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PERSPECTIVE ARTICLE

Oxygen therapies and their effects on wound healing

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ABSTRACT

Oxygen is an important factor for wound healing. Although several different therapies investigated the use of oxygen to aid wound healing, the results of these studies are not unequivocal. This systematic review summarizes the clinical and experimental studies regarding different oxygen therapies for promoting wound healing, and evaluates the outcomes according the methodological details. A systematic literature search was conducted using Embase, Medline, Web of Science, Cochrane, PubMed publisher, and Google Scholar libraries. Clinical and experimental studies investigating oxygen for wound healing were selected. Included articles were categorized according to the kind of therapy, study design, and wound type. The methodological details were extracted and analyzed. Sixty-five articles were identified and divided in three different oxygen therapies: Local oxygen therapy, hyperbaric oxygen therapy, and supplemental inspired oxygen therapy. More than half of the included local oxygen and hyperbaric oxygen studies had one or more significant positive outcomes, 77 and 63%, respectively. Supplemental inspired oxygen therapy during gastrointestinal and vascular surgery was more likely to have a positive result than during other surgical interventions reducing surgical site infections. These many positive outcomes promote the use of oxygen treatment in the stimulation of wound healing. However, the lack of clinical studies and vast methodological diversity made it impossible to perform a proper comparison within and between the different therapies. Further randomized clinical studies are warranted to examine the value of these therapies, especially studies that investigate the more patient-friendly oxygen dressings and topical wound oxygen therapies. Also, to achieve more solid and consistent data, studies should use more standardized methods and subjects.

Wounds represent a major health problem, representing a significant source of cost to both patients and the health system.[1,2] It is estimated that 4% of the total healthcare costs are due to wound care.[1,3] This percentage is increasing, especially due to chronic wounds such as diabetic, venous and pressure ulcers.[3]

In normal wound healing oxygen is required for almost every step of the wound healing process, whether it is an acute, chronic, or surgical wound.[4,5] Oxygen is involved in increasing energy production for reparative processes such as cell proliferation, collagen synthesis, reepithelialization and for defense against bacteria.[6,7] Furthermore, oxygen and oxygen-derived hydrogen peroxide (H_2O_2) stimulate the production of reactive oxygen species (ROS).[8] ROS, for instance superoxide, are bacteriotoxic and important stimulators of angiogenesis.[5,9–13] In brief, oxygen is an essential element for success in the wound healing process.

Wounds, especially chronic wounds, often manifest reduced oxygen supply, leading to impaired leukocyte bactericidal activities and impaired wound healing.[14] Over the past decades, different supplemental oxygen therapies have been used to aid wound healing. Some therapies aim for a localized delivery of oxygen to the wound by external administration such as oxygen dressings and topical oxygen therapy (TWO_2). For TWO_2, a portable oxygen device is used to deliver a continuously flow of transdermal non-pressured oxygen directly to the wound bed. Other therapies focus on systemic oxygen administration, for example by supplemental oxygen inspiration during and after surgery. Supplemental inspired oxygen therapy delivers a high percentage of oxygen to the wound in a systemic way

but only when there is an intact blood supply to the wound tissue. Hyperbaric oxygen therapy (HBOT) is another way of systemic supplemental oxygen administration in which patients breathe 100% oxygen at a pressure greater than one atmosphere (ATM). In summary, there are three different forms of oxygen therapies examined and used in wound healing: local oxygen therapy such as oxygen dressings and TWO_2, HBOT, and supplemental inspired oxygen therapy.

The effects of the different kinds of oxygen therapies are still not clear. Numerous experimental and clinical studies investigated the effects of these therapies on wound healing of different wounds. However, the results are not unequivocal. Some of these studies reported positive results, whereas others reported no, or negative results.[6,15] Inconsistencies with regard to methodology were also noticed in these studies. We hypothesized that the use of oxygen might have a positive influence on wound healing under different, specified conditions, but that the inconsistent results of studies are partly due to differences in methodology. The purpose of this systematic review was to summarize the clinical and experimental studies known to date regarding the various oxygen therapies and to evaluate the outcomes highlighting the methodological details of the studies included.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement was used as a guideline for the reporting procedures of this systematic review.[16]

Literature search

A Biomedical Information Specialist of the Erasmus University Medical Center Library formulated a systematic search with the input and assistance of two reviewers (GdS, AM). Using the population, intervention, comparison, outcomes, and study design (PICOS) framework the search strategy was composed.[17] The following databases were used as information sources: EMBASE, Medline via OvidSP, Web of Science, Cochrane, PubMed as supply by the publisher and Google Scholar. These databases were systematically searched on February 23, 2016. Full search strategies and number of articles per database are shown in Supporting Information Appendix 1. After fulfilling the comprehensive search 3,814 articles were identified of which 3,060 articles remained after removal of duplicate articles.

Data selection

All clinical or experimental studies investigating oxygen for wound healing were included. There was no limit in date of publication except for studies investigating HBOT for wound healing, due to a systematic review of Wang et al.[18] that included all clinical HBOT articles published until August 2001. Hence, we included only clinical HBOT studies that were published after August 2001.

Two reviewers (GdS and LK) independently judged and included or excluded the 3,060 articles by title and abstract, using Endnote X6 for software management. Articles were only included if all reviewers independently included the article. When only one or two of the reviewers included an article, it was discussed and inclusion or exclusion was performed by consensus. The search was restricted to publications in English. Reviews, letters to the editor, and presentations were excluded.

All relevant references of each included article were checked manually. This references crosscheck was done to ensure major additional studies were not missed and to investigate whether the first literature search was done correctly.

Eventually, all included articles were obtained and studied in detail by two investigators (GdS and LK). A total of 65 articles were included in the final selection. The specific results of the search are shown in a PRISMA flow diagram (Figure 1).

Data extraction

Included articles were analyzed independently and extracted by two investigators (GdS, LK), looking mainly at the level of evidence, the descriptive nature and methodological quality of each study. To assess the quality of each included study the level of evidence was established according to the Oxford Centre for Evidence Based medicine levels of evidence.[19] The extracted characteristics, interventions and outcomes were systematically arranged and the study design and quality are described in the results. The following characteristics were classified: therapy, year of publication, first author, level of evidence (LoE), subject (animal species or human), number of subjects, nature of wound, treatment, duration of treatment, control treatment, measured endpoints, and outcome (positive significant [$p < 0.05$]/nonsignificant [$p > 0.05$]).

RESULTS

A total of 3,060 articles were identified of which 65 studies were judged eligible and included for final data analysis (Figure 1). The included articles were divided according the type of oxygen therapy and the kind of wound (Table 1).

Among these 65 studies, 17 studies tested the use of local oxygen therapy of which 7 studies tested an oxygen dressing therapy, 29 studies tested HBOT, 16 studies tested perioperative inspired oxygen for surgical site infections (SSIs), 1 study tested both TWO_2 and HBOT, and the remaining two studies tested other oxygen therapies. All methodological characteristics and outcomes of each included study are shown in Table 1.

