OPEN ACCESS

Research Article

Clinical results of the application of a hemoglobin spray to promote healing of chronic wounds

Klinische Ergebnisse zur Anwendung eines Hämoglobin-Sprays zur Förderung der Heilung chronischer Wunden

Peter Arenberger[1]
Peter Engels[2]
Monika Arenbergerova[1]
Spyridon Gkalpakiotis[1]
Francisco Javier García Luna Martínez[3]
Americo Villarreal Anaya[3]
Laura Jimenez Fernandez[4]

1 Department of Dermatology, Charles University in Prague, Third Faculty of Medicine, Prague, Czech Republic

2 EngelsConsult, Bergisch Gladbach, Germany

3 Secretaria de Salud, Ciudad Victoria, Tamaulipas, Mexico

4 Hospital Civil, Ciudad Victoria, Tamaulipas, Mexico

Abstract

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 hemoglobin 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 shown that the application of the hemoglobin spray promoted wound healing in all analyzed cases.

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. 9 patients from a series of therapy observations in Monterrey (Mexico) showed similar observations. 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: The application of hemoglobin spray can promote healing of chronic wounds.

Within the framework of the clinical investigation, the treatment observations, and the individual healing experiments the hemoglobin 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 hemoglobin spray.

Keywords: chronic wounds, hypoxia, hemoglobin, chronic venous insufficiency (CVI), arterial occlusion, diabetes mellitus

Zusammenfassung

Ein neuer technologischer Ansatz zur Versorgung hypoxischer chronischer Wunden mit dem zur Heilung benötigten Sauerstoff ist eine feuchte Wundbehandlung mit wässrigen Lösungen, in denen gut gewebeverträgliche Sauerstoff-Binder eine erleichterte Diffusion von Sauerstoff aus der Umgebung (Raumluft aus einer offenporigen Wundauflage) zum Ulcus-Gewebe ermöglichen. Ein Produkt in Entwicklung enthält als Sauerstoff-Binder Hämoglobin vom Hausschwein (Hämoglobin-Spray). Klinische Untersuchungen (eine klinische Studie, Therapiebeobachtungen und individuelle Heilversuche) werden präsentiert, aus denen sich klinische Daten zur Wirksamkeit und Unbedenklichkeit ergeben.

Alle durchgeführten Anwendungen des Hämoglobin-Spray ergaben, dass die Wundheilung gefördert wurde. In einer klinischen Studie und einer unmittelbar nachfolgenden Serie von Therapiebeobachtungen konnten bei 39 von 42 Patienten (93%) die behandelten Wunden komplett geheilt werden. In gleicher Weise wurden die Wunden von

9 Patienten einer weiteren Serie von Therapiebeobachtungen in Monterrey (Mexiko) bis zur Abheilung behandelt. Individuelle Heilversuche in Witten (Deutschland; 6 von 8 Wunden (75%) abgeheilt) und in Prag (Tschechische Republik; 5 von 5 Wunden (100%) geheilt) bestätigen diese Ergebnisse: Anwendungen des Hämoglobin-Sprays können die Heilung chronischer Wunden fördern.
Dabei wurden die Anwendungen des Hämoglobin-Spray ausnahmslos gut vertragen, sämtliche beobachteten unerwünschten Ereignisse während der Anwendungen hatten andere Ursachen.
Im Rahmen der klinischen Studie, der Therapiebeobachtungen und der individuellen Heilversuche wurde das Hämoglobin-Spray über 2.000-mal in den chronischen Wunden von 82 Patienten angewendet. Es wurde durchgehend gut vertragen, und es gab keine unerwünschten Ereignisse, die verdächtig waren, möglicherweise unerwünschte Reaktionen auf das Hämoglobin-Spray zu sein.

