MEDICINA:

Aspectos Epidemiológicos, Clínicos e Estratégicos de Tratamento

Benedito Rodrigues da Silva Neto
(Organizador)

Atena Editora
Ano 2021

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APRESENTAÇÃO

De forma geral sabemos que a Epidemiologia “é a ciência que tem como foco de estudo a distribuição e os determinantes dos problemas de saúde – assim como seus fenômenos e processos associados - nas populações humanas”. Ousamos dizer que é a ciência básica para a saúde coletiva, principal ciência de informação de saúde, fornecendo informações substanciais para atividades que envolvem cuidado, promoção de saúde, prevenção e/ou terapia pós dano ou pós adoecimento, envolvendo escuta, diagnóstico e orientação/tratamento.

As Ciências médicas são o campo que desenvolve estudos relacionados a saúde, vida e doença, formando profissionais com habilidades técnicas e atuação humanística, que se preocupam com o bem estar dos pacientes, sendo responsáveis pela investigação e estudo da origem de doenças humanas. Além disso, buscam proporcionar o tratamento adequado à recuperação da saúde.

Ressaltamos com propriedade que a formação e capacitação do profissional da área médica parte do princípio de conceitos e aplicações teóricas bem fundamentadas desde o estabelecimento da causa da patologia individual ou sobre a comunidade até os procedimentos estratégicos paliativos e/ou de mitigação da enfermidade.

Portanto, esta obra apresentada aqui em seis volumes, objetiva oferecer ao leitor (aluno, residente ou profissional) material de qualidade fundamentado na premissa que compõe o título da obra, ou seja, identificação de processos causadores de doenças na população e consequentemente o tratamento. A identificação, clínica, diagnóstico e tratamento, e consequentemente qualidade de vida da população foram as principais temáticas elencadas na seleção dos capítulos deste volume, contendo de forma específica descritores das diversas áreas da medicina,

De forma integrada e colaborativa a nossa proposta, apoiada pela Atena Editora, consegue entregar ao leitor produções acadêmicas relevantes desenvolvidas no território nacional abrangendo informações e estudos científicos no campo das ciências médicas. Finalmente destacamos que a disponibilização destes dados através de uma literatura, rigorosamente avaliada, fundamenta a importância de uma comunicação sólida e relevante na área médica.

Desejo uma excelente leitura a todos!

Benedito Rodrigues da Silva Neto

SUMÁRIO

CAPÍTULO 26

TOPICAL OXYGEN THERAPY IN WOUND HEALING: A SYSTEMATIC REVIEW

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ABSTRACT: Oxygen is recognised as an essential element in the wound healing process and, it is suggested that the topical application of oxygen may be a promising therapy in wound care. Thus the aim of this study was to conduct a systematic review of the current evidence for this therapy through the analysis of primary research studies published between January 2004 and December 2014. Published literature was identified using Scopus, B-On, Scielo, Pubmed, Ebsco Host and Medline databases. Exclusion criteria and quality indicators were applied and a total of 11 articles with different designs were included in the review. The results show that this therapy had potential in wound healing. The analysed literature presents the results of its effects in its various forms: pressurized, continuous and dissolved. Although the current results show this therapy has potential, randomised clinical trials are necessary to increase the scientific evidence of its effectiveness and to establish ideal parameters for its use in different types of wounds.

KEYWORDS: Oxygen; Topical administration; Wound Healing; Wounds and Injuries.

APLICAÇÃO TÓPICA DE OXIGÊNIO NA CICATRIZAÇÃO DE FERIDAS: REVISÃO SISTEMÁTICA DA LITERATURA

RESUMO: O oxigênio é reconhecido como um elemento essencial no processo de cicatrização de feridas e, sugere-se que a aplicação tópica de oxigênio pode ser uma terapia promissora no tratamento de feridas. Assim, o objetivo deste estudo foi realizar uma revisão sistemática das evidências atuais para esta terapia por meio da análise de pesquisas primárias publicadas

entre janeiro de 2004 e dezembro de 2014. A literatura publicada foi identificada usando as bases: Scopus, B-On, Scielo, Pubmed, Ebsco Bancos de dados Host e Medline. Critérios de exclusão e indicadores de qualidade foram aplicados e um total de 11 artigos foram incluídos na revisão. Os resultados mostram que esta terapia tem potencial na cicatrização de feridas. A literatura analisada apresenta os resultados de seus efeitos em suas diversas formas: pressurizado, contínuo e dissolvido. Embora os resultados atuais mostrem potencial dessa terapia, ensaios clínicos randomizados são necessários para aumentar as evidências científicas da sua eficácia e estabelecer parâmetros ideais para o seu uso em diferentes tipos de feridas.
PALAVRAS - CHAVE: Oxigênio; Administração tópica; Cicatrização de feridas; Feridas e lesões.

1 I INTRODUCTION

In the past few years there has been a worldwide increase in the prevalence of chronic wounds, leading to different levels of morbidity, decreased quality of life (1), increased health care costs (2) and a growing concern of healthcare professionals (3). Inevitably, new treatments that promote and speed up wound healing are necessary (4).

The term “chronic wound” is generally accepted but it has been debated and no simple definition has been agreed upon yet (5). According to Kirketerp-møller et al. (5) the most common concept suggests that the term chronic should be applied to “wounds older than 3 months of age”, however Kumar, Leaper (6) consider that a chronic wound is defined as a wound that does not heal in a period of 6 weeks. In addition, definitions such as “those not following normal wound healing trajectory” have been proposed (5). In fact, the exact mechanisms that contribute to poor healing of chronic wounds are still a subject of controversy but it is accepted that they result from both systemic and local factors (2). The aetiology of these wounds is diverse, however, more than 80% are associated with venous insufficiency, high blood pressure or diabetes mellitus (7).

Normal wound healing is a complex biological process in response to tissue injury (8). It involves a range of biochemical regulators (9) and sequential cell interactions that ensure the development of the healing process in its different phases: vascular, inflammation, proliferation and maturation (2).

The evidence that oxygen (O2) is essential in all phases of the wound healing process is significant (2,8,10–12). Hypoxia, which is the reduction of the partial pressure of oxygen (pO2) in tissues, caused by a decrease in blood supply, as well as vascular complications and other systemic limitations, is a key factor that limits healing (10,11). The levels of O2 in the wound result from the balance between its availability and its consumption. Not only can its availability be compromised by the factors previously mentioned, but also can demand be high as a consequence of metabolic needs in the different phases of the wound healing process (8).