Local oxygen therapy

Local oxygen therapy can be divided into two main subgroups: (1) oxygen dressings and (2) TWO_2. Although both have the same route of oxygen administration, oxygen dressings contain multiple chemicals that may affect wound healing. Furthermore, oxygen dressings have a continuous oxygen exposure in contrast to TWO_2.

Oxygen dressing therapy

Seven studies regarding oxygen dressing therapy were included.[20,21,23–26,84] Among these, two studies tested the dressing for chronic wounds and five studies tested this

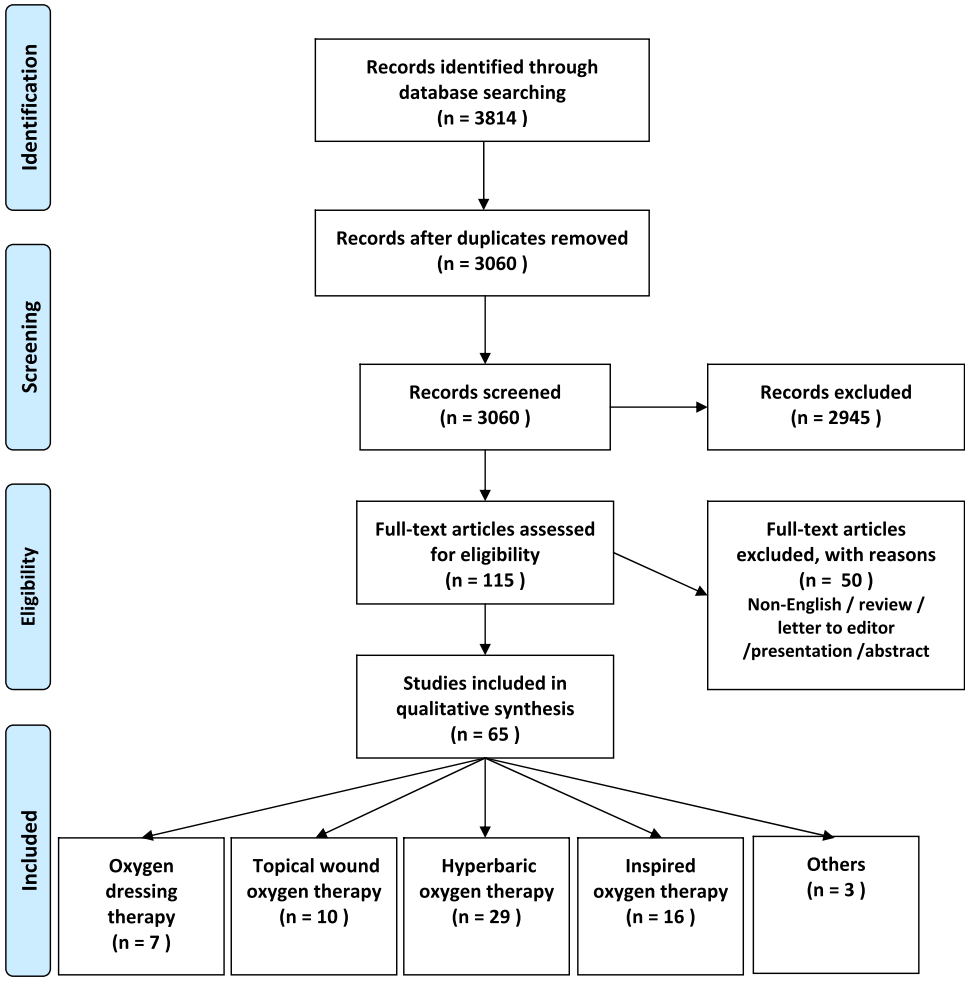

Figure 1. Prisma flow diagram.
Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. [Color figure can be viewed at wileyonlinelibrary.com]

therapy for acute wounds. Three studies obtained positive outcomes,[24,25,84] one study found no significant differences[20] and three studies evaluated several wound parameters, of which half proved positively.[21,23,26] The details of the dressings used in these studies are shown in Table 2.

Two clinical studies, one prospective randomized controlled trial[24] and one case study,[20] evaluated the use of oxygen dressings. Lairet et al. showed that patients treated with the oxygen-diffusion dressing (OxyBand) for their skin-graft donor sites had a significant 3-day decrease in wound healing time (compared with the Xeroform gauze dressing).[24] However, the follow-up was not defined in detail and other chemical characteristics than solely oxygen may have contributed to the positive effect in this small-sized study-group. This made it impossible to confirm the positive effect.

The case reports of Queen et al, demonstrated a complete healing within 28 days of wounds existing from one month up to two years in four patients after treatment with hydrogen peroxide.[20] Although only four patients with different co-morbidity were treated in this study, Queen et al. suggested that this oxygen dressing promotes wound healing.

Five experimental studies evaluated the effect of oxygen dressings. Chandra et al. tested a peroxide-based topical wound dressing on porcine full-thickness wounds.[22] Significantly faster reepithelialization, wound closure and more collagen were seen in the oxygen dressing treated wounds compared to the wounds in the control group.[22]

An enhanced rate of reepithelialization was also found in the partial-thickness study and the second-degree burns study of Davis et al.[25]

In the study of Zellner et al., a skin-flap model was used to determine if dissolved oxygen dressing would decrease skin flap failure rates.[23] Tissue treated with the oxygen dressing displayed significantly less dermal and subcutaneous inflammation, significant less bacterial load and significantly less dermal fibrosis and necrosis compared to the control dressing.[23] However, tissue located in the most distal 25% of the flaps treated with the oxygen dressing demonstrated significantly more subcutaneous fibrosis and necrosis than skin flaps treated with the control dressing.[23] Furthermore, the three abovementioned studies tested their different oxygen dressings in a porcine models and studied different anatomical depths of well

Table 1. Synopsis of results

Year	Author	LoE	Subject	*n* (wounds/ subject)	Type of wound	Treatment/duration	Control	Endpoints	Outcome
Oxygen dressing									
2007	Queen et al.[20]	4	Human	4	Chronic	Continuous	–	Wound surface	–
1995	Tur et al.[21]	5	Guinea	18	Chronic	Continuous	Placebo	Wound surface, perfusion	–, +
2015	Chandra et al.[22]	5	Porcine	5 (6–7)	Acute	Continuous	Control dressing	Wound closure, epithelialization, collagen	+, +, +
2014	Zellner et al.[23]	5	Porcine	4 (4)	Acute	Continuous	Hydrogel dressing	Necrosis, inflammation, ischemia fibrosis, bacterial load	–, +, –, +
2014	Lairet et al.[24]	2b	Human	17	Acute	Continuous	Xeroform gauze dressing	Wound closure	+
2007	Davis et al.[25]	5	Porcine	16 (240)	Acute	Continuous	No treatment	Epithelialization	+
2007	Harrison et al.[26]	5	Mice	16	Acute	Continuous	Placebo	Necrosis, breaking strength	+, –
Topical oxygen therapy									
2015	Azimian et al.[27]	1b	Human	100	Chronic	20 min 3 × day	Routine care	Wound closure, wound surface	+, +
2013	Tawfick et al.[28]	1b	Human	132	Chronic	180 min 2 × day	Conventional compression dressing	Wound closure	+
2012	Lo et al.[29]	5	Mice	15	Chronic (diabetic)	240 min/day	Room air	Wound closure, collagen	–, –
2010	Blackman et al.[30]	2b	Human	28	Chronic (diabetic)	60 min/day	Silver-based dressing	Wound closure	+
2010	Asmis et al.[31]	5	Mice	20 (2)	Chronic (diabetic)	Continuous	No treatment	Wound closure, epithelialization, collagen	+, +, +
2009	Tawfick et al.[32]	1b	Human	83	Chronic	180 min 2 × day	Conventional compression dressing	Wound closure	+
2009	Hirsh et al.[33]	4	Human	*6*	Chronic (diabetic)	Continuous	–	Wound closure	–

Table 1. Continued.

