pure form or provided discontinuously via a biochemical reaction in a hydrogel.

The problem with the previously mentioned topical oxygenation options is that O_2 has difficulty penetrating the diffusion barrier consisting of wound fluid and therefore only a small portion of the O_2 generated actually reaches the wound. In order to improve the diffusion of O_2 in fluids such as wound exudate, an approach using native hemoglobin as a diffusion enhancer was developed. This improves the availability of O_2 in the wound area by (when introduced into the wound fluid) binding atmospheric oxygen and transporting it to the wound bed, thereby breaking through the diffusion barrier [6]. The hemoglobin is applied to the wound as a spray. Its effectiveness has been demonstrated in randomized clinical trials (RCT) and numerous case studies [3–5, 7, 41]. Chronic wounds of various etiologies show a clearly positive healing effect.

With respect to all available oxygenation options, it must be observed that these are additive rather than substitutive measures, and that they cannot replace conventional wound care. Each wound must continue to be treated in accordance with existing standards as part of physiological wound care, and the effectiveness of oxygenation must be verified. To ensure good oxygenation, wound cleansing and adequate debridement according to the specific requirements of the wound should be performed prior to treatment [53].

Hemoglobin spray

Composition

The spray contains hemoglobin purified from pig's blood, which is present in carbonylated form in water as a 10 % solution with 0.7 % phenoxyethanol, 0.9 % sodium chloride and 0.05 % N-acetylcysteine.

Mechanism of action

The mechanism of action of hemoglobin spray is based on the physiological principle of facilitated O_2 diffusion by means of hemoglobin, which was already described by Scholander and Wittenberg back in the 60s [47, 57]. Hemoglobin is found in red blood cells of mammals and is composed of a complex of four globin subunits, each of which binds an iron-II-complex in their center. Each of these, in turn, can bind an O_2 molecule. Thanks to the good solubility of hemoglobin in water, it can also easily transport O_2 outside of the red blood cells, thus facilitating the diffusion of the molecule [6, 47, 57]. This natural mechanism of action was developed in Germany for use in moist wound healing by Barnikol et al. to improve oxygen supply in wounds [8]. After application to the wound, the hemoglobin transports O_2 from the ambient air to the wound bed. The diffusion rate, which the fluid barrier of wound exudate severely limits for molecular O_2, increases significantly [6]. O_2 is released at the wound bed, diffusing into the cells and improving the supply there. The mechanism of action is a purely physical process that can occur more than once because the hemoglobin is not used up. Figure 1 shows a schematic representation of this mechanism of action.

Indication

Treatment with hemoglobin spray is indicated for chronic wounds, such as diabetic foot ulcers, secondary healing surgical wounds, venous ulcers, arterial leg ulcers, arterial-venous leg ulcers as well as burns up to grade IIb and bedsores.

Contraindications

- ulcerating (fungating) tumors;
- wound management in a palliative situation, when healing is impossible;
- burns from grade III upwards;
- non-conditioned wounds (e.g. with an untreated infection.);
- sealed wounds (e.g. through massive fibrosis or necrosis);
- pregnancy (not enough data available yet).

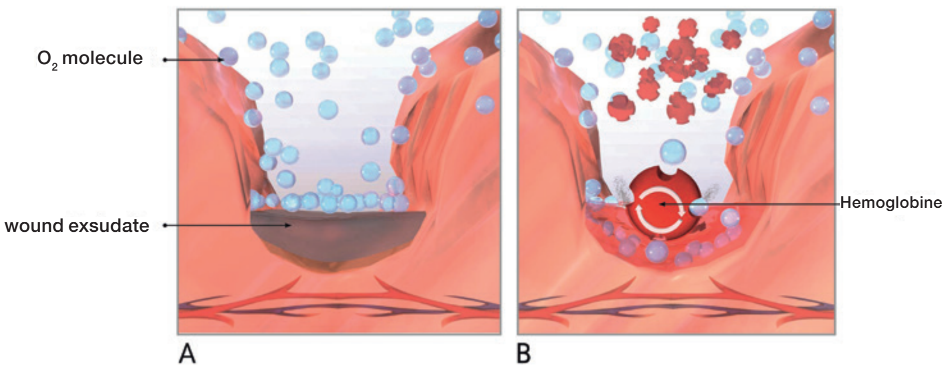

Figure 1
Schematic representation of hemoglobin's mechanism of action in wounds. A: Oxygen supply is prevented by the wound exudate barrier. B: Hemoglobin transports oxygen from the environment to the wound bed. (Figure by courtesy of SastoMed GmbH).