Introduction

Reduced blood and oxygen supply to the skin and fatty tissue beneath it are some of the aspects commonly associated with chronic wounds [1], [2], [3], which are always ulcerations (defective tissue wounds). Hypoxia can be observed, in particular, in case of arterial occlusions (PAOD), Diabetes mellitus (Dm) and chronic venous insufficiency (CVI) – these three diseases are the main cause of 90% of chronic wounds with an internal wound healing disorder. Possibly, tissue hypoxia is the common etiology for pathological mechanisms underlying wound healing disorders [4], [5], [6], [7], [8].
An overall positive effect on wound healing through improvement in its oxygen supply is undisputed today [4], [5], [6], [7], [8]. Other recognized components for the treatment of chronic wounds are surgical (vascular surgery), medicinal (to improve local blood supply) and technical (normobaric and hyperbaric, local and systemic oxygen treatments) methods in clinical application.
The wound healing processes demand a sharply higher oxygen supply to the tissue so as to build up defenses against pathogens (respiratory burst, formation of ROS) [9] as well as to meet the increased metabolic demands for physiologic wound debridement and replacement of defective tissue with newly developing granulation tissue. These cell proliferation processes – including neo-vascularization and production of new intercellular matrix (in particular collagen synthesis) – require high levels of oxygen [10].
One therapeutic possibility is to supply the wound bed with the required amount of oxygen from outside. However, transudate and exudate excreted into the base of the wound from the exposed tissue, form an effective barrier for the diffusion of oxygen into the tissue in the region of the wound bed. Moist wound treatment is currently the recognized treatment standard especially for chronic wounds, since the healing of wounds is hindered when they dry up [1], [2], [3]. For the moisture to remain in the wound bed, the diffusion barrier must be removed – at least partly. This is made possible using a concept by Barnikol et al. [11] – e.g. with oxygen transporters that are brought onto the wound bed in aqueous solutions. The oxygen transporters clearly augment diffusion of oxygen by facilitated diffusion. However, these oxygen transporters should not hinder the wound healing process in any way and be non-toxic to cells. Hemoglobin taken from mammals is well suited as a transporter and, since it is soluble, can also transport oxygen molecules outside the erythrocytes. Moreover, it can be obtained cheaply and in almost unlimited quantities from slaughter animals intended for human consumption, it is naturally present in large amounts in animal bodies and is definitely not intrinsically toxic.
The preparation of this solution includes hemoglobin obtained from domestic pigs, as this hemoglobin does not pose any considerable or even life threatening health risks – for instance, pigs do not suffer from any prion diseases (TSE). This pig hemoglobin solution can be sprayed onto wounds (hemoglobin spray).
Clinical results obtained to date are presented below and are the basis for discussion with respect to the efficacy of the hemoglobin spray.

Methods

Hemoglobin spray

Hemoglobin spray is an aqueous liquid preparation (solution) containing pig hemoglobin. This is sprayed onto the wound bed following wound cleansing and is covered with a thin, nanofiber wound dressing which is permeable to air. The hemoglobin contained in the spray supplies the tissue at the wound bed with oxygen over a long period of time through diffusion [11].
The hemoglobin spray has a purely physical effect on the wound and does not contain any medicinally effective constituents.

Indications for use

Indications for the application of the hemoglobin spray include chronic wounds (ulcers) of the skin, crural ulcers (*Ulcus cruris*) of venous, arterial or mixed genesis, diabetic

ulcers, wounds that do not heal after amputations and pressure ulcers.
There are some medical prerequisites for application of the spray. The causative disorders and conditions *lege artis* must be treated: improvement of venous backflow through surgical sensitization or compression therapy, the possibility of surgical sensitization of chronic wounds of arterial origin, regulation of blood sugar level, release of pressure from amputation stumps, decubitus wounds etc.
Patients should not be allergic to any of the spray's contents or animal proteins.
Optimally, wounds should not exceed 35 cm^2, but their depth may reach deeper than the papillary dermis.
Hemoglobin spray must not be used on wounds in conjunction with other topical therapeutic medications or wound antiseptics since they might react with each other.

Scheme of application – wound conditioning and use of hemoglobin spray

The wound were cleansed as thoroughly as possible prior to application of the hemoglobin spray (removal of adherent deposits and crusts could take some days) so that the wound bed was laid free and the spray could come into direct contact with the sub-ulcerous tissue. After the wound bed was dried out using an absorbent cloth, the hemoglobin solution was sprayed in a thin layer (Figure 1 shows an example) and the wound was covered with an open-porous dressing. The spray was generally applied initially if possible on daily basis and if the wound healing process shows good progress, treatment intervals were lengthened (e.g. to every second or third day).