Year	Author	LoE	Subject	*n* (wounds/subject)	Type of wound	Treatment/duration	Control	Endpoints	Outcome
2005	Said et al.[34] Fries et al.[35]	5	Rabbit	46 (8)	Acute	Continuous	No treatment	Epithelialization, collagen	+, –
2005	Kalliainen et al.[36]	5	Porcine	4 (10)	Acute	180 min/day	Room air	Wound closure	+
2003	Azimian et al.[27]	4	Human	32 (52)	Chronic and Acute	90 min 4 × day	–	Wound closure	–
Hyperbaric oxygen therapy									
2016	Fedorko et al.[37]	1b	Human	107	Chronic (diabetic)	2.4 ATA, 90 min/day (30 sessions)	1.27 ATA, 27% O_2, 90 min/day	Amputation rate, wound surface	–, –
2015	Opasanon et al.[38]	1b	Human	40	Chronic and acute	2.0/2.4 ATA, 90 min/day	–	Wound surface	+
2014	Aydin et al.[39]	4	Human	10	Chronic (diabetic)	2.4 ATA, 120 min/day	–	Amputation rate	–
2014	Tuk et al.[40]	5	Rat	20 (2)	Chronic (diabetic)	2.4 ATA, 90 min/day	Room air	Perfusion, angiogenesis, inflammation, breaking strength	–, –, –, –
2013	Ma et al.[41]	1b	Human	36	Chronic (diabetic)	2.5 ATA, 90 min/day	Room air	Wound surface	+
2012	Kaur et al.[42]	1b	Human	30	Chronic	2.5 ATA, 90 min/day	Room air	Wound surface	+
2011	Feldman-Idov et al.[43]	2b	Human	385	Chronic	2.0/2.4 ATA, 90 min/day (29 median)	–	Wound surface	–
2010	Löndahl et al.[44]	1b	Human	75	Chronic (diabetic)	2.5 ATA, 85 min/day	Hyperbaric room air	Wound closure	+
2009	Kaya et al.[45]	4	Human	184	Chronic (diabetic)	2.4 ATA, 120 min/day	–	Amputation rate	–
2009	Chen et al.[46]	2b	Human	44	Chronic (diabetic)	2.5 ATA, 120 min/day (>10 sessions)	HBOT treatment (<10 sessions)	Wound closure	+
2008	Duzgun et al.[47]	1b	Human	100	Chronic (diabetic)	2–3 ATA, 90 min/day	Room air	Wound closure	+
2008	Ong[48]	4	Human	45	Chronic (diabetic)	2.5 ATA, 90 min/day	–	Wound healing	–

Table 1. Continued.

Year	Author	LoE	Subject	*n* (wounds/ subject)	Type of wound	Treatment/duration	Control	Endpoints	Outcome
2003	Kessler et al.[49]	2b	Human	27	Chronic (diabetic)	2.5 ATA, 90 min 2 × day	Room air	Wound surface	+
2003	Abidia et al.[50]	2b	Human	18	Chronic (diabetic)	2.4 ATA, 90 min/ day	Room air	Wound surface, wound closure	+, +
2002	Kalani et al.[51]	2b	Human	38	Chronic (diabetic)	2.5 ATA, 90 min/day (40–60 sessions)	Room air	Wound closure, amputation rate	–, –, –
2014	Nolen et al.[52]	2b	Human	89	Acute	HBO therapy	Room air	Infection	–
2014	Yildirim et al.[53]	5	Rat	63	Acute	2.5 ATA, 120 min/ day	Room air	Edema, necrosis, inflammation	–, –, +
2013	Selcuk et al.[54]	5	Rat	32	Acute	2.5 ATA, 90 min/ day	Room air	Necrosis, epithelialization, fibrosis, inflammatory cell response	+, +, +, +
2012	Selcuk et al.[55]	5	Rat	32	Acute	2.5 ATA, 90 min/ day	Room air	Flap survival, vascularization, granulation, inflammatory cell response	+, +, +, –
2011	Vishwanath[56]	2b	Human	10	Acute	2.5 ATA, 60 min/ day (7 sessions)	Standard treatment	Flap survival, flap edema, venous congestion, period of postoperative recovery	–, –, –, –
2008	Roje et al.[57]	2b	Human	99	Acute	2.2/2.8 ATA	Room air	Skin graft lysis, necrosis, granulation, deep soft tissue infection, osteomyelitis	+, +, +, +, –
2007	Zhang et al.[58]	5	Rat	38	Acute	2.5 ATA, 90 min/ day	Room air	Necrosis, granulation, vascularization	+, +, +

Table 1. Continued.

Year	Author	LoE	Subject	*n* (wounds/ subject)	Type of wound	Treatment/duration	Control	Endpoints	Outcome
2005	Sheikh et al.[59]	5	Mice	29	Acute	2.1 ATA, 90 min 2 × day	Xeroform gauze dressing	Angiogenesis	+
2005	Bilic et al.[60]	5	Rat	70	Acute	2.5 ATA, 60 min/ day	Hyperbaric hypoxia	Edema, angiogenesis, necrosis, leukocytes margination, regeneration active follicles, epithelialization	+, +, –, –, +, +
2005	Zgonis et al.[61]	2b	Human	35	Acute	2.0 ATA, 120 min/ day	–	Level of amputation, use of revascularization procedures, wound closure, *n* HBO treatments	–, –, –, –
2004	Tümerdem et al.[62]	5	Rat	30	Acute	2.5 ATA, 80 min (46 sessions in 20 days)	Room air	Graft survival area	–
1998	Quirinia et al.[63]	5	Rat	60	Acute	2.4 ATA, 90 min/ day	Hydrocolloid dressing and no dressing	Necrosis, wound surface, breaking strength	–, –, +
2005	Hopf et al.[64]	5	Mice	–	None (matrix model, Murine Matrigel®)	1.0/2.0/2.5/3.0 ATA, 90 min 2 × day	Hypoxia and normoxia	Angiogenesis, VEGF	+, +
2000	Sheikh et al.[65]	5	Rat	63	None (wound cylinder)	2.1 ATA, 90 min 2 × day	Room air	VEGF	+
Supplemental inspired oxygen									
2016	Schietroma et al.[66]	1b	Human	239	Surgical wound	80% Peroperative	30% inspired oxygen	SSI	+
2015	Kurz et al.[67]	1b	Human	555	Surgical wound	80% Peroperative	30% inspired oxygen	SSI	–

Table 1. Continued.