Depending on the level of hypoxia in wounds, the cells may develop some adaptive

responses, such as increasing the rate of glycolysis and conservationof energy, or undergo cell death. Generally, acute mild to moderate hypoxia supports adaptation and survival but, in contrast, chronic extreme hypoxia leads to tissue loss (13). In the proliferative phase of wound healing acute hypoxia and reactive oxygen species (ROS) are important stimulators of angiogenesis, as both stimulate macrophages, fibroblasts, endothelial cells and keratinocytes to synthesize vascular endothelial growth factor (VEGF). VEGF stimulates endothelial cells to migrate, proliferate and form new capillaries (10,13,14).

The chronic hypoxia cannot sustain this process because a threshold level of oxygenation is required to support the metabolic needs of tissue remodeling (10). In the collagen maturation process that takes place in the extracellular matrix, the essential enzymes require O2 as a co-factor. In cases of chronic hypoxia, the cross-linking of the newly formed collagen is much poorer, with negative effects on the quality of new scar tissue. In turn, blood vessels cannot grow into the new extracellular matrix, in order to supply other cells, such as the fibroblasts necessary for collagen synthesis, with O2 and nutrients. Reepithelialization is also accompanied by high metabolic activity, whereby the different steps are dependent on O2 and ROS. Also the final stage of wound healing when there is a further restructuring of the extracellular matrix, is a highly O2 dependent process which only takes place suitably at a partial pressure of oxygen greater than 30 mmHg (3.999671 KPa) (14).

Thus, as previously mentioned, the importance of O2 in the tissue healing process is evident from considering the different processes outlined above, namely in the ATP synthesis; production of reactive oxygen species (ROS), which stimulate VEGF synthesis; and microbial growth inhibition through the promotion of macrophage chemotaxis, and the increase in leukocyte activity (15). Moreover, O2 increases the rate of collagen deposition, an important step in healing, which supplies the matrix for angiogenesis and tissue maturation (2,3,10,11,15–17).

According to Brimson, Nigam (3) wound bed hypoxia, particularly in chronic wounds can impair healing when dealth with by conventional care. Thus, improving wound bed oxygenation by increasing O2 delivery has been proposed as an alternative and innovative therapy in the treatment of these hard to heal wounds (3). In this way, Feldmeier et al. (18), Ishii et al. (4), Ladizinsky, Roe (8) and Schreml et al. (7) emphasise two oxygen wound therapies in order to promote the healing process: hyperbaric oxygen therapy (HBO) and topical pressurized oxygen therapy. Topical continuous oxygen therapy, also called continuous diffusion of oxygen and topical dissolved oxygen therapy are two additional therapies referred to in recent publications (8,15). Nevertheless, evidence is scarce, and that is the reason why studies are being developed in order to research the biological basis of this treatment, explain its mechanism and assess its effectiveness in comparison with standard therapies.

In HBO the patient is subjected to the inhalation of high percentage O2 at a pressure

of 2 to 3 atmospheres, in a hyperbaric chamber. Under these conditions, the paO2 of the blood is significantly increased, thus increasing the O2 carrying capacity of the blood and O2 delivery to the tissues. Several studies refer to the benefits of this therapy in chronic wound healing, where reduced O2 delivery to the wound may be a problem. However, these beneficial effects rely on an adequate blood supply to the wounded tissue and are affected by poor vascular supply. Therefore, pathologies associated with a reduction in vascular supply, such as diabetes mellitus, may compromise its effectiveness, since O2 delivery to the wound tissue will still be reduced (8). Also HBO is not without complications, the excessively high paO2 can be damaging, increasing the risk of multiorgan toxicity (7,8,19–21).

In order to overcome some of these risks, topical pressurized oxygen therapy was introduced in 1969 by Fischer as a healing promoting therapy (22). Originally called "topical hyperbaric oxygen" and, more recently, called “topical oxygen therapy”, it differs a lot from HBO (16). Topical pressurized oxygen therapy consists of putting a portable device (bag, boot or chamber) around the affected area or limb. The device is then inflated with O2 at pressures slightly above atmospheric pressure (usually less than 1.07 atmospheres) and with a high flow rate (5-60 L/min), creating an O2 rich environment along the wound surface. This therapy is generally carried out in 90-minute to 4-hour sessions, 3 to 5 days a week (8,15). TOT’s main goal is to supply adequate quantities of O2 to the wound tissue in order to keep a pO2 concentration close to 40 mmHg (5.332895 Kpa), usually found in healthy tissues with good blood perfusion (12).

Thus, according to PICO format (23) this systematic review intends to answer the research question “In chronic wounds, how does topical oxygen therapy affects wound healing?”. It was considered chronic wounds for “patient population or disease of interest”, topical oxygen therapy for “intervention or issue of interest” and wound healing for “outcome”. However “comparison intervention or group” and “time frame” were not applicable.

The aim of this systematic review was to identify and assess the quality of the evidence of topical oxygen therapy (TOT) in chronic wound care.

2 | METHODS

2.1 Design

The study was a systematic review which aimed to gather all the available evidence that fulfilled pre-determined eligibility criteria in order to answer the research question. The design of the review was checked against relevant criteria from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist (24) and the Cochrane Handbook for Systematic Reviews of Interventions (25).

2.2 Search methods

An electronic literature search was performed from September 2014 to December 2014 in different languages, such as Portuguese, English and Spanish and covered studies published between January 2004 and December 2014. Table 1 provides an overview of the search strategy.

Databases	DeCS[1] and MeSH[2] descriptors	Descriptor combinations considered
Scopus;	"Topical Administration";	"Oxygen" and "Wound Healing";
B-On;	"Oxygen";	"Oxygen" and "Wounds and Injuries";
Scielo;	"Hyperbaric Oxygenation";	"Oxygen" and "Wounds and Injuries" and "Wound Healing";
Pubmed;	"Wounds and Injuries";	"Hyperbaric Oxygenation" and "Wound Healing";
Ebsco Host;	"Wound Healing".	"Hyperbaric Oxygenation" and "Wounds and Injuries";
Medline.		"Hyperbaric Oxygenation" and "Wounds and Injuries" and "Wound Healing";
		"Topical Administration" and "Hyperbaric Oxygenation";
		"Topical Administration" and "Hyperbaric Oxygenation" and "Wound Healing";
		"Topical Administration" and "Hyperbaric Oxygenation" and "Wounds and Injuries";
		"Topical Administration" and "Oxygen";
		"Topical Administration" and "Oxygen" and "Wound Healing";
		"Topical Administration" and "Oxygen" and "Wounds and Injuries".