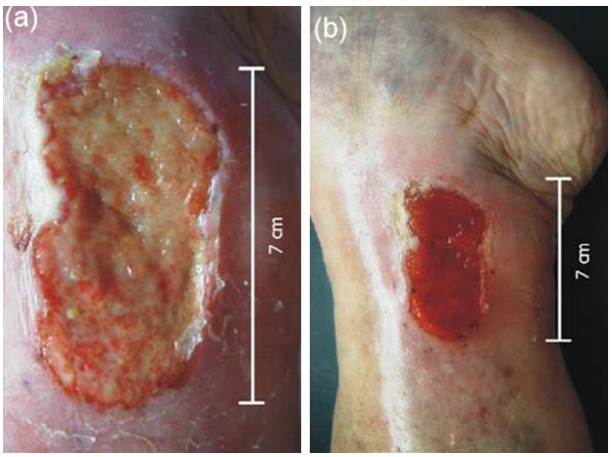

Figure 1: A chronic wound (a) after debridement and (b) after application of the (intensive red colored) hemoglobin spray

Patients and wound treatments

Patients and their wounds, as well as deviations from the general application scheme as described above can be found in the following chapters of the different treatments.

Clinical trial and treatment observations in Ciudad Victoria (Tamaulipas, Mexico)

In Cd. Victoria, capital city of the Mexican province of Tamaulipas, the health minister (*Secretaria de Salud*) in the province's government (Gobierno de Tamaulipas) carried out a clinical trial to determine the efficiency of hemoglobin spray treatment of chronic wounds in lower leg region.
The trial consisted of a clinical comparison between a group of patients who were treated with hemoglobin spray and a second group who received on-the-spot treatment with a method common in the region ("moist" wound treatment through water-impermeable occlusion of the wound surface with Vaseline° after intensive antisepsis, followed by use of a sterile bandage).
The total number of patients included in the study was 28 (see below).
The patients were randomly assigned to each of the two groups. The primary end point of the study was the time at which the chronic wounds healed completely.
The study type was prospective and longitudinal, monocentric and open-label, wounds were at least 8 weeks old and had until then been unsuccessfully treated using common local therapeutic methods, participation in the study was on a voluntary basis. All patients were informed about it and agreed with it, patients were randomly assigned to either of the two groups, diagnosis of vascular function by determining venous backflow (color Doppler sonography), venous refilling time using the "muscle pump" test (quantitative photoplethysmography), ankle brachial pressure index (ABI) as well as ischemic hypoxia through peri-ulcerous measurements of transcutaneous oxygen tensions.
The inclusion criteria were age over 20 years, wounds localized in the distal lower leg region (ankle region), adequate therapy of causative diseases, a wound surface of less than 35 cm^2, local restriction of an inflammation, and depth of wound not deeper than the subcutis (grade 2 or 3 according to Daniel [12]).
The exclusion criteria were known allergy against any component of the hemoglobin spray, a local macrovascular obstruction of the leg, severe lipodermatosclerosis, eroded wound borders, a severe systemic disease, smoking of over 20 cigarettes daily, alcohol or drug abuse as well as pregnancy.
After six months an intermediary evaluation of the comparative study was conducted, and due to the distinct positive results the study was closed.
The verum group was treated according to the general application scheme for hemoglobin spray (see above), and the traditional treatment consisted of antisepsis of the chronic wound and mechanical debridement by consecutive rubbing the wound bed with cotton pads immersed with 2 different antiseptics (benzalconium chloride, 0.12% and iodine solution, 0.8%), occlusion of the wound with a thin layer of Vaseline° (pharmaceutical

grade petroleum jelly), and sterile covering with cotton pads every second day.
All patients with wounds that had not healed after the first 6 month were now further treated with hemoglobin spray and therapeutic observations were conducted without involvement of a control group (not controlled).
In this part of the study, some additional patients were brought in who had wounds that did not meet the inclusion criteria for the comparative study.
In this way, the number of patients treated with hemoglobin spray increased to 42.

Therapeutic observations in Monterrey (Nuevo Leon, Mexico)

In Monterrey, patients were treated at a private (commercial) wound clinic (*Clinica Sangui*) using a hemoglobin spray that had been provisionally allowed in Nuevo Leon at that time. The severity of the wounds and the duration of the treatment varied largely.
The results of the treatment of 9 patients were documented completely in detail.
The following wounds were treated: 4 *Ulcus cruris mixtum*, from which 1 with Diabetes mellitus and 2 with arterial hypertension, and 5 *Ulcus cruris venosum*, from which 1 with Diabetes mellitus. All 9 patients suffer from long term chronic venous insufficiency.
All 9 patients' wounds had existed for several months or even a few years (on average 144 weeks, varying between 45 and 312 weeks).
Treatments were carried out following the general application scheme as described above.

Single patient uses at the University of Witten/Herdecke in Witten (Germany)

In Witten, the following patients and their varying wounds, which had been classified as “therapy resistant” or even as “untreatable” after analysis carried out by their previous physician, were treated in various single patient uses.