Year	Author	LoE	Subject	*n* (wounds/ subject)	Type of wound	Treatment/duration	Control	Endpoints	Outcome
2014	Schietroma et al.[68]	1b	Human	81	Surgical wound	80% Peroperative and for 6 hours after surgery	30% inspired oxygen	SSI	+
2014	Von Bormann et al.[69]	2b	Human	66,226	Surgical wound	100% Peroperative	30% inspired oxygen	SSI	+/–
2014	Wadhwa et al.[70]	1b	Human	400	Surgical wound	80% After extubation until first postoperative morning	30% inspired oxygen	SSI	–
2013	Duggal et al.[71]	1b	Human	831	Surgical wound	80% Peroperative and for 1 hour after surgery	30% inspired oxygen	SSI	–
2012	Thibon et al.[72]	1b	Human	434	Surgical wound	80% Peroperative	30% inspired oxygen	SSI	–
2011	Bickel et al.[73]	1b	Human	210	Surgical wound	80% Peroperative and for 2 hours after surgery	30% inspired oxygen	SSI	+
2011	Scifres et al.[74]	1b	Human	585	Surgical wound	80% Peroperative and for 2 hours after surgery	25–30% inspired oxygen	SSI	–
2011	Turtiainen et al.[75]	1b	Human	274	Surgical wound	30% For 48 hours after surgery	Room air	SSI	–
2008	Gardella et al.[76]	1b	Human	143	Surgical wound	80% Peroperative and for 2 hours after surgery	30% inspired oxygen	SSI	–
2007	Myles et al.[77]	1b	Human	2050	Surgical wound	80% Peroperative	30% inspired oxygen	SSI	+
2005	Belda et al.[78]	1b	Human	291	Surgical wound	80% Peroperative and for 6 hours after surgery	30% inspired oxygen	SSI	+
2005	Mayzler et al.[79]	2b	Human	38	Surgical wound	80% Peroperative and for 2 hours after surgery	30% inspired oxygen	SSI	–
2004	Pryor et al.[15]	1b	Human	160	Surgical wound		35% inspired oxygen	SSI	–

Table 1. Continued.

Year	Author	LoE	Subject	*n* (wounds/ subject)	Type of wound	Treatment/duration	Control	Endpoints	Outcome
						80% Peroperative and for 2 hours after surgery			
2000	Greif et al.[80]	1b	Human	500	Surgical wound	80% Peroperative and for 2 hours after surgery	30% inspired oxygen	SSI	+
Other									
2014	Sano et al.[81]	5	Mice	24 (4)	Chronic (diabetic)	Continuous topical oxygen	–	Wound surface, granulation, vascularization	+, +, –
2008	Gordillo et al.[82]	2b	Human	57 (32 HBO - 25 TO)	Chronic	2.0–2.5 ATA HBOT, TWO2: 90 min/day	–	Wound closure: HBO, TO, VEGF expression: HBO, TO	–, +,–, +
1994	Pandit et al.[83]	5	Rabbit	18 (4)	Acute	Topical oxygen, 180 min/day (70%)	–	Wound surface, wound healing, collagen, vascularization, inflammatory response, epithelialization	–, +, –, –, –, +

ATA, atmospheres absolute; LoE, level of evidence; SSI, surgical site infection; VEGF, vascular endothelial growth factor.
+, positive significant outcome ($p < 0.05$).
–, nonsignificant outcome ($p > 0.05$).

Table 2. Dressing used in the included studies investigating oxygen dressing therapy

Study author	Type of dressing	Chemical structure main component	Trade name	Manufacturer
Queen et al.[20]	Oxygenating hydrogel dressing	H_2O_2	Oxyzyme Dressing	Insense (Sharnbrook, UK)
Tur et al.[21]	Hydrogen peroxide cream	H_2O_2 (3%)	–	Karin Herzog (Basel Switzerland)
Davis et al.[25]	Topical oxygen emulsion	Perfluorocarbon	–	TherOx Inc (Irvine, CA)
Harrison et al.[26]	Sodium percarbonate (SPO)	$2Na_2CO_3 \cdot 3H_2O_2$	–	SPO (Geel, Belgium)*
Zellner et al.[23]	Dissolved oxygen dressing	Polyacrylamide polymer†	OxyGenesys	AcryMed (Beaverton, OR)
Lairet et al.[24]	Oxygen-diffusion dressing		OxyBand	OxyBand (St. Louis, MO)
Chandra et al.[27]	Sodium percarbonate (SPO) and calcium peroxide (CPO)	$2Na_2CO_3 \cdot 3H_2O_2$	SPO/CPO dressing	Sigma-Aldrich (St. Louis, MO)

*In collaboration with others for additional components and processing.
†Acts like an oxygen reservoir.
Additional Supporting Information may be found in the online version of this article.

vascularized and avascular tissues, which made comparison between these studies impossible.

Tur et al. tested a hydrogen peroxide dressing for ischemic ulcers in guinea pigs.[21] They found a significant higher blood flow in the treatment group on day 2 and 15 of treatment, when compared to the placebo group.[21] However, visual observations of the wound surface showed no significant differences between groups.[21] Also no histological analysis was performed in this study.

Harrison et al. tested the feasibility of using implantable oxygen releasing biomaterials (polymeric oxygen generation [POG]) to provide a sustained release of oxygen to tissues with the goal of prolonging tissue survival and decreasing necrosis.[26] Only at early time points: 2 and 3 days, the POG group did show a significant better flap survival with less necrosis when compared to the control group.[26]

Topical oxygen therapy

A total of ten studies were included which examined the use of TWO_2 on skin wounds.[27–36] Seven studies tested this therapy for chronic wounds, two studies tested this therapy for acute wounds and one study tested TWO_2 for chronic wounds as well as for acute wounds. Seven studies had at least one or more significant positive outcomes.[27,28,30–32,34,35]

Six clinical studies, three randomized controlled trails,[27,28,32] one prospective controlled study[30] and two case studies[33,36] investigated the use of TWO_2. Tawfick et al. measured the effect of TWO_2 in wound healing of refractory venous ulcers (RVUs) using the primary endpoint of the proportion of ulcers healed at 12 weeks, in comparison with the conventional compression dressing (CCD) therapy.[32] The proportion of ulcers, completely healed by 12 weeks was 80% in the TWO_2 group in contrast to 35% of the CCD group.[32]