[1] http://decs.bvs.br/

[2] http://www.ncbi.nlm.nih.gov/mesh

Table 1. Search strategy

Articles were assessed for inclusion by five reviewers. If consensus could not be reached, another reviewer was consulted. Initial screening of articles was based according to their title and abstract and those who did not refer wound care were excluded. Therefore, there were a total of 624 articles potentially eligible for review. After this, selection criteria were used reading the abstracts of all the articles previously obtained. The defined exclusion criteria were applied, and those which only approached HBO, wound healing and studies made on animals were rejected, so a total of 31 articles was obtained. From these, the studies with total access for consulting and analysis were considered, resulting in 27 potential articles for this review. The quality of the 27 studies was assessed using the QualSyst tool (26) and those that not had a minimum threshold of a summary score of 0,55 were excluded. Finally, a total of 11 articles were included in the review (see Figure 1).

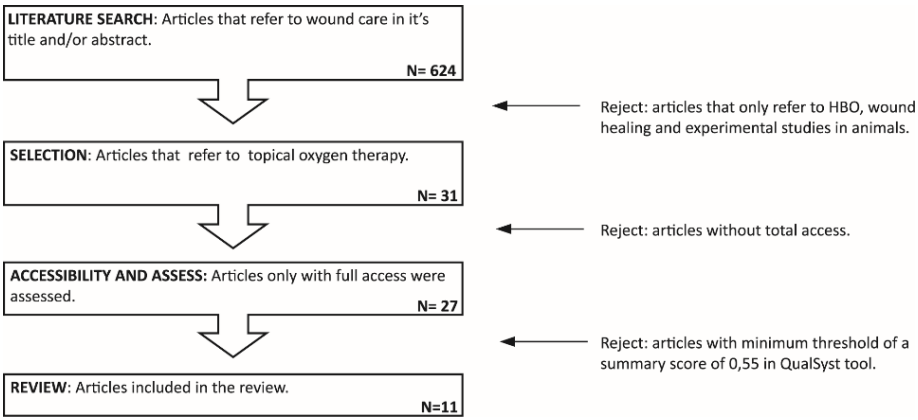

Figure 1. Flow diagram of the study selection process.

2.3 Quality appraisal

The quality of the 27 studies was assessed using the QualSyst tool. This tool incorporates two scoring systems to evaluate the quality of the studies potentially eligible for inclusion in our review: one for qualitative research and one for quantitative research (26).

The QualSyst tool for qualitative studies is a validated checklist consisting of 10 items with scores from 0 to 2, with the maximum total score of 20. A summary score was independently calculated for each study by 2 raters adding the total score obtained across the 10 items and dividing them by the total possible score of 20 (26). The median score between the two raters raters was then calculated.

The QualSyst tool for quantitative studies is a validated checklist consisting of 14 items with scores from 0 to 2 and the possibility to score "not applicable". Items "not applicable" to a particular study were marked "n/a" and were excluded from the calculation of the summary score. A summary score was calculated for each study by summing the total score obtained across relevant items and dividing by the total possible score of 28 (i.e.: 28 – (number of "n/a" x 2)) (26). As in qualitative studies, the evaluation was performed by two raters and the median score was calculated.

Of the 27 articles analised, 16 were excluded based on a minimum threshold of a summary score of 0,55 (26). Table 2 provides the quality assessment of the 11 articles using the QualSyst tool.

Study	Overall score					
	Qualitative sample			Quantitative sample		
	Rater 1	Rater 2	Median	Rater 1	Rater 2	Median
Feldmeier et al. (18)	0,60	0,50	0,550			
Gordillo, Sen (11)	0,60	0,50	0,550			
Howard et al. (15)	0,60	0,55	0,575			
Ladizinsky, Roe (8)	0,55	0,50	0,550			
Orsted et al. (21)	1	0,95	0,975			
Blackman et al. (16)				0,773	0,773	0,773
Gordillo et al. (10)				0,773	0,727	0,750
Ishii et al. (4)				0,700	0,700	0,700
Roe et al. (12)				0,889	0,889	0,889
Tawfick, Sultan (27)				0,909	0,773	0,841
Woo et al. (2)				0,800	0,800	0,800

Table 2. Quality assessment with the QualSyst tool

In addiction, five reviewers extracted and assessed in detail the data from the included studies (see Table 3). A structured data extraction was performed, focusing on: study design, country where the study was conducted, sample type and size, sample inclusion and exclusion criteria, aims and study limitations.

Study & Origin	Type of study	Sample type and size	Sample inclusion and exclusion criteria	Study aims	Study limitations
Blackman et al. (16) (Canada)	Prospective controlled study	Non probability Sampling, n=28	Inclusion: - Written informed consent; - Aged ≥ 18 years old; - Ankle-brachial index of at least 0.5 in the affected limb; - DFU with a grade 2-A or worse according to the University of Texas. Exclusion: - Chronic wound of non-diabetic origin; - Deep venous thrombosis; - Pregnancy or lactating; - Patients receiving palliative care; - HbA1c above 10%; - Non-adherent with therapy.	Compare the success rate of healing diabetic foot chronic wounds in the topical pressurized oxygen therapy group with the ones healed in the control group; compare the recurrence rate 24 months after in both treatment groups.	Potential selection bias: the allocation of people for treatment groups was based on its preferences and on the topical pressurized oxygen therapy device availability. The ulcers duration and area, which were bigger in the topical pressurized oxygen therapy treatment group than in the control group, may have underestimated topical pressurized oxygen therapy benefits. Lack of randomisation in the allocation.
Feldmeier et al. (18))	Review	Non probability Sampling, n=17.	Inclusion: - Studies in which topical pressurized oxygen therapy was the only treatment.	Analyse the outcomes and the level of evidence of the selected articles about topical pressurized oxygen therapy in chronic wounds.	Narrative review concerning different articles about the effectiveness of topical pressurized oxygen therapy in wounds: 13 out of the 17 articles included in the study represent a low level of evidence.
Gordillo et al. (10) (USA)	Non randomised controlled study	Non probability Sampling, n=57.	Inclusion: - Aged 30-70 years old; - Wounds with more than 4 weeks; - Non immunosuppressed or hypo-coagulated patients; - Written informed consent. Exclusion: - Patient previous treated with oxygen therapy to which will be submitted.	Assess and compare the effects of HBO and topical pressurized oxygen therapy in wound healing and in the expression of oxygen sensitive genes, including VEGF in biopsies collected from the wound edge.	Potential selection bias: the allocation of people for the treatment groups was based on its preferences and on the criteria established by the physician. Lack of randomisation in the allocation. However, the study allowed determining if topical pressurized oxygen therapy and HBO share the same action mechanism.