Possible combinations with hemoglobin spray

As part of the wound treatment, hemoglobin spray can be combined with different products such as wound irrigation solutions, wound dressings and other treatments. For some wound irrigations, however, the combination is only possible if the wound is thoroughly rinsed before using hemoglobin spray, as these products can destroy the hemoglobin. The same applies for proteolytic debridement. The effect of the simultaneous use of topical antibiotics has not yet been sufficiently studied, so combined use is not recommended in this case. At this point, it must be noted that their use in the treatment of chronic wounds is generally not recommended in Germany and that antisepsis is preferable [13]. The wound dressings used in combination must be semi-occlusive, as occlusive pads seal the wound and thus prevent the supply of oxygen [44]. Table 1 provides an overview of the possible combinations.

Evidence of the efficacy of topical hemoglobin in the healing of chronic wounds

Numerous clinical studies have examined the efficacy of hemoglobin spray in wound healing. A total of 37 publications and poster presentations demonstrate the effectiveness of hemoglobin spray today.

Arenbergerova et al., for example, compared wound healing in patients that had venous leg ulcers for longer than eight weeks and who were treated with hemoglobin spray in a 13-week RCT (with a control group) [4]. The inclusion criterion was the presence of a chronic venous leg ulcer, which showed no significant positive response to standard therapy within two weeks of in-patient hospital stay, so-called hard-to-heal wounds. The 36 patients per group were sprayed either with hemoglobin spray or a physiological saline solution following debridement. The wounds were subsequently covered with a wound dressing that was identical for both groups. All patients received additional compression therapy. The evaluation of the wound surface and the wound condition over 13 weeks resulted (in the group treated with hemoglobin) in a statistically significant reduction in relative wound size (53 %, $p \leq 0.0001$), while in the control group no significant wound size reduction was measurable. There was even an average wound expansion of 20 %, which can be explained by the non-response of hard-to-heal wounds to standard treatment. A more significant decrease (compared to the control group) in fibrinous (42 % vs. 12 %) and necrotic (48 % versus 17 %) coatings and increased granulation (75 % versus 18 %) and epithelization (78 % vs. 7 %) were also noted. Adverse events associated with the hemoglobin treatment were not reported. An analysis of the sensation of pain using the visual analogue scale (VAS) showed a significant reduction in pain of 68 % ($p \leq 0{,}001$) for the hemoglobin group, accompanied by a significant improvement in quality of life, whereas only a reduction of 7 % ($p > 0.05$) was measured in the control group.

A further publication by Arenberg et al. presented an RCT on chronic wounds of various etiologies (arterial and venous leg ulcers as well as DFU) in Mexico as well as further observations on hemoglobin treatment from Germany, the Czech Republic and Mexico [3]. The study showed that wound healing was significantly promoted by the topically applied hemoglobin; complete healing of wounds was achieved in 93 % of the patients included. The case observations from the Czech Republic (5 wounds) and Mexico (9 wounds) reported wound closure for all patients; six of the eight wounds examined in the German study closed up successfully.

A controlled cohort study was also performed on 40 patients with DFU [27]. The control group consisted of patients with the same wound characteristics who had been treated in the same period during the previous year in the same hospital by the same team with identical measures except for the hemoglobin spray (see Figure 2A). To ensure the same initial conditions for the hemoglobin and the control group, both groups were compared with regard to relevant factors such as age, wound size and healing rate, vascular involvement, ulcer type and SINBAD parameters (site, ischemia, neuropathy, bacterial infection, and depth). Significant differences in group heterogeneity could be excluded by means of statistical tests. Evaluation of the data after eight weeks of treatment showed a significantly increased healing rate of wounds in patients treated with hemoglobin spray (Figure 2B). Furthermore, all 20 wounds treated with hemoglobin spray had no more coatings after the eight weeks of treatment. This effect was only visible on four of the 20 treated wounds in the control group. Further analysis of the data after 28 weeks of treatment confirmed the significantly positive effect of hemoglobin spray on wound healing. A preliminary estimate of the cost development after 28 weeks of treatment showed that – despite short term higher costs due to the additional hemoglobin treatment – the total cost of treatment was significantly reduced thanks to the significantly faster healing of wounds and the associated shorter duration of treatment for patients.