After this study, Tawfick et al. examined the mid-term efficacy of TWO_2 in managing RVUs and the recurrence rates, after a 5-year follow-up of 132 patients.[28] The median time to full ulcer healing was 57 days in the TWO_2 group, in contrast to 107 days in the CCD group.[28] During follow-up, 3 of the 51 healed TWO_2 managed ulcers showed signs of recurrence, in the CCD group 14 of the 30 fully healed ulcers showed signs of recurrence.[28] In the second study, Tawfick et al. enlarged their patient group by adding new patients to the initial patient group of their first study. Although the primary endpoints of the last study were the mid-term and long-term efficacy of TWO_2, they also investigated the same hypothesis of their first study. Despite that they mentioned this in their second publication, we have to be aware of the so called "salami slicing" of publications.[85]

Azimian et al. tested the use of TWO_2 on nondiabetic pressure ulcers in 100 patients.[27] After 12 days of treatment, the oxygen treated group showed a significantly greater number of complete wound healing when compared to the control group.[27] Also, the total mean of wound surface in the oxygen treated group was significantly lower than that of the control group.[27] Despite this positive effect, they only tested TWO_2 on pressure ulcers located on the ischial and sacral areas of the body and not on peripheral ulcers, which most studies investigated.

Blackman et al. compared the healing rates of chronic diabetic foot ulcers (DFUs) treated with pressurized TWO_2 for 60 minutes per day vs. DFUs treated with advanced moist dressing therapy (AMDT) in a prospective controlled study of 28 patients.[30] They found a statistically significant greater proportion of completely healed ulcers in the TWO_2 compared to the AMDT group.[30] Also, the authors described a selection bias in favor of the control group. The TWO_2 group would cover more serious wounds or wounds with a larger surface. In spite of these worse baseline characteristics in the TWO_2 group, the outcome was better.

Hirsh et al. evaluated the use of a transdermal sustained oxygen delivery system to promote the healing of chronic lower extremity wounds in six patients with diabetes.[33] Of the six wounds, which were nonresponsive to previous

treatments, five healed completely within 20 weeks after oxygen treatment.[33]

Kalliainen et al. evaluated the efficacy of TWO_2 as an adjunct to wound healing too, but they also determined which type of wounds were most responsive to this type of intervention.[36] In this case series, 58 wounds in 32 patients were treated with topical oxygen. No complications were found to be associated with this kind of therapy.[36] Furthermore, TWO_2 showed beneficial indications in promoting wound healing.[36] Especially, patients with venous stasis and diabetic hand ulcers showed a good response to TWO_2, with healing rates of respectively 92 and 91%.[36] Post-surgical lower extremity wounds, pressure ulcers, and neuropathic foot ulcers showed to be the least responsive to TWO_2.[36]

Four experimental studies investigated TWO_2. Asmis et al. examined whether the continuous treatment of wounds with pure oxygen at low flow rates would accelerate wound closure and would improve wound healing in a murine model of diabetic skin wounds.[31] A significant acceleration of wound closure as well as reepithelialization and collagen deposition were observed in the oxygen treated group.[31]

In another mice study by Lo et al., TWO_2 therapy showed no difference in closure rate between oxygen-treated and nontreated diabetic wounds.[29] Both studies used different types of oxygen delivery devices, which may have affected the outcomes. In addition, Asmis et al. used a continuous administration of oxygen to the wound bed whereas Lo et al. had an oxygen administration of 4 hours per day.

Said et al. investigated whether local oxygen delivery would be efficacious in an established and carefully controlled wound model in rabbits.[34] At day 5 and 8 after starting the oxygen therapy on the full-thickness wounds, a significantly greater epithelial coverage was seen in the oxygen treatment when compared to control group values.[34]

Fries et al. also tested the efficacy of TWO_2 in a full-thickness wound model, observing a significantly accelerated wound closure in the wounds treated with TWO_2.[35]

Hyperbaric oxygen therapy

In 2003, Wang et al.[18] wrote a systematic review on HBOT for treating wounds in humans, including studies up to August 2001. Fifty-seven studies (of which seven were RCTs) involving over 200 patients were included. Fifty-five studies were about different types of skin wounds, two about osteomyelitis. The overall found methodological quality was low and all studies were performed in a very heterogeneous group of patients. In summary, they concluded that HBOT might aid in wound healing for several different types wounds: (1) The authors of two randomized controlled trials concluded that HBOT provides a better graft survival, complete wound healing and less infection on compromised skin grafts. (2) Two randomized controlled trails and one case series investigated HBOT on osteoradionecrosis. However, these studies did not adjust for some important characteristics such as age and sex, the authors concluded that HBOT reduces osteoradionecrosis rates. (3) Thirteen case series investigated HBOT on soft tissue radionecrosis. Although not every study determined statistically significant differences, all studies reported positives effects. (4) Seventeen studies evaluated the efficiency of HBOT on gas gangrene looking mostly at rates of amputations, infection and clinical improvement. Most studies showed a beneficial effect of HBOT, but due to the great differences between studies, it is difficult to evaluate the therapeutic value of the effectiveness of HBOT on gas gangrene. (5) Three of the nine studies investigating HBOT on progressive necrotizing infections found significantly decrease in mortality rates in the HBO treated group compared to the control group. (6) Eight studies (two RCTs, four nonrandomized studies and two case series) investigating HBOT on nonhealing diabetic wounds concluded that HBOT significantly reduces wound size.[18]

HBOT articles in our review were published after August 2001 or were experimental studies.

A total of 29 studies using HBOT for skin wound healing were included.[37–65] Fourteen studies investigated HBOT for chronic wounds, 12 studies investigated HBOT in acute wounds, one study investigated HBOT in both chronic and acute wounds and two studies were performed in experimental wound models. Eighteen studies (62%) showed at least one or more significant positive outcomes.[38,41,42,44,46,47,49,50,54,55,57–60,63,64]

Eighteen clinical studies, five randomized controlled trails, five prospective cohort studies and three case series investigated the use of HBOT.

Randomized controlled trials

Löndahl et al. and Ma et al. both evaluated the effect of HBOT in the management of chronic DFUs.[41,44] Löndahl et al. found that at 1-year of follow-up, the HBOT group represented significant more patients with a completely healed wound.[44]

In the study of Ma et al., the reduction of the wound bed was significantly greater in the HBO-treated group.[41]

Kaur et al. evaluated the role of HBOT in the healing of chronic nonhealing wounds.[42] The HBOT group showed a 59% reduction of the wound area vs. 26% increase wound area in the control group.[42] After 30 days, completed wound healing was seen in three out of fifteen patients in the HBOT group vs. none in the control group.[42] No further follow-up was reported.

Duzgun et al. investigated the use of HBO for the treatment of foot ulcers in diabetic patients.[47] Foot ulcers in the HBOT group were more likely to heal and to undergo amputation distally to the metatarsophalangeal joint compared to the control group.[47]

Fedorko et al. also investigated the efficacy of HBOT in reducing the need for major amputations in patients with diabetes and chronic DFUs.[37] The indications for amputation and the wound healing were not statistically significant different between the HBOT group and the control group.[37] This study had a relatively short follow-up of 12 weeks. A longer follow-up may have resulted in other outcomes. However, numerous studies show a reduction in wound surface within the first weeks after starting HBOT.[49] Moreover, all five abovementioned studies have a relatively small simple size making external validity controversial.