Study & Origin	Type of study	Sample type and size	Sample inclusion and exclusion criteria	Study aims	Study limitations
Gordillo, Sen (11) (USA)	Review	Non probability Sampling not mentioned	Inclusion: - Articles from pre-clinical and clinical in vitro studies which illustrate the mechanisms of topical pressurized oxygen therapy in promoting wound healing.	Analyse the outcomes and the level of evidence of topical pressurized oxygen therapy in wound healing and create a protocol for using this therapy.	Narrative review concerning several articles about the effectiveness of topical pressurized oxygen therapy in wounds, without a clear description of its selection. Lack of clarification about the sampling.
Howard et al. (15) (USA)	Review	Non probability Sampling, n=12.	Inclusion: - Studies on topical pressurized oxygen therapy, HBO and/ or topical continuous oxygen therapy.	Review the role of oxygen in wound healing; discuss the different action mechanisms, advantages and disadvantages of the three great therapies based on using oxygen (HBO; topical pressurized oxygen therapy; topical continuous oxygen therapy).	Narrative review concerning 12 articles about the effectiveness of TOT in wounds, without a clarification of the sampling criteria.
Ishii et al. (4) (Japan)	Case series	Non probability Sampling, n=2.	Not mentioned	Treat two cases of refractory foot ulcers with topical pressurized oxygen therapy. Monitor oxygen concentration in the device bag during the treatment.	Limitation in the size of the sample. Lack of aims and inclusion and exclusion criteria. No study limitations.
Ladizinsky, Roe (8) (USA)	Review	Non probability Sampling, n= not mentioned	Not mentioned	Review the importance of oxygen in wound healing. Explain the physiology of oxygen supply by HBO and topical pressurized oxygen therapy. Compare topical pressurized oxygen therapy and topical dissolved oxygen therapy.	Narrative review concerning different articles about the effectiveness of topical dissolved oxygen therapy or topical pressurized oxygen therapy in wounds, without a clear description of its selection. Lack of clarification about the sampling.

Study & Origin	Type of study	Sample type and size	Sample inclusion and exclusion criteria	Study aims	Study limitations
Orsted et al. (21) (Canada)	Systematic review	Non probability Sampling, n=9.	Inclusion: - 6 articles were selected because they approached topical pressurized oxygen therapy very specifically; - 1 website was considered because it included usage recommendations by the product manufacturer; - 2 articles were considered because they established the best approach on treatment and wound assessment patterns.	Put together a group of specialists to formulate a systematic review based on Delphi method, which supports the evidence and the clinical decision-making concerning topical pressurized oxygen therapy.	The sample does not include randomised clinical trials.
Roe et al. (12) (USA)	Pre-clinical study	Not applicable	Inclusion: - Samples of viable human skin with three types of thickness.	Determine the depth and extent of dissolved and pressurized oxygen penetration in skin samples.	
Tawfick, Sultan (27) (Ireland)	Parallel observational comparative study	Non probability Sampling, n=83.	Inclusion: - Aged ≥18 years old; - Written informed consent; - Chronic venous ulcer with more than 2 years without improvement in the last year; - Normal ankle-brachial index ≥ 0.9 and digital pressures (toe pressure) ≥ 0.7. Exclusion: - Bed ridden patients; - Ischaemic ulcers; - Diabetic ulcers; - Osteomyelitis; - Gangrene; - Deep venous thrombosis.	Analyse the safety and effectiveness of topical pressurized oxygen therapy in venous ulcers care and compare the outcome between this therapy and the conventional compression therapy.	Potential selection bias, because people's allocation for the treatment groups was based on their preferences. Ulcer duration and area, which were bigger in the topical pressurized oxygen therapy treatment group than in the control group, may have underestimated the benefits of this therapy. Lack of randomisation in the allocation.

Study & Origin	Type of study	Sample type and size	Sample inclusion and exclusion criteria	Study aims	Study limitations
Woo et al. (2) (Canada)	Pilot study	Non probability Sampling, n=9.	Inclusion: - Wounds with at least 1cm2 and 1 month of duration; - Ankle-brachial index >0.65, palpable pulse or toe pressure >50 mmHg (6.666118 KPa).	Assess the efficiency of transdermal continuous TOT in chronic wound healing of 9 people.	Limitation in the sample size, with multiple wound aetiologies and without control group. Age range, coexistence of other diseases and medications.

Table 3. Quality indicators of included studies

3 I RESULTS

3.1 Characteristics of the studies

The final sample included a systematic review from Orsted et al. (21), 3 non-randomised control studies from Blackman et al. (16), Gordillo et al. (10) and Tawfick, Sultan (27), 1 case series from Ishii et al. (4), 1 pilot study from Woo et al. (2), 4 reviews from Feldmeier et al. (18), Gordillo, Sen (11), Howard et al. (15) and Ladizinsky, Roe (8) and a pre-clinical trial from Roe et al. (12). Table 4 provides an overview of the characteristics of each study.

The sample type of the 11 articles is non-probability sampling. In the Orsted et al. (21) study, the sample is made of 9 articles. The samples size of the 3 non-randomised controlled studies ranges from 83 (27) , 57 (10) and 28 participants (16). In the Ishii et al. (4) and Woo et al. (2) studies the sample size is 2 and 9 respectively. Amongst the reviews, Feldmeier et al. (18) review is the one which quantifies the sample size (n=17). Finally, the pre-clinical trial does not quantify the number of human skin samples used, but it identifies the use of three types of skin thickness (2).

Except for Woo et al. (2), all the articles show evidence concerning topical pressurized oxygen therapy, 3 referred to topical continuous oxygen therapy (2,15,21) and 2 referred topical dissolved oxygen therapy (8,12). There are different contexts in the approach of these three forms of TOT in the different studies. This range of outcomes was to be expected as a result of the different types of design which constitute the sample and it broadens the set of results. Thus, presenting it in a more individualised way becomes pertinent.