- m., 39 yrs: chronic wounds in amputation section of the forefoot (left) according to Lisfranc after an plastic acc. to Emmert (nail wedge excision) of the left big toe, PAOD Stage 4 (according to Fontaine),
- f., 83 yrs: chronic *Ulcus cruris mixtum* (ulcer of the medial ankle of the left foot) in CVI and PAOD – Stage 2
- m., 71 yrs: stagnant flat *Ulcus cruris* (ulcer of the right calf, lateral) in a *Papillomatosis cutis lymphostatica* (stasis dermatitis with eczema) with primary lymph edema
- f., 54 yrs: *Ulcus cruris venosum* (ulcer of the medial ankle of the right foot) in CVI with dermoepidermitis since several years
- m., 78 yrs: *Ulcus cruris venosum* (ulcer of the lateral ankle of the right foot in an old surgical scar) in CVI and PAOD – Stage 4
- f., 66 yrs: chronic *Ulcus cruris* (ulcer of the lateral ankle of the left foot) in CVI over a stiffened ankle joint (left leg paralyzed and shortened since birth), in addition local arteriovasculitis
- f., 52 yrs: therapy refractory medial malleolar ulceration (left.) in CVI, *Morbus Raynaud* and rheumatic collagenosis
- f., 70 yrs.: *Ulcus cruris* (ulcer of the medial ankle of the right foot) in a region of marked dermatoliposclerosis, recurrent over several years.

The patients were treated according to the general application scheme as described above with minor individual deviations, because the scheme was developed in the first place with these patients.

Single patient uses at the University Dermatology Department in Prague (Czech Republic)

In Prague, individual healing trials were carried out on 5 patients at the Charles University Dermatology Department using hemoglobin spray, with the support of a research grant provided by the Health Ministry of the Czech Republic, No. IGA NS/10093-3. During wound treatment under a thin wound dressing made of nanofibers and permeable to air, treatment with hemoglobin spray was also carried out according to the recommended mode of application.
All patients who were treated here were men, at least 65 years old (65, 69, 70, 71, and 74 years), were being treated for Diabetes mellitus over several years and had chronic wounds in the lower leg. The wounds had existed for at least 9 months and, in case of patient No. 4, the wound existed for 3 years without showing any tendency to heal. Treatment of the chronic wounds thus far carried out had followed the current therapy standards.
The hemoglobin spray was implemented as an additional step in the routine wound care protocol. After appropriate wound debridement and wound antisepsis the spray was applied. As wound dressing, in all cases an open porous polyurethane foam dressing was used. Patients were treated once daily, 5 days a week.

Results

Clinical trial and treatment observations in Ciudad Victoria (Tamaulipas, Mexico)

In Cd. Victoria, capital city of the Mexican province of Tamaulipas, the health minister (*Secretaria de Salud*) in the province's government (Gobierno de Tamaulipas) carried out a clinical trial to determine the efficiency of hemoglobin spray treatment of chronic wounds in lower leg region.
A set of data regarding disease status and epidemiology of patients included in the study or subsequent therapeutic observation was generated summarized in Table 1.

Table 1: Patient data relating to epidemiology and diseases

	Number	Proportion	Range	Average
Age	42		19–81	63.7
Sex – – Women	29	67%		
– Men	13	33%		
Smokers	2	2.4%		
Diabetes	27	69%		
Hypertension	24	57%		
BMI	42		17–41	29.4
Overweight	26	62%		
Venous insufficiency	38	90%		
Atherosclerosis	36	86%		
Peri-ulcerous hypoxia	35	85%		
Time period of wounds (weeks)	42		4–816	44.8

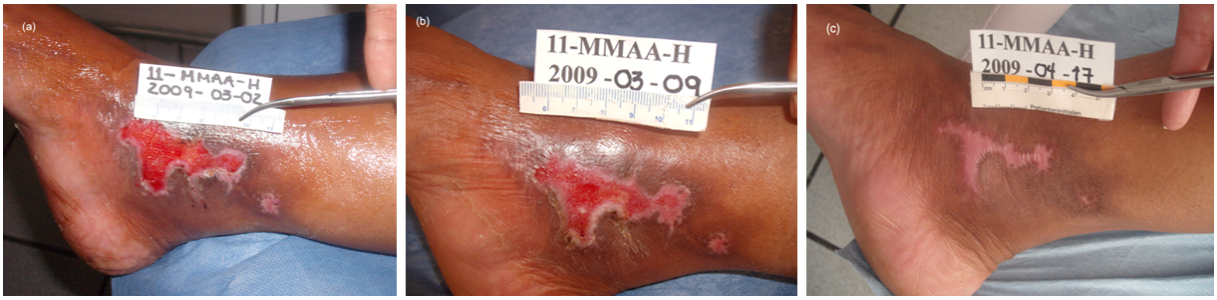

Figure 2: An example of a chronic wound at the beginning of the therapy (a), during treatment (b) and after healing (c) (Pat. 11-MMAA)