Another case study with the same study design and a duration of eight weeks included 100 patients with DFU, burns, leg ulcers and trauma wounds (Hunt et al., personal communication). After only eight weeks of treatment, both a significantly increased healing rate of wounds (40 vs. 7 healed wounds) and a statistically significant reduction in total treatment costs of 23 % ($p < 0.001$) in the hemoglobin group compared to the control group could be shown. The fact that the costs decreased significantly after only a relatively short treatment time is due to the fact that cured patients no longer needed the treatment and were thus no longer included in the cost data evaluation.

In further case studies on patients with diabetic foot ulcers and with poorly healing coated wounds, patient and caregivers

Table 1
Possible combinations with hemoglobin spray.

Wound care strategies	Combinations with hemoglobin spray
Irrigation solutions and antiseptics	
Chlorhexidine	Yes, thorough rinsing necessary
Electrolyzed water	Yes
Local antibiotics	No
Octenidine	Yes, thorough rinsing necessary
Polihexanide	Yes
PVP[1] iodine	Yes, thorough rinsing necessary
Ringer	Yes
Sodium chloride 0.9%	Yes
Sterile water	Yes
Dressings	
Alginate	Yes
Collagen	Yes, in consultation with the attending physician
Occlusive polyurethane film	No
Nonocclusive polyurethane film	Yes
Fine-pored polyurethane foam / hydropolymer dressing	Yes
Fatty gauze / protective wound dressing	Yes
Hydrocolloid dressing	No
Hydrofibre	Yes
Hydrogel	Yes
Superabsorbent	Yes
Therapies	
Compression therapy	Yes
Hyperbaric oxygen therapy (HBOT[2])	Yes
Local oxygen therapy (TOT[3], TCOT[4])	Yes
Local negative pressure therapy / Vacuum therapy (NPWT[5])	Yes, in consultation with the attending wound expert
Skin graft	Yes
Systemic antibiotic therapy	Yes

Abbreviations: [1]Polyvinylpyrrolidon; [2]Hyperbaric Oxygen Therapy; [3]Topical Oxygen Therapy; [4]Transdermal Continuous Oxygen Therapy; [5]Negative Pressure Wound Therapy reported rapid reduction of wound surfaces and coatings, good tolerance and easy handling of the hemoglobin spray [9, 10]. These results have also been confirmed by a case study by Norris on 17 patients with venous leg ulcers [41] and a current pilot study by Tickle on patients with bedsores [55]. All the cases showed rapid reduction in wound surface given hemoglobin treatment.

A new method called photoacoustic tomography (PAT) – originally developed to detect melanoma metastases – allows the non-invasive measurement of O_2 saturation in the depth of the entire wound. Unlike many other methods, PAT facilitates the identification of wound areas in which O_2 deficiency is particularly acute – an important factor in determining a wound's oxygenation status [17]. A recent pilot study on five patients with chronic leg ulcers measured O_2 concentration before the one-time application of hemoglobin spray as well as 5 minutes and 20 minutes afterwards [43]. The result shows a significant increase in O_2 saturation from 56.4 % before application to 69 % ($p = 0.042$) after 5 minutes and 78.8 % ($p = 0.043$) after 20 minutes. It was thus shown for the first time in patients that topical application of hemoglobin actually increases O_2 saturation and may thus be responsible for the improved wound healing shown in the clinical trials.

Consensus of the expert panel

Hemoglobin spray for the oxygenation of wounds has been available on the market since 2012. After sufficient experience from clinical trials and daily practice had been collected on this product and a positive effect on wound healing reported, the experiences as well as the advantages and disadvantages of using hemoglobin spray in the treatment of wounds needed to be discussed in detail by an expert panel. The aim of the interdisciplinary and inter-professional panel of experts from Germany, Austria and Switzerland (DACH region) was to develop a practice-oriented algorithm for the use of hemoglobin spray. The results thereof were formulated as a consensus and are summarized below.