The systematic review (21) and the 2 reviews (11,18) analysed the level of scientific evidence concerning topical pressurized oxygen therapy. The 2 remaining reviews (8,15) approach a more comprehensive topic emphasising also the importance of O_2 in wound healing. The non-randomised control studies assessed topical pressurized oxygen therapy effectiveness in comparison with other therapies: one of them compared it with HBO (10), the other one with the conventional compressive therapy (27) and the other one with silver

dressings (16) . For chronic wound care, the case series used topical pressurized oxygen therapy (4) and the pilot study used topical continuous oxygen therapy (2) . Finally, in the pre-clinical trial (12) , samples of human skin with three types of thickness were used in order to determine the dissolved or pressurised depth and extent of O_2 penetration in the samples.

Study	Study global topic	Type of device, forms of TOT and treatment duration	Type of wound	Patients/wound characteristics	Treatment effects
Blackman et al. (16)	Topical pressurized oxygen therapy effectiveness in diabetic foot chronic wounds in comparison with conventional treatment.	Topical pressurized oxygen therapy -used through a chamber. Treatment duration: daily 60 minutes, 5 days a week, during 90 days.	Diabetic foot chronic wounds.	Patients of both genres aged more than 18 years old with ankle-brachial index of at least 0.5 in the affected limb and diabetic foot ulcer(s) with a grade 2-A or worse, according to the University of Texas.	The rate of complete cure was significantly greater in the group with topical pressurized oxygen therapy care than in the control group. 14 out of 17 (82.4%) and 5 out of 11 (45.5%) respectively presented complete epithelialisation of the wound. In the follow-up stage during 24 months there was no recurrence in the area of the healed ulcer in any of the groups.
Feldmeier et al. (18)	Analyse the level of evidence of the selected articles about topical pressurized oxygen therapy role in chronic wounds.	Topical pressurized oxygen therapy The studies included in this review refer different forms of topical pressurized oxygen therapy (the chamber and the polyethylene bag are the most referred to).	The studies included cover topical pressurized oxygen therapy in wounds with different aetiologies (for example, diabetic wounds, venous ulcers, burnt, etc.).	Not applicable.	Up to date topical pressurized oxygen therapy in not adequately supported by scientific data as a strategic wound healing therapy.

Study	Study global topic	Type of device, forms of TOT and treatment duration	Type of wound	Patients/wound characteristics	Treatment effects
Gordillo et al. (10)	HBO and topical pressurized oxygen therapy effects in wound healing and in the expression of oxygen sensitive genes, including VEGF.	For topical pressurized oxygen therapy care, a disposable device connected to a portable oxygen supplier was used. Treatment duration: daily 90 minutes, 4 consecutive days in a week, until 14 weeks.	Venous ulcers, pressure ulcers surgical wounds, etc.	People: aged between 30-70 years old; non immunosuppressed or therapeutically hypo-coagulated; 52% diabetic; 52% male. Wounds: with at least 4 weeks; average 3.3 cm^3 of volume.	Increase of pO_2 in the wound tissue. The article supplies the first evidence that topical pressurized oxygen therapy significantly induces VEGF in wound edge tissue.
Gordillo, Sen (11)	Topical pressurized oxygen therapy level of evidence analysis in wound care and presentation of a protocol for using this therapy.	According to the Guideline presented in the study: disposable device (boot) connected to an oxygen cylinder or a concentrator which supplies 100% oxygen slightly above 1 atmosphere.	The selected studies cover topical pressurized oxygen therapy in chronic wounds with different aetiologies (for example: diabetic wounds, venous ulcers, etc.).	Not mentioned.	Topical pressurized oxygen therapy represents an additional tool for refractory wound treatment. There is evidence that justifies the usage of this therapy since it increases the collagen deposition, decreases the infection, induces a VEGF progressive increase and increases angiogenesis.
Howard et al. (15)	HBO, topical pressurized oxygen therapy and topical continuous oxygen therapy role in wound healing.	The studies on topical pressurized oxygen therapy use a bag, a boot or a chamber around the affected area. Refer topical continuous oxygen therapy through devices which supply a low oxygen continuous flow (3-12 ml/hour).	The studies covered in this review mention TOT in wounds with different aetiologies (for example: diabetic wounds, venous ulcers, burnt, etc.).	Not mentioned.	Increase of VEGF expression and angiogenesis, improvement in wound healing, reduction of multi-resistant infections, pain and venous ulcers recurrence.

Study	Study global topic	Type of device, forms of TOT and treatment duration	Type of wound	Patients/wound characteristics	Treatment effects
Ishii et al. (4)	Topical pressurized oxygen therapy effectiveness in 2 cases of foot refractory ulcers.	Polyethylene bag. Treatment duration: until wound was completly healed.	Severe foot refractory ulcer.	Case 1: - 49-year-old woman; - Wound: right heel with 5 cm diameter and necrosis. Case2: - 86-year-old woman; - Wound in the right hallux with necrosis, infection and exposed cartilage.	Wounds in both cases healed successfully.
Ladizinsky, Roe (8)	Importance of oxygen as a substrate and sign in wound healing. Compare topical pressurized oxygen therapy with topical dissolved oxygen therapy.	The review refers devices which surround the affected limb and supply O_2 in the gaseous form. It also refers a device which has diffusive dissolved oxygen connected to a conveyor for TOT dissolved in wounds.	Not mentioned	Not mentioned	Studies included in the review show that TOT is more effective in the dissolved form than in the gaseous form because the latter is biologically available immediately after the administration, allowing a better metabolic support for the cell function, a more effective infection control and a faster healing.
Orsted et al. (21)	Assessment of the level of evidence concerning topical pressurized oxygen therapy by a group of specialists.	The studies of topical pressurized oxygen therapy covered in this systematic review use a bag, a boot or a chamber around the affected limb or area.	The selected studies cover topical pressurized oxygen therapy in wounds with different aetiologies: diabetic wounds, venous ulcers, neuropathic foot ulcers and pressure ulcers.	Not mentioned.	The response to the therapy is very fast, occurring changes in the wound bed during 3 to 5 days, such as: size reduction, perilesional edema reduction, increase of granulation tissue, drainage reduction, pain reduction, wound bed hypoxia decrease, pO_2, VEGF and collagen synthesis increase, and recurrence decrease.