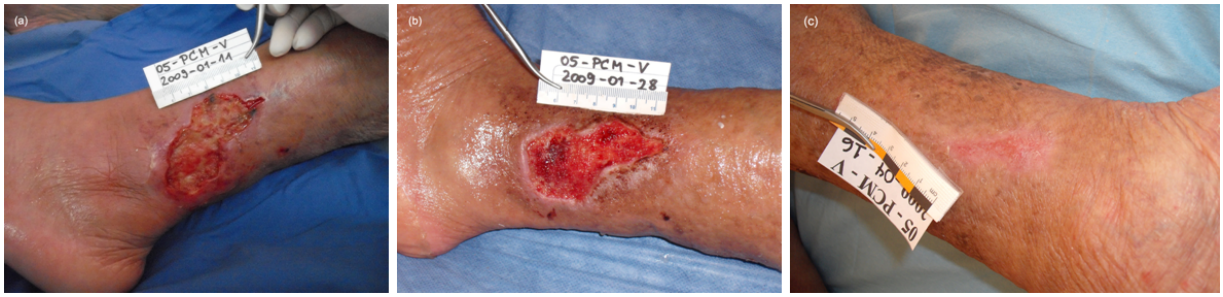

Figure 3: Second example for a chronic wound at the beginning of the therapy (a), in course of the treatment (b) and after healing (c) (Pat. 05-PCM)

After about 6 months 14 patients were taken into each of the two groups and treated accordingly. In the hemoglobin spray group the chronic wounds of 13 patients (93%) healed, whereas in the control group the wounds of only one patient (75%) were healed.

Due to the positive results achieved by the hemoglobin spray in the intermediary evaluation, after six months the comparative study was discontinued and switched to therapeutic observations.

Through treatment with hemoglobin spray, the wounds completely healed for 39 of the 42 patients. From the 3 patients whose wounds could not heal, two had vasculitis and the other one had osteomyelitis.

Only 2 patients, who were discharged after complete healing of their wounds, developed a recurrence of lesions in the same region due to venous insufficiency and social negligence.

Figure 2 and Figure 3 show examples of wound healing by initial, intermediate and final pictures of wounds of 2 patients (encoded with: 11-MMAA-H, and 05-PCM-V).

Within the framework of the clinical investigation carried out at the *Hospital Civil de Cd. Victoria*, the hemoglobin spray was applied almost 1,500 times on chronic wounds. In all cases, the spray was well tolerated and there were no undesirable events that might have resulted due to the application of the hemoglobin spray.

Therapeutic observations in Monterrey (Nuevo Leon, Mexico)

In Monterrey, patients with chronic wounds were treated using the hemoglobin spray that had been provisionally allowed by local authorities in Nuevo Leon for this pur-

Table 2: Duration of selected wound before treatment in Monterrey (weeks), number of treatments with hemoglobin spray in the clinic in Monterrey and total duration of treatment until complete healing of chronic wounds (weeks)

Duration of wound before treatment	Treatments with Hb-Spray	Duration of treatment until wound healing
Weeks	No.	Weeks
210	16	13.3
312	22	15.0
260	11	8.0
52	8	**19.7**
156	4	6.0
52	13	12.7
52	7	5.6
45	3	13.0
156	3	**4.0**
Σ	**9.7**	**10.8**

Table 3: Duration of selected wound before treatment in Witten (weeks), number of treatments with hemoglobin spray at the University in Witten and total duration of treatment until complete healing of chronic wounds (weeks)

Duration of wound before treatment	Treatments with Hb-Spray	Duration of treatment until wound healing
Weeks	No.	Weeks
26	(75)*	(53.1)*
≈ 104	38	26.1
6	7	1.9
12	12	2.3
≈ 234	24	21.3
48	120	31.8
71.7	**40.2**	**16.6**

Patient (*) turned out to be intermittently uncooperative and his treatment was interrupted for a 13 week period

pose. The severity of the wounds and the duration of the treatment varied largely.