The advanced concept for local treatment of chronic wounds

In the case of chronic wounds, treatment always begins with diagnosis and causal treatment. The subsequent local treatment of every chronic wound should be guided by the principles of moist wound healing. It is accordingly often based on the TIME concept, which comprises the factors of tissue management, infection control, moisture balance and wound edge [50]. A recent statement by Wund-D.A.CH, the umbrella organization of German-speaking wound healing societies and associations, however recommends extending this concept to include supportive substances or methods, such as growth factors (support) and oxygen, in order to also take these additional needs of wound healing into account [18]. It should be noted that these additive therapies should be applied successively rather than simultaneously, and be tested for efficacy. If a treatment does not lead to any improvement in the condition of the wound after a maximum of four weeks, the selected treatment regimen and the use of hemoglobin spray should be reviewed and possibly a different regime selected. Figure 3 shows a graphical representation of the extended concept of local chronic wound treatment.

Clinical positioning and treatment algorithm for hemoglobin spray

Hemoglobin spray is particularly suitable for poorly healing wounds that fail to show any significant improvement in condition even after 4 weeks of standard therapy. Figure 4 shows a graphical representation of the recommended clinical treatment algorithm.

Hemoglobin spray is recommended for acute and chronic wounds that fail to show any surface area reduction ≥40 % after 4 weeks of standard therapy. This indication is based on the statistically significant predictor for the probability of healing for leg ulcers after 12 and 24 weeks [20]. Before application, there should be adequate wound cleaning, possibly with antiseptic treatment as well as debridement according to the requirements of the wound. Subsequently, the spray is applied thinly and evenly to the wound, with 1 to 2 seconds of spraying being sufficient for an area of about 2 × 3 cm. This process must be repeated for each dressing change. Hemoglobin spray should be applied every three days as a rule. If, after 4 weeks of treatment, there is no improvement in wound condition compared to the previous treatment without hemoglobin spray, the treat-

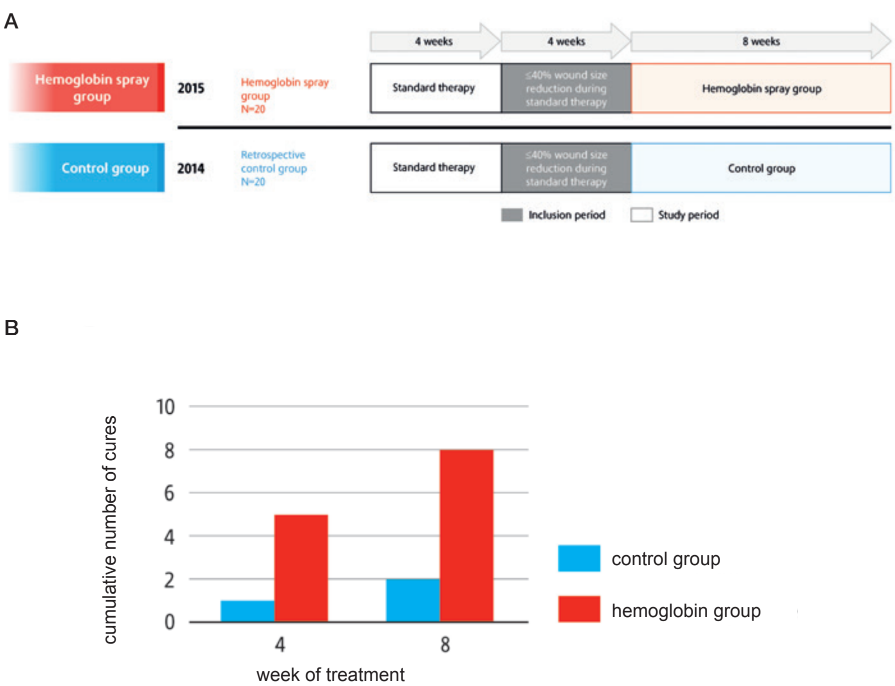

Figure 2
Results of a cohort study on patients with DFU:
A: Overview of the study.
B: Cumulative number of cures during the study period.

ment should be discontinued, as no benefit can be expected. However, if the healing process does show progress, further treatment with hemoglobin spray is recommended. The healing progress should be reevaluated in 4-week intervals or in the event of complications and treatment continued only if healing progresses.