Study	Study global topic	Type of device, forms of TOT and treatment duration	Type of wound	Patients/wound characteristics	Treatment effects
Roe et al. (12)	Determine the dissolved and gaseous oxygen penetration depth and extent in skin samples.	TOT device in the dissolved and gaseous form.	Viable human skin samples with different thicknesses.	Not applicable.	Topically applied oxygen penetrates better through dermis than epidermis. TOT device in the dissolved form is more effective in penetration extent than TOT device in the gaseous form.
Tawfick, Sultan (27)	Compare topical pressurized oxygen therapy and conventional compression therapy in chronic venous ulcers care.	Device/chamber around the affected limb or area subject to a 50mbar pressure which supplies moistened oxygen at a rate of 10L/min (AOTI Hyper-Box™) during 180 minutes, twice a day, 7 days a week, during 12 weeks.	Chronic venous ulcers.	People aged ≥18 years old, who have a chronic venous ulcer for more than 2 years without improving in the last year; normal ankle-brachial index ≥0.9 and digital pressures (toe pressure) ≥ 0.7.	After 12 weeks, 80% of the chronic venous ulcers treated with topical pressurized oxygen therapy were healed. The average time for complete healing was 45 days. The threshold of pain improved from 8 to 3 in only 13 days, in a numerical scale from 0 to 10.
Woo et al. (2)	Effectiveness topical continuous oxygen therapy in chronic wound care of 9 people.	Disposable electrochemical membrane (EPIFLO®) which supplies 3ml/h of O_2 directly to the wound bed providing a continuous care through a fixed cannula with a compress and optimised adhesives 2-3 times/week until 4 weeks of care.	Lower extremities chronic ulcers: diabetic foot ulcers, surgical ulcers, venous leg ulcers.	People with lower extremities ulcers with at least 1cm^2 and for a month; palpable pulses ≥80 mmHg (10.665789 KPa); ankle-brachial index > 0.65; digital pressures (toe pressure) > 50 mmHg (6.666118KPa).	Topical continuous oxygen therapy can promote chronic wounds cure. The average area of wound surface reduced significantly from 12.03 to 9.60cm^2 during the 4 weeks of observation. This therapy can be beneficial fighting wound infection and increasing angiogenesis.

Table 4. Results and TOT evidence

3.2 TOT evidence in wound care

For the 11 studies concerning TOT, there were differences in the design and results. Thus, a description of each article was carried out according to the main categories which best described the therapy and its usefulness: type of device, forms of TOT and treatment duration, type of wounds and patients/wounds characteristics, and treatment effects (see

Table 4).

3.2.1 Type of device, forms of TOT and treatment duration

In the analysed articles, TOT is referred to in the pressurised, continued and dissolved forms. As the last two therapies are still recent, the results obtained are reduced.

Except for Woo et al. (2), all the analysed articles in this review study TOT in its pressurised gaseous form. The main types of devices used for enclosing the wound are: the chamber, the polyethylene bag, the disposable boot. The pressure of the O_2 delivered to the wound did not vary significantly among the studies, being less than 1.07 atmospheres. Four articles refer to the high oxygen flow used. Ishii et al. (4) applied 5L/min of O_2 and 2 minutes after beginning the care, the flow was reduced to 2L/min. Feldmeier et al. (18) used a flow rate of 10L/min flow as did Tawfick, Sultan (27) in their study. Howard et al. (15) increased the oxygen flow used from 5 to 60 L/min. Five articles highlight the necessity to humidify the O_2 applied in the pressurised gaseous form (15,16,18,21,27).Without adjunctive humidification systems, high flow O_2 rate may cause oxidative damage and drying effects to tissues, which would prevent O_2 solubilization in the wound fluid and dramatically reduce O_2 transport into the wound (15,18).

The duration of the topical pressurized oxygen therapy sessions and the frequency of the therapy differed from study to study. In the non-randomised control studies the sessions ranged from 60 (16), 90 (10) and 180 (27) minutes, from once (10,16) to twice (27) a day and during 4 (10), 5 (16) and 7 (27) days a week. The total duration of the course of the therapy ranged from 3 months (10,16,27) to completely wound closer in both Ishii et al. (4) case series**.** However, Orsted et al. (21) stated that the total duration used depends on the wound aetiology, its response to the therapy and the patient's tolerance. Thus, they present a protocol with the care frequency and duration appropriate for three different types of wounds (diabetic wounds, venous ulcers and pressure ulcers).

Blackman et al. (16) refer the usage of occlusive dressings, embedded in saline solution, between each care session of TOT. However, Orsted et al. (21) defend that the usage of occlusive dressings must be weighted according to the wound aetiology and the daily re-application, since the necessity to remove the dressings once or twice a day must not interfere with healing or cause trauma by removal.

Topical continuous oxygen therapy consists of the application of non-pressurised oxygen through a cannula placed directly in the wound bed (21), which supplies a low continuous oxygen flow (3-12ml/hour) (15). Woo et al. (2) used this form of TOT for chronic wound care through an electrochemical membrane for 4 weeks. This therapy presupposes an occlusive wound environment to avoid O2 exit. Thus, absorbent and moistened dressings were used to cover the wound and the cannula placed in its bed. Then, these were reinforced with secondary dressings and adhesives.

The topical dissolved oxygen therapy used in the Roe et al. (12) study used a system to catalytically produce dissolved oxygen connected to a conveyor which allows its direct application in the wound bed.

3.2.2 Type of wound and patients/wound characteristics

As far as the etiology of the wounds where TOT was used, 10 studies referred to chronic wounds of the lower extremities. However, one of them used it only in diabetic foot ulcers (16) and another one used it in chronic venous leg ulcers (27).

In the 3 non-randomized control studies (10,16,27), the case series (4) and the pilot study (2) was defined inclusion sample criteria related to age and gender of patients, ankle-brachial index, type and average of wounds and other specifics characteristics.

3.2.3 Treatment effects

In the 3 non-randomised controlled studies, the experimental groups treated with topical pressurised oxygen therapy demonstrated significantly improved healing compared to the control groups. In Blackman et al. (16) study of diabetic foot wounds, 82.4% of the experimental group achieved complete healing compared to 45% in the control group healed with silver dressings. There were no adverse effects in both groups and at 24 month follow-up there were no recurrences. In Tawfick, Sultan (27) study, there was a complete epithelialisation in 80% of the chronic wounds in the experimental group compared with 35% in the control group healed with conventional compressive therapy. There were no recurrences in the experimental group, whereas in the control group 5 out of the 13 healed ulcers receded. Pain threshold was assessed in the experimental group, registering in 13 days an improvement from 8 to 3, in a numerical scale from 0 to 10. This study also assessed the average time for complete healing, the average of ulcer surface reduction and the decrease of infection with considerably more satisfactory results in the experimental group. Gordillo, Sen (11) registered statistically significant better results in the wound size in the experimental group, unlike what happened in the control group healed with HBO. Also Ishii et al. (4) case series obtained the healing of two foot refractory wounds with topical pressurised oxygen therapy.