All wounds of the 9 patients with a completed documentation were completely healed after a few weeks of therapy (on average 10.8 weeks, varying between 4.0 and 19.7 weeks).

Table 2 shows the number and duration of treatments performed to reach the clinical results.

Even wounds which were present for more than 3 years (156, 210, 260, and 312 weeks) were healed within less than about 15 weeks of treatment.

The number of documented cases in which the spray was applied totaled 231 – altogether, 24 patients were individually treated around 48 times with hemoglobin spray.

A total of 9 adverse events were reported in 2 patients. In none of these cases, a local inflammation, local or generalized allergic reaction, skin irritation, burning, pain or maceration of skin were reported that might have had an undesired effect of suspicious nature. The photographic documentation of the observations in the course of treatment also depicts good tolerability for the product.

Single patient uses at the University of Witten/Herdecke in Witten

The chronic wounds of the first 6 patients (75% of all patients) could be healed through application of the hemoglobin spray.

The wounds existed for 71.7 weeks on average (varying between 6 and 234 weeks) and were healed after treatment with the hemoglobin spray (after 16.6 weeks on average, varying between 1.9 and 31.8 weeks). Table 3 summarizes the results.

The 1st patient turned out to be intermittently uncooperative and, during his treatment, avoidable worsening of his wounds occurred, besides the fact that his treatments were interrupted for a 13 week period. Hence, these time values were not used to calculate the average value.

The 2nd patient, who lived around 45 km away, was alternately treated conventionally (moist wound padding) by a local community nurse.

The initially presented wound of the 6th patient healed after 74 treatments (76 days), but the scarred skin lying distally to the initial wound, in an area of pronounced *Atrophie blanche*, died off (through immunological obliteration?) rapidly (within a few days) and fell off in a moist

state during treatment of the wound. The healing of this (second, slightly larger) wound lasted till the 219th day.
These results obtained from single patient uses carried out on chronic wounds of varying genesis also clearly prove the efficacy of hemoglobin spray.
With regard to the safety of the use of hemoglobin spray, no adverse events were observed in any of the 276 applications in which the spray was applied on 8 patients (applied 150 times on one patient).

Single patient uses at the University Dermatology Department in Prague

The results of the treatment on the 5 patients in Prague also showed a positive influence on the healing of chronic wounds. In all five cases healing of the wounds treated with hemoglobin spray was observed within a time period of 8 to 12 weeks. Positive changes in the wounds could already be observed within the first two weeks following the start of the therapy. By the 3rd to 5th week there were clear signs of healing. Due to the treatment with hemoglobin spray, 3 of the 5 patients were discharged from the therapy after 8 weeks, while the two other patients had complete wound closure after 12 weeks.
Regarding compatibility, no allergic reactions or other irritations were observed. There was no pain when the spray was applied. All patients were very satisfied with the treatment.
Irrespective of the statistically small number of patients treated in this case, the observations here also show an effectiveness and good tolerability of treatment with hemoglobin spray.

Discussion

Oxygen is of utmost importance in the healing of acute and chronic wounds. Various studies have shown that oxygen is involved in all steps of wound healing including inflammation, granulation, neo-angiogenesis, re-epithelization and tissue modeling [5]. Therefore it is not surprising that reduced oxygen supply is a major driver of pathogenesis of chronic wounds. As in many cases, oxygen delivery is disturbed due to alterations in the vascular system (artheriosclerosis/micro- or macro-angiopathies/venous hypertension) leading to a hypoxic wound environment. In particular, chronic wounds are maintained due to this hypoxic status of the surrounding tissue. Several therapies have been proposed to improve the hypoxic status of tissues.
Hyperbaric oxygen therapies (HBOT) have shown to be effective. But, it seems to be important that the vascular system is functional and therefore HBOT may be less effective in the degenerated tissue of chronic leg ulcers [13]. Nevertheless, hyperbaric oxygen therapy is becoming an accepted treatment due to an increasing number of studies showing potential mechanisms of action, in particular as an adjunctive therapy.