Prospective cohort studies

Kessler et al. studied 28 patients with nonischemic chronic DFUs, undergoing HBOT.[49] Only after 2 weeks of

treatment, the reduction of the ulcer surface area in HBOT patients was significantly greater.[49] In the 4th week, the reduction of the ulcer was comparable between groups.[49]

Another prospective cohort study of Abidia et al. studied diabetic patients with nonhealing ulcers, undergoing HBOT.[50] At 6 weeks follow-up, there was a significant decrease of the median wound surface in the HBOT group of 100% compared with 52% in the control group.[50] Furthermore, five out of eight ulcers in the HBOT group were completely healed after one year, compared to one out of eight ulcers in the control group.[50]

Opasanon et al. studied 40 patients with nonhealing complex wounds, undergoing HBOT.[38] After 10 HBO treatments, wound size significantly reduced by an additional 16.9%.[38] However, the heterogeneous patient population and the lack of a control group in this study made conclusion of the positive effect complicated. Also, the more intensive wound care of the included patients may affect the outcome positively.

Kalani et al. investigated the long-term effect of HBO in treatment of DFUs.[51] After a follow-up of three years, 76% of the patients in the HBOT group were healed in contrast to 48% in the conventional group.[51] Amputation numbers were two of seventeen patients (HBOT) vs. seven of 21 patients (conventional).[51] However, the patients in the HBO treated patient group were significantly younger. This patient group may have had a better potential wound healing.

Vishwanath investigated the effects of HBOT on free flaps.[56] Flap survival, flap edema, venous congestion, and period of postoperative recovery were evaluated. None of these findings were significantly different.[56]

Retrospective studies

Feldman-Idov et al. described patients with ischemic wounds improving following HBOT.[43] 77.7% of the wounds improved and 15.2% fully recovered after HBOT.[43] Patients included in this study suffered from various underlying diseases that affect wound healing, making this a very heterogeneous study population.

Zgonis et al. investigated the relationship between HBOT and the outcome of partial foot amputations in diabetic patients.[61] Looking at the healing of the amputation site, absence of ulcers and further operations after their last HBO treatment, the patients were divided in a successful or failed postsurgical outcome group. When they compared these two groups, no significantly differences were seen in number of HBO treatments and days to final outcome.[61]

Chen et al. also evaluated the effectiveness of HBOT in the treatment of infected diabetic feet.[46] One group of 21 patients received less than ten sessions of HBOT and one group of 21 patients received more than ten sessions. Patients who received more than ten sessions (average of 22.8) showed a significant higher rate of successful wound healing.[46]

Roje et al. analyzed data of 388 male patients undergoing reconstructive surgery for Gustilo type 3 A, B, and C war wounds of the extremities.[57] Ninety-nine patients received HBOT. Deep soft-tissue infection, skin graft lysis and flap necrosis occurred significantly less in the HBOT group.[57] Osteomyelitis was also less frequent (15%) in patients receiving HBOT.[57] However, since only war patients were treated in this study, these outcomes are not representative for clinical patients.

Nolen et al. compared the complications in free flap reconstruction for mandibular osteoradionecrosis in patients treated with or without HBOT.[52] Although no significant differences in free flap reconstruction complications were found between both groups, there was marginal significance of increased infections in the patients treated with HBOT.[52] In addition, the authors provided limited information about the timing between HBOT and surgery.

Case series

Ong also studied diabetic patients undergoing HBOT for their foot ulcers.[48] Of the 45 cases Ong investigated, 32 patients (71%) had a positive outcome to HBOT.[48] No follow-up period was mentioned.

Kaya et al. evaluated whether HBOT could decrease major amputation rates for patients with DFUs.[45] Of the 184 patients treated with HBO, 115 (62.5%) completely healed, 31 (16.8%) showed no improvement and 38 (20.7%) underwent amputation of which 29 (76.3%) were minor and nine (23.7%) were major amputations.[45] Major amputations were associated with an increased Wagner grade classification of the DFU, the age of the patient and the wounds.[45]

Aydin et al. investigated the amputation rate in patients undergoing HBOT for diabetic hand infections.[39] Of the ten patients Aydin et al. investigated, ulcers of eight patients healed completely and two patients had to have one finger amputated.[39] No statistically differences were given.[39] The case series of Ong, Kaya et al. and Aydin et al. were of poor quality due to the absence of control groups and limited number of cases.

Eleven experimental studies evaluated the efficacy of HBOT on wound healing. To examine the effects of HBOT in wound healing impaired by diabetes, Tuk et al. evaluated the degree of wound tissue perfusion, inflammation, angiogenesis, and tissue breaking strength in a diabetic rat model.[40] No effects on the degree of inflammation and number of blood vessels could be observed. The tissue breaking strength improved, but did not reach statistical significance.[40] Only the quantity of hemoglobin in micro-blood vessels was significantly increased as well as the oxygen saturation of the hemoglobin at the venous end of the capillaries.[40] Unfortunately, the oxygenation of the wound bed itself could not be obtained.

Bilic et al. used rats with partial thickness burns to evaluate the effects of HBOT.[60] The main outcome measure was wound healing, characterized by edema formation, neoangiogenesis, regeneratory active follicles, necrosis, margination of leukocytes, and epithelialization. Edema formation, neoangiogenesis, regeneratory active follicles and epithelialization had positive significant outcomes in contrast to the control group.[60]

Quirinia et al. investigated the effect of HBOT vs. hydrocolloid dressing without HBOT and in combination with HBOT on the healing of ischemic incisional wounds and on flap survival in rats.[63] Only strain at breaking was significant decreased in the HBOT group.[63]

Yildirim et al. used 63 rats with soft tissue trauma to investigate the effects of HBOT on edema, necrosis and

inflammation.[53] A significant decrease in inflammation was detected in the HBO group compared to the control group.[53]

Tümerdem et al. investigated the effect of HBOT on the survival of a full-thickness skin graft applied on a previously irradiated area.[62] There were no statistically significant differences in graft survival rate and histological findings.[62]

Selçuk et al. investigated also the effect of HBOT on the survival of skin flaps using a rat model.[55] The HBOT had a significant positive effect on flap survival and vascularization and granulation tissue formation.[55] No statistically differences were found in inflammatory cell response.[55]

In addition to the previous study, Selçuk et al. investigated the effect of HBOT using a rat-model for burn wounds.[54] Necrotic areas were observed to be the smallest in the HBO treated group, the lowest rates of inflammation and fibrosis were found in the HBO group, which had better epithelialization too.[54]

Zhang et al. determined if HBOT improved random pattern skin flap survival in diabetic rats.[58] On the 7th postoperative day the reduction in necrosis of the flap area was significant better in the HBOT group.[58] Also, new-growth capillary vessels and granulation tissue thickness were significant improved in the HBOT group.[58]