However, 2 studies document contraindications to TOT in wounds. Orsted et al. (21) suggest that deep venous thrombosis (DVT) and thrombophlebitis as contraindications, arguing that the positive pressure produced by the device increases the risk of displacing a blood clot, which might lead to a stroke, a myocardial infarction, pulmonary embolism or sudden death. This view is supported by Tawfick, Sultan (27) who also stated DVT as one of the exclusion criteria for their study.

Three of analysed studies mention topical continuous oxygen therapy effects. Howard et al. (15) refers that studies carried out in humans suggest the effectiveness of

this form of TOT. This assumption is supported by results obtained in Woo et al. (2) study, in which continuous oxygen was used in chronic wounds from 9 patients. It was shown that the wound's surface area reduced significantly from 12.03 to 9.60 cm^2 in 4 weeks. The same study refers that this therapy is beneficial fighting infection and increasing angiogenesis. Although Orsted et al. (21) also mention this therapy, they do not present results concerning its effects in wound healing.

Finally, topical dissolved oxygen therapy effects are also referred in 2 articles. Ladizinsky, Roe (8) mention studies which reveal a higher effectiveness in this therapy compared with topical pressurized oxygen therapy because this one is biologically available right after the administration, allowing a better methabolic support for cell function, an infection control and a quicker healing. Roe et al. (12) confirm these clinical findings in their study, since they get to the conclusion that not only dissolved oxygen penetrates more than 700μm in human skin, but also that 0_2 penetrates skin more effectively in the dissolved form than in the gaseous one.

Several analysed articles refer that additional oxygen has different benefits such as: the increase of ATP and cellular metabolism (2,8,12,15,16), fibroblast proliferation and differentiation (4,8,10,12,15,16,21), collagen production rate (2,4,8,10–12,15,16,21), collagen fibers tensile strength (15,21), VEGF (10,11,15,21), granulation tissue (8,12,15,21), angiogenesis (2,8,10,11,15,16), ROS (11,15,21), leukocytes function (12,15,16,21) and macrophages chemotaxis (15); and the decrease of hypoxia in the wound bed, perisional edema, exsudate (21), wound size (10,15,21,27), pain, recurrence (15,21,27) and microbial eradication (2,4,10,11,15,16,21,27). However, wounds must consist of at least 50% viable tissue in order to allow the O_2 to penetrate the wound bed (21). Thus, six studies mention that tissue debridement is crucial in order to achieve maximum benefit from the therapy (2,11,16,18,21,27). In Blackman et al. (16) study, wounds were debrided on average once a week before the patient received TOT. Gordillo, Sen (11), also suggest that optimisation of the wound condition is essential before topical pressurized oxygen therapy, particularly the removal of necrotic tissue from the wound surface, reducing oedema maintaining the temperature of the wound and ensuring the patient is adequately hydrated. Woo et al. (2) also suggest the prescription of antibiotics for any infection.

Furthermore, for the TOT process to happen without any incident, the patient must be informed about the necessary care to have with the wound, the procedures and the benefits for the patient's well-being and quality of life. Thus, the interdisciplinary team must work with the patient and relatives in order to clarify the importance of each one's lifestyle optimisation, the care complexity and demand and the questions which may arise. The patient's or the relative's fear related to the pain control, the dressing application and removal and the identification of infection signs and symptoms must be clarified before starting the treatment (21).

4 | DISCUSSION

In the 3 non-randomised controlled studies, the experimental groups treated with topical pressurized oxygen therapy achieve significantly better outcomes in comparison with the control groups. Woo et al. (2) suggest also that topical continuous oxygen therapy can promote complete healing. However, according to Ladizinsky, Roe (8), the best results are achieved with topical dissolved oxygen therapy.

Nevertheless, through this systematic review, no definite conclusions on the effectiveness and safety of TOT in wound healing can be drawn, since there is not sufficient robust evidence. In fact, as far as the 11 articles included are concerned, the weaknesses in study design and outcome measures make direct comparison difficult.

Considering 4 requirements, Orsted et al. (21) organised a group of 10 specialists who have made a systematic review based on the Delphi method, which resulted in a consensus of opinion regarding the most important information on topical pressurized oxygen therapy in wound care. The methods used allowed organising the information in eight categories in order to assess knowledge and define the level of evidence concerning the topic. This study has also shown where it is necessary to invest in future research in order to increase the evidence concerning the protocols and the topical pressurized oxygen therapy effectiveness.

According to Melnyc, Fineout-Overholt (28) hierarchy a systematic review of randomized clinical trials is considered the highest level of evidence. However, the Orsted et al. (21) study proved to be an asset for this systematic review, although its sample does not include a randomised clinical trial.

In Blackman et al. (16), Gordillo et al. (10) and Tawfick, Sultan (27) studies, the authors showed the aims, people's characteristics, inclusion and exclusion criteria and the most important results achieved, sustaining the strength of the studies (29). Moreover, Blackman et al. (16) and Tawfick, Sultan (27) directed their studies towards the care of one type of wound, venous ulcers and diabetic foot ulcers respectively, allowing a higher precision in the results and therapy benefits. Tawfick, Sultan (27) have also recognised a secondary cause for the three wounds which did not show signs of healing in the topical pressurized oxygen therapy care group and Blackman et al. (16) identified the people who partially participated in the care and who did not have the criteria to be included in the follow-up and the study results, avoiding a follow-up bias. However, in these 3 studies, potential limitations to its strength were evident, such as: the selection bias, since the people's allocation for the care groups was based on their preferences (10,16,27), on the topical pressurized oxygen therapy device availability (16) and on the criteria established by the physician (10); the ulcer's duration and area, which were higher in the topical pressurized oxygen therapy care group than in the control group, probably due to the selection bias, and they may have underestimated topical pressurized oxygen therapy benefits in the studies

from Blackman et al. (16) and Tawfick, Sultan (27); the hospital internment of the people who submitted to treatment in the TOT group which may suggest a higher reliability in comparison with the people who, in Tawfick, Sultan (27) study, submitted to the conventional care in outpatient treatment (29); and the fact that TOT is not the only treatment variable between experimental groups and control groups. The lack of randomisation in allocation decreased the level of evidence of the 3 studies and the relevance of the topical pressurized oxygen therapy scientific applicability and it can underestimate its effect in wound healing. Likewise, Ishii et al. (4) case series and Woo et al. (2) pilot study presented results supporting TOT in wound healing. Woo et al. (2) also refer limitations of his study, like sample size, age range, coexistence of other diseases and medication regimen, multiple wound aetiologies in which the care was carried out and the lack of control group. Although they do not present limitations, Ishii et al. (4) have a reduction in the study strength by the sample size, the lack of aims and inclusion and exclusion criteria.