Heng et al. [14] compared topical oxygen therapy with the standard treatment for necrotic gangrenous wounds lacking blood supply. Forty patients were included in the study, and 90% of patient ulcers that received topical HBO healed compared with 25% of patient ulcers treated with standard wound management therapy. No oxygen reperfusion damage was noted. The authors also demonstrated that the ulcers treated with topical oxygen had increased angiogenesis in the wound bed.
An alternative and attractive, while easy to handle, approach is the topical oxygen delivery or conveyance of oxygen via a transport system. Although several different topical oxygen delivery systems have been described for wound healing, most of them revealed only poor results in clinical trials. This may be due to inadequate delivery of oxygen across the wound base exudate layer, which acts as an oxygen diffusion barrier and prevents sufficient supply of oxygen to fibroblasts, keratinocytes and inflammatory cells necessary for wound healing.
The approach to facilitate oxygen diffusion by a transporter molecule like hemoglobin generated the possibility to enable a constant supply of oxygen to the wound bed after topical application of the hemoglobin spray to the wound. The evaluation of the clinical data summarized above showed a clear improvement of wound healing in terms of time and quality. With more than 50 documented cases analyzed, patients with a long treatment history of the chronic wound were released from therapy with closed wounds. Therefore, the use of hemoglobin to facilitate oxygen diffusion seems to be an ideal way to increase the oxygen supply to the wound bed and, as a result, enhancing the underlying wound healing processes. This is supported by the observations of fast onset of proliferative processes, in many cases within the first 2–4 weeks after first application of hemoglobin to the chronic wound.
All treatments using hemoglobin spray have shown that the healing of wounds was promoted and in many cases even accelerated. The clinical study carried out in Ciudad Victoria – aimed at getting hemoglobin spray approved in Mexico – with its focus on a homogeneous range of lower leg wounds and criteria set for the inclusion and exclusion of patients has produced a very clear result:
The healing of chronic lower leg wounds in 93% of the verum group in contrast to 7% in the control group in the initial clinical comparative study proves a clinical efficacy which goes well beyond the asserted objective of healing chronic wounds.
The decision of the authorities to discontinue deprivation of the patients in the comparison group from the hemoglobin spray on ethical grounds is clear proof that the clinical efficacy of the spray lies well above the efficacy of conservative treatment methods carried out in the region.
The study was opened ahead of schedule since it was no longer considered ethically acceptable for the personnel in charge to deprive the patients in the comparison group from a clearly better form of treatment (with the hemoglobin spray). In essence, the study resulted in a resounding affirmation of the efficacy of hemoglobin spray (which

is now approved for use as a medicinal product all over Mexico).

Follow-up therapeutic observations (with a widened spectrum of chronic wounds) confirmed this outcome: Almost all wounds could be healed through treatment with hemoglobin spray.

The success rate for all patients amounted to 93% (39 out of 42 patients) at the end of the treatments. Both results – the result of the comparative study as well as the overall result – revealed the same picture: Through treatment with hemoglobin spray, more that 90% of chronic wounds could be treated.

The therapeutic observations in Monterrey (Mexico) and the individual healing trials carried out in Witten (Germany) and Prague (Czech Republic) also support the overall result. The application of hemoglobin spray promotes the healing of chronic wounds.

Regarding tolerability, hemoglobin spray was always well tolerated and all the adverse events that were observed in the course of the treatments had other causes. Adverse events/reactions include, in particular, allergic reactions of the patients against animal hemoglobin. However, no such allergic reactions were observed in over 2,000 cases where the spray was applied on 65 patients. Currently, there is no evidence of limited tolerability of hemoglobin spray.

Conclusion

As described for the recent case studies in Prague, the only change of treatment regimen was to add the hemoglobin spray in the daily wound care routine. Therefore, the use of the hemoglobin spray can be perceived as a simple implementation in an existing wound care management procedure, but without any major changes of the established protocol – as the aqueous solution contains no further ingredients interfering with the wound healing process.

Notes

Funding

This study was partly aided through the research grant of the Health Ministry of Czech Republic No. IGA NS/10093-3.

Competing interests

The authors declare that they have no competing interests. Peter Engels has been consultant for SastoMed GmbH.

Acknowledgement

Dr. Jacob Rosales Velazquez, Director of Health Quality and Education as well as Dr. Jesus Flores Robles, Director of the Hospital I Civil de Cd. Victoria, worked with great engagement, sense of responsibility and good leadership skills within the framework of a clinical study at Hospital Civil de Cd. Victoria.

Dres. A. Teslenko and H. Pötzschke of the Department of Clinical Physiology at the University of Witten/Herdecke supported the concept and examined it clinically in the course of several single trial uses.