Sheikh et al. concluded that Doppler imaging is able to detect and quantify wound tissue angiogenic enhancement due to HBOT, which increased wound perfusion in a mouse full-thickness wound model.[59]

Hopf et al. and Sheikh et al. evaluated if hyperoxia, created by HBOT, would influence vascular endothelial growth factor (VEGF) expression.[64,65] In both studies the VEGF production increased significantly, which would enhance neovascularization.[64,65]

Supplemental inspired oxygen

Sixteen studies regarding perioperative inspired oxygen therapy were included.[15,66–80] All, except for two,[69,79] were randomized controlled trials and investigated the influence of high-concentration supplemental inspired oxygen on the incidence of SSIs in a variety of surgical procedures. Of these surgical procedures, five of the seven studies investigating inspired oxygen in gastrointestinal surgery had significant positive outcomes on SSI.[66,68,73,78,80] Despite these positive outcomes, the previous meta-analysis of Patel et al. showed no evidence in reducing SSIs by the use of high inspired perioperative in abdominal surgery.[86] Also, in the meta-analysis of Klingel et al., no evidence is found that administration of high inspired oxygen would reduce the risk of SSIs in women undergoing cesarean section.[87]

Schietroma et al. investigated the effect of 80% inspired oxygen compared to 30% inspired oxygen perioperatively on the incidence of SSI in 81 patients undergoing elective colorectal surgery for rectal cancer.[68] The 80% oxygen group showed a significant lower incidence of SSI.[68]

Belda et al.,[78] Greif et al.,[80] Kurz et al.,[67] and Mayzler et al.[79] tested the same hypothesis in a comparable patient population, also undergoing colorectal surgery. Belda et al. enrolled 300 patients, Greif et al. 500 patients, Kurz et al. 555 patients, and Mayzler et al. a small group of 38 patients who underwent colorectal resection. Kurz et al. and Mayzler et al. found no significant difference between the 80% and the 30% oxygen groups.[67,79] Whereas Belda et al. and Greif et al. showed that the 80% oxygen group had a significantly lower incidence of SSI compared to the 30% oxygen group.[78,80]

Schietroma et al. again investigated the effect of supplemental inspired oxygen but this time in a population of 239 patients who underwent open surgery for perforated peptic ulcer.[66] The risk of SSI infection was significantly lower in the 80% group compared to the 30% group with 48%.[66]

Another significant decrease of the incidence of SSI was reported in the study of Bickel et al.[73] Here, the authors investigated the influence of 80% inspired oxygen on SSI in 210 patients undergoing open appendectomy.

Wadhma et al. tested if extending intraoperative supplemental 80% oxygen would reduce the risk of SSI and other complications in morbidly obese patients undergoing open or laparoscopic bariatric surgery.[70] Evaluation of 400 patients showed no significant difference between groups.[70]

In addition three comparable studies evaluated whether 80% supplemental inspired oxygen during and for one to two hours after cesarean delivery would decrease SSI.[71,74,76] Combining these studies together, a total of 1,559 patients underwent cesarean delivery. None of the three studies showed positive outcomes.[71,74,76]

Myles et al. evaluated whether peri-operative 80% supplemental inspired oxygen would decrease the duration of hospital stay after major surgery and reducing postoperative complications, such as wound infections.[77] Although patients in the 80% oxygen group had a significant lower incidence of postoperative complications, including SSI, no difference in the duration of hospital stay was observed between the 80 and 30% oxygen groups.[77]

Pryor et al. determined whether the routine use of supplemental oxygen would alter the incidence of SSI in a general surgical population, investigating 165 patients undergoing major intraabdominal surgical procedures.[15] Remarkably, the incidence of SSI was significant higher in the group receiving 80% oxygen than in the group receiving 35% oxygen.[15] However, because of the diversity of surgical procedures no subgroups of patients who might benefit from this therapy could be identified.

Thibon et al. also investigated if the use of 80% perioperative supplemental oxygen during routine abdominal, gynecologic and breast surgery would decrease the frequency of SSI in the first 30 days.[72] The frequency of SSI was 7.2% in the 30% oxygen group and 6.6% in the 80% oxygen group no significant difference was found.[72]

Von Bormann et al. evaluated whether the use of 100% oxygen would decreases SSI in patients undergoing general, gynecological, orthopedic and vascular surgery.[69] SSI decreased in all subgroups, but this was only statistically significant in the general surgery group and in patients undergoing peripheral vascular surgery.[69]

Turtiainen et al. investigated the effect of inspired oxygen on the incidence of SSI in patients undergoing lower limb revascularization.[75] The study group, consisting of 137 patients, received 30% supplemental inspired oxygen for the first 24 hours after surgery, while the 137 patients of the control group received normal breathing room air.

Sixty-three patients developed SSI of which 25 patients in the study group and 38 patients in the control group.[75] This outcome suggested that supplemental inspired oxygen tended to decrease the incidence of SSI, but this did not reach statistical significance. However, when looking only at the groin incisions, the SSI incidence in the supplemental oxygen group was decreased significantly.[75]

Other

Gordillo et al. observed the effects of HBO and TWO_2 therapies for chronic wounds in two patients groups.[82] A significantly improved wound closure as well as a significantly higher VEGF expression was seen in the TWO_2 treated wounds.[82] In the HBOT group no significantly differences were found, neither for wound closure nor for VEGF expression.[82] The small simple size, an unequal distribution of types of wounds and the different patient inclusion criteria of these two groups made comparison between HBO and TWO_2 impossible.

Two studies[81,83] investigated the effect of an oxygen permeable dressing or membrane in contrast to an oxygen impermeable dressing or membrane on wound healing. One from Pandit et al. used full-thickness defects in rabbits, the permeable dressing group receiving 70% oxygen. Only at week 3 of treatment, a significant decrease was observed with regard to the contraction, epithelialization, and healing of the wound in the oxygen group compared to the hypoxic group.[83]

The other study from Sano et al. compared a hypoxia group with a normoxic group to investigate the influence of hypoxia on diabetic wound healing in mice. Wound size significantly decreased and the granulation tissue was significant thicker in the normoxic group than in the hypoxic group.[81]

DISCUSSION

Oxygen is known to be an important factor in wound healing.[4] Impaired wound healing is thought to be partially caused by tissue hypoxia.[14,81] Several therapeutic modalities have been tried to improve tissue oxygenation and thus wound healing. These interventions vary from applying oxygen locally (both in air and in dressings) to systemic oxygen submission (normobaric or hyperbaric). The aim of this review was to summarize the studies regarding the use of oxygen therapy for improving wound healing. In general, we found that oxygen therapy might be beneficial in wound healing. We found that there is a wide range of differences in type, duration, and frequency of treatment. Also, the type of wounds studied varied greatly between studies. These and other factors will be discussed below.