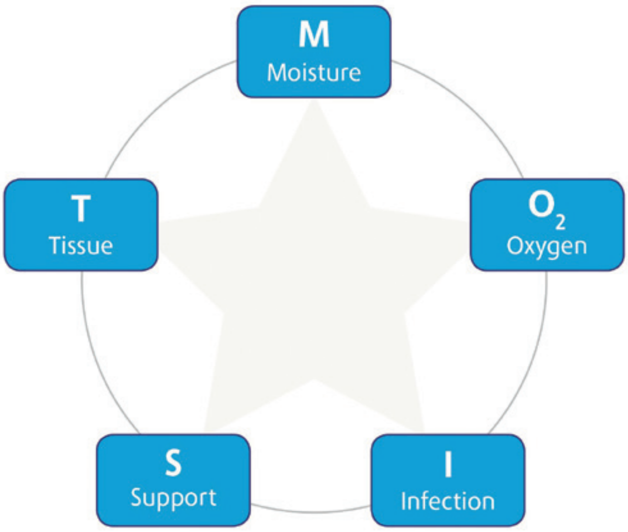

Figure 3
M.O.I.S.T. concept of local treatment of chronic wounds [18].

Benefit of hemoglobin spray in everyday care

The advantages of using hemoglobin spray in comparison to other oxygenation options are:

- simple application; hemoglobin spray can be applied independently by any therapist and possibly even by the patients themselves;
- location-independent application;
- low material costs;
- high application safety thanks to the good tolerance;
- versatile usage for nearly all types of wounds;
- fast impact thanks to the effectiveness immediately after introduction into the wound; the impact can be terminated just as quickly by discontinuation of the treatment.

Disadvantages of using hemoglobin spray in comparison to other oxygenation options are:

- Production from animal tissue. The hemoglobin is extracted from pig's blood, which – like any animal-derived materials – carries a potential risk of contamination. A rigorous manufacturing process can however reduce this danger to the point that the approving authorities have classified the potential residual risk as negligible.
- Muslims and other religious communities whose customs prohibit the consumption of pork and pig's blood must be informed about the origin of the active ingredient, as the use of hemoglobin spray for these groups can be problematic.
- The preparation's hemoglobin-related red color can leave marks on the clothes of patients and caregivers. Clinical experience however suggests that evaluating the progress of wound healing is not affected by the red color, as the spray can be easily washed from the skin with cold water.
- Hemoglobin spray requires a storage temperature of 2 °C to 8 °C. During the period of daily use, however, the product can be stored at room temperature for up to six week to facilitate handling. This can facilitate treatment in patients who find the spraying on of cold product to be unpleasant.

Potential limitations for the use of hemoglobin spray

- No positive effect may be expected from the hemoglobin spray for wounds that are not adequately cared for with respect to the causes. A rescue effect may nevertheless be achieved over a short period.
- The spray is not effective on heavily fibrin-coated wounds. However, if, for example, the fibrin layer is reduced or removed by debridement, subsequent application can be quite effective. If the wound shows sclerosis, shaving should be done before applying hemoglobin.
- Concomitant use with local antibiotics should be avoided because possible interactions have not yet been sufficiently tested.
- Hemoglobin spray is one of several treatment options in wound care. Although the benefit has been demonstrated by clinical studies and clinical experience, not all wounds necessarily benefit from the treatment.