References

1. Deutsche Gesellschaft für Phlebologie. Leitlinien der Deutschen Gesellschaft für Phlebologie – Diagnostik und Therapie des Ulcus cruris venosum, Version 8. Mannheim; 2008. Available from: http://www.phlebology.de/Deutsche-Gesellschaft-fur-Phlebologie/diagnostik-und-therapie-des-ulcus-cruris-venosum.html [01.12.2011]
2. Morbach S, Müller E, Reike H, et al. Diagnostik, Therapie, Verlaufskontrolle und Prävention des diabetischen Fußsyndroms, Update. In: Scherbaum WA, Haak Th, eds. Evidenzbasierte Leitlinie der Deutschen Diabetes-Gesellschaft. Düsseldorf: Deutsche Diabetes Gesellschaft; 2008. Available from: http://www.deutsche-diabetes-gesellschaft.de/redaktion/mitteilungen/leitlinien/EBL_Fusssyndrom_Update_2008.pdf [01.12.2011]
3. Deutsche Gesellschaft für Angiologie/Gesellschaft für Gefäßmedizin. Leitlinien zur Diagnostik und Therapie der peripheren arteriellen Verschlusskrankheit (PAVK) – Stand: 27. April 2009. Karlsbad; 2009. Available from: http://www.awmf.org/leitlinien/detail/ll/065-003.html [01.12.2011]
4. Chambers AC, Leaper DJ. Role of oxygen in wound healing: A review of evidence. J Wound Care. 2011;20(4):160-4.
5. Schreml S, Szeimies RM, Prantl L, Karrer S, Landthaler M, Babilas P. Oxygen in acute and chronic wound healing. Br J Dermatol. 2010;163(2):257-68. DOI: 10.1111/j.1365-2133.2010.09804.x
6. Sen CK. Wound healing essentials: Let there be oxygen. Wound Repair Reg. 2009;17(1):1-18. DOI: 10.1111/j.1524-475X.2008.00436.x
7. Rodriguez PG, Felix FN, Woodley DT, Shim EK. The role of oxygen in wound healing: A review of the literature. Derm Surg. 2008;34(9):1159-69. DOI: 10.1111/j.1524-4725.2008.34254.x
8. Dissemond J, Körber A, Jansen T, Schneider LA. Sauerstoff in der Therapie des Ulcus cruris. Z Wundheil. 2005;10(6):252-6.
9. Gottrup F. Oxygen in wound healing and infection. World J Surg. 2004;28(3):312-5. DOI: 10.1007/s00268-003-7398-5
10. Grant ME, Prockop DJ. The biosynthesis of collagen. N Engl J Med. 1972;286:291-300. DOI: 10.1056/NEJM197202102860604
11. Barnikol WKR, Teslenko A, Pötzschke H. Eine neue topische Behandlung chronischer Wunden mit Hämoglobin und Sauerstoff: Verfahren und erste Ergebnisse. Z Wundheil. 2005;10(3):98-108.
12. Daniel RK, Hall EJ, MacLeod MK, Pressure sores-a reappraisal. Ann Plast Surg. 1979;3(1):53-63.
13. Löndahl M, Fagher K, Katzman P. What is the role of hyperbaric oxygen in the management of diabetic foot disease? Curr Diab Rep. 2011;11(4):285-93. DOI: 10.1007/s11892-011-0194-y
14. Heng MC, Harker J, Csathy G, Marshall C, Brazier J, Sumampong S, Paterno Gomez E. Angiogenesis in necrotic ulcers treated with hyperbaric oxygen. Ostomy Wound Manage. 2000;46(9):18-32.

Erratum

Originally Barrikol WK was indicated as eighth author.

Corresponding author:
Prof. Dr. Dr. Peter Arenberger
Dept. of Dermatology, Third Faculty of Medicine, Charles University in Prague, Srobarova 50, CZ-10034 Prague 10, Czech Republic, Phone: +420 267 163 000, Fax: +420 267 162 270
pa@avemedica.cz

Please cite as
Arenberger P, Engels P, Arenbergerova M, Gkalpakiotis S, García Luna Martínez FJ, Villarreal Anaya A, Jimenez Fernandez L. Clinical results of the application of a hemoglobin spray to promote healing of chronic wounds. GMS Krankenhaushyg Interdiszip. 2011;6(1):Doc05. DOI: 10.3205/dgkh000162, URN: urn:nbn:de:0183-dgkh0001621

This article is freely available from
http://www.egms.de/en/journals/dgkh/2011-6/dgkh000162.shtml

Published: *2011-12-15*
Published with erratum: *2011-12-28*