Local oxygen therapy

Oxygen dressing therapy

Except for one study, all six included oxygen dressing studies had one or more significant positive outcomes. Looking at the endpoints of the studies, the oxygen dressing provided a faster wound closure and less inflammation. Also, the perfusion of the wounds treated with the oxygen dressing was improved. The majority of included studies were experimental animal studies. This made the overall level of evidence relatively low (Table 1).

Limitations: There was a great heterogeneity in type of study (human, animal), type of wound (chronic, acute), type of evaluation, and endpoints. This group mostly consisted of experimental studies and the number of subjects was small, especially in the human studies (only case reports). Wounds created in an experimental setting are not comparable to wounds of patients with potential underlying diseases. However, these identical wounds create perfect circumstances to compare different dressings or therapies. Also, exact compositions of the dressings are not clear and differ from one another and other chemical components may have played a part in the wound healing process (Table 2).

Recommendations: To conclude on the possible advantages of the oxygen dressings, further studies are required, especially clinical randomized studies, which investigate only one type of wound per study. These studies should standardize methodology, mentioning the main components of the dressings used and treat the control group with a placebo dressing instead of different types of dressings. Only then it is possible to compare oxygen dressings with other oxygen treatments.

Topical oxygen therapy

TWO_2 ensured a significant accelerated wound closure in the majority of TWO_2 studies including the three randomized controlled trials.

Limitations: Of all included TWO_2 studies, three studies were randomized controlled trails, with a high level of evidence. Although this type of oxygen therapy appeared to have a positive effect on wound healing, there are considerable differences in the way of application, especially duration of oxygen exposure. Furthermore, the low amount of studies makes comparison difficult. Nevertheless, this therapy and the oxygen dressing therapy are both relatively cheap and easy to use.

Recommendations: More investigation is necessary to determine if TWO_2 can be used in a clinical setting for wound care. To achieve this, further clinical studies should homogenize their way of application and duration of oxygen exposure and use a more standard control group. A cost-effectiveness analysis would be recommended when comparable studies investigating the different therapies have been published.

Hyperbaric oxygen therapy

Most HBOT studies included in this systematic review had a positive outcome. When focusing on the study endpoints, HBOT appeared to have a positive effect on wound closure, wound surface, vascular perfusion and angiogenesis.

Limitations: In this systematic review, the HBOT group comprised the most included studies. This group consisted of five randomized controlled trails and several clinical and experimental studies. Therefore, the level of evidence in the HBO studies is disparate (Table 1). Whilst there are some clear positive results, these disappeared after a longer period of follow-up. However, considering that HBOT induces angiogenesis, it has other clinical indications compared to the topical and supplemental inspired oxygen

therapies. Although HBOT is promising and well tolerated among most patients, it has several disadvantages: HBOT is potentially more toxic, more expensive and has more complications than the local oxygen therapy.[5]

Recommendations: Additional studies are needed to investigate the results of HBOT in comparison to the other therapies mentioned in this review, when suited. Also, more studies should consider and investigate the many contrasts between therapies and investigate which types of wounds have a better response on HBOT and which have not.

Supplemental inspired oxygen

A minority of included studies found a significant lower incidence of surgical site infection, when treated with high supplemental inspired oxygen during and after surgery. However, five out of the seven studies that investigated the use of supplemental inspired oxygen for exclusively gastrointestinal surgery had positive outcomes. This might be due to the generally frequent comorbidities of the study population and the high complication rate of gastrointestinal surgery, partly because of the potentially high bacterial load perioperatively. This positive outcome corresponds to the Cochrane review of Wetterslev et al.[88] Here, they also concluded that high supplemental inspired oxygen during colorectal and abdominal surgery decreases the risk of SSIs.[88] However, a large trial of Meyhoff et al., that investigated high-inspired oxygen during abdominal surgery showed no differences in SSIs rates between patients receiving 30 and 80% oxygen.[89] Although this randomized clinical trial included a great amount of various types of abdominal surgical procedures, they did not investigate the risk of SSI for every surgical procedure separately.

Limitations: All included supplemental inspired oxygen studies, except for two studies,[69,79] were randomized controlled trails. Therefore, the level of evidence is high (Table 1).

There were some differences in duration of therapy. Apart from that, supplemental oxygen might be harmful to patients suffering from chronic obstructive pulmonary disease, since their ventilation is oxygen-driven instead of carbon dioxide-driven. The application of this therapy was particularly investigated in abdominal and thoracic surgery, while the use of supplemental inspired oxygen during surgery of the extremities has still not been investigated properly. Furthermore, supplemental oxygen therapy is only applicable during the peri-operative period and not continuously or daily like the other oxygen therapies. Although some previous meta-analyses have shown no benefit of the supplemental inspired oxygen, these meta-analyses included heterogeneous studies. The included studies differed especially in the type of surgical procedure, the diagnosis of SSIs and the technical skills of the surgeons.[86,87]

Recommendations: Further investigation is needed to determine what kind of surgical interventions benefits from the use of high supplemental oxygen to lower the incidence of SSI, so more homogeneous patients groups can be evaluated. Also, the use of this therapy has to be investigated in surgery of the extremities during vascular, plastic, and orthopedic surgery.

In conclusion, all three different oxygen therapies investigated in this systematic review showed positive outcomes that might promote the use of oxygen as a therapeutic agent to improve wound healing. However, the lack of clinical studies, the vast methodological diversity and the different physiological mechanisms made comparison within and between these therapies, and the therapeutic value of each therapy impossible.

When the different therapies are summarized separately:

- Oxygen dressings seem to accelerate wound healing, providing less inflammation and a better perfusion of the wound. This relatively new therapy delivers a continuous high amount of oxygen to the wound bed. Furthermore, oxygen dressings are more patient-friendly in comparison with other oxygen therapies. However, the majority of studies that investigated oxygen dressings are experimental studies. Therefore more clinical studies are warranted.
- Topical oxygen therapy also delivers a high flow of oxygen by external administration directly to the wound bed. Most included studies showed a faster wound closure when treated with TWO_2. Also, this therapy is well suited to treat chronic wounds in the home situation.
- Hyperbaric oxygen therapy delivers 100% oxygen in a systemic way by a pressure greater than one atmosphere. HBO appeared to have a positive effect on wound healing, wound surface, vascular perfusion, and angiogenesis. It is a promising and well tolerated therapy but it has several disadvantages.
- Supplemental inspired oxygen (SIO) is only applicable during the perioperative period, possibly reducing SSIs in patients undergoing gastrointestinal surgery. SIO might be beneficial in decreasing SSIs rates in patients undergoing other surgical procedures too, but this remains to be investigated.

The different therapeutic modalities differ in costs, practical use and patient burden. In that perspective, focusing on local therapeutic modalities (i.e., oxygen dressings or topical oxygen) might be beneficial to create a possibility to treat patients at home, instead of during clinical admission.

In view of the generally positive outcome, the use of oxygen treatment seems promising in stimulating wound healing. To achieve more solid and consistent data, new studies must standardize methods and subjects. If done so, steps can be made to provide clinically applicable oxygen treatment.

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