Healthcare economic aspect

An estimated 1 % of the population develops chronic wounds of various etiologies in the course of their lifetime, with the incidence increasing with age [1, 34]. With regard to the demographic development of the population, it can be assumed that this figure will continue to increase in the coming years. Besides the obvious impact on the patient's quality of life, this represents a burden on the health system. In 2011, the Institute for Health and Care Economics (IGP Bremen) published a cost-benefit assessment of the treatment of chronic wounds that revealed an average cost of treatment per patient and treatment week of € 255.50 [29]. In case of treatment with hemoglobin spray (Granulox®), additional costs in the amount of € 9.72 /week (application every 3 days) are incurred. In relation to the total cost of treatment, this represents a relatively moderate increase of only 3.8 %, which is justifiable if treatment results in significant reduction of treatment time. To examine this effect, a meta-analysis (personal communication, SastoMed GmbH) consisting of three independent studies on treatment duration was conducted, which showed an average healing time reduction of 57 % (95 % KI [43 %; 71 %], $p<0.001$) given use of hemoglobin spray compared to the duration of treatment without using the spray. Although the methodological approach has

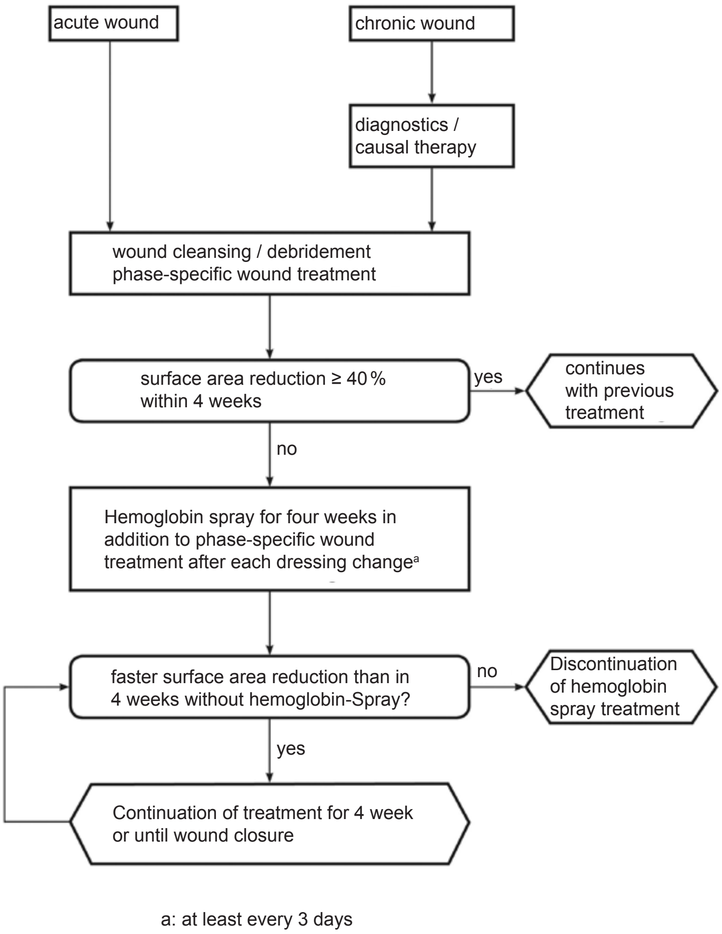

Figure 4
Application algorithm for hemoglobin spray in the treatment of wounds.

weak points and further healthcare economic studies would be desirable, the data available to date indicates that the significant acceleration of the healing process more than offsets the additional cost of the spray, and also offers an economic advantage alongside the patient benefit.

Conclusion of the expert consensus

Hemoglobin spray is well suited to supply wounds with supplemental oxygen and thus to promote healing processes in hypoxic wounds, particularly when no sufficient improvement in wound healing could be achieved beforehand through good standard therapy. Compared to other oxygenation options, it offers the advantage of simple application with few side effects and can often be applied by the patients themselves. From a healthcare economic perspective, the use of hemoglobin spray has benefits if the application is carried out in accordance with the clinically recommended algorithm and the effectiveness for each wound is checked regularly. Given the described usage recommendations as part of modern wound management, hemoglobin spray is an effective product that can be expected to achieve a healthcare economic effect thanks to the resulting healing time reductions.

Hemoglobin spray is suitable for acute and chronic wounds that fail to show any surface area reduction ≥40 % after 4 weeks of standard therapy. Treatment success should be evaluated at 4-week intervals and treatment should only be continued in case of healing progress.

Conflict of interest

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[1] **Chronic wounds: Hypoxia prevents healing! (Wundmanagement 2012; 5: 212–217)**

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