In fact, our sample shows a consensus on the effectiveness and applicability of this therapy. However, the limitations inherent to the corresponding study designs and the lack of studies with higher level of evidence, limited the quality assessment of the results obtained with this systematic review. During the selection process, the difficulty accessing some studies, during the accessibility phase, and the lack of relevant primary studies, especially randomised clinical trials, are potential limitations for this study (28). This way, analysing systematically different study designs concerning the new therapy has proved to be essential.

As mentioned the analysed articles referred to different forms of TOT. Among the three modalities, topical pressurized oxygen therapy is the most studied one and it was referred to in the majority of the sample. Topical continuous oxygen therapy and topical dissolved oxygen therapy are relatively recent therapies and there are few clinical findings about them which make a comparative critical analysis based on the evidence between the three forms of TOT difficult.

There are different devices in the market to use topical pressurized oxygen therapy (30). None of the articles has compared the three types of devices or has compared the advantages and disadvantages between them. However, Howard et al. (15) stated that the therapeutical devices for topical continuous oxygen therapy tend to be portable and smaller in comparison with topical pressurized oxygen therapy, allowing a better access of the population to this therapy, the people's mobility and lower costs. Nevertheless, what seems to be relevant is the application criteria of O_2 through them. Using the high oxygen flow is mentioned, although its usage between 2 to 60 L/min is registered. The application of a pressure close to the normobaric one, less than 1.7 atmospheres, was common in the articles which studied this type of therapy and the necessity to moisten it was also mentioned. The duration and the care protocols differed from study to study, and it can be a key factor in the care effectiveness and in the results obtained.

TOT is used in a wide range of wounds, especially chronic wounds. Some optimisation principles of this type of wounds are mentioned in the analysed articles and they can be a crucial factor in the therapy success. These results meet the wound bed preparation concept described by Falanga (31) who considers it an essential element to get the greatest benefit of the used products in its care. The same author states the following critical targets for the wound bed optimisation: necrotic or fibrinous tissue removal; edema control; achieving a good wound bed vascularisation; bacterial load reduction and exsudate minimisation/ elimination. Besides local optimisation, Sibbald et al. (32) also consider crucial identifying and caring the wound cause and co-factors which affect its healing process, assessing and supporting the management of concerns centered in the patient (pain and quality of life), as well as educating for health in order to increase the compliance to the care plan. For better results, they also refer that eduction and evidence basis must be bound by interdisciplinary teams in cooperation with the health care systems. This way, it is shown that in clinical practice an holistic care approach is essential, considering the patient first and the wound afterwards (32).

In Feldmeier et al. (18) review, Leslie et al. (33) article, with a higher level of evidence and the only one randomised, did not achieve significant results with topical pressurized oxygen therapy in diabetic aetiology wounds care. In this prospective, controlled and randomised study, all 28 patients were treated for 2 weeks with intravenous antibiotics, with local dressings and rest. The only difference in the care protocol between the experimental group made of 12 people and the control group made of 16 people was that the former received care with topical pressurized oxygen therapy, while the latter did not. Overall there was a tendency of delay in the experimental group healing. Heng et al. (34) have also carried out a study which they classified as prospective and randomised in order to confirm the effectiveness of this therapeutical modality in stimulating angiogenesis and wound healing. The participants, 40 people with 79 necrotic/gangrenous wounds who fulfilled the inclusion criteria, were selected for the topical pressurized oxygen therapy care group or for the standard wound care group, applied for 4 weeks. The results have shown 90% of the healed wounds in the experimental group compared to 22% in the control group. These results are promising, although Feldmeier et al. (18) several advantages over systemic hyperbaric oxygen including decreased cost, increased safety, decreased complications and putative physiologic effects including decreased free radical formation and more efficient delivery of oxygen to the wound surface. With topical oxygen an airtight chamber or polyethylene bag is sealed around a limb or the trunk by either a constriction/tourniquet device or by tape and high flow (usually 10 liters per minute refer that the study was not truly randomised, since every time the two available topical pressurized oxygen therapy systems were used, the eligible participants were arbitrarily included in the control group. Thus, these authors consider that this study is in a lower level of evidence than Leslie et al. (33) study. However, Leslie et al. (33) study was carried out in a short period of time which may have had a

significant impact on the results, compared to Heng et al. (34) study which was carried out during the double time. The sample size was also greater in Heng et al. (34) study. Moreover, the 3 non-randomised controlled studies included in this systematic review also show a significant difference in results between the experimental and the control group.

In fact, additional O_2 reduces hypoxia and triggers the mechanisms already identified in this systematic review: it induces VEGF which is believed to be the most prevalent, effective and long-term mediator known for stimulating angiogenesis in wounds (17,34–36); it leads to increased ATP production, the energy necessary for several cellular functions; when oxidised, ROS are created and they have an antimicrobial activity essential for infection control and reepithelialisation increase; it increases keratinocyte differentiation and migration and the production of fibroblasts and endotelial cells, crucial in the proliferation process; and finally, it is also involved in proline and lysine hydroxylation in procollagen, crucial in the collagen synthesis process (17,36).

An additional benefit reported is that pain is reduced. When Tawfick, Sultan (27) compared topical pressurized oxygen therapy with conventional compression therapy in chronic venous wounds care, they observed an improvement in pain threshold in the experimental group treated with topical pressurized oxygen therapy. This result is consensual with the conclusions presented in Mani's (37) paper which describes a topical pressurized oxygen therapy potential device used in 10 patients with venous ulcers for 6 weeks. At the beginning of the treatment, the average pain reported by patients was approximately 5 on a numerical scale of 0 to 10. And 6 weeks later, the average had decreased to approximately 2.

Although there are still questions about the exact mechanisms of this treatment and it is necessary to carry out randomised studies, the current results suggest that this therapy plays an important role in restoring the O_2 balance in the wound bed necessary for healing (36). These findings show the potential of this therapy in promoting healing of chronic wounds and improving people's quality of life. In addition, there are many other potential advantages related to its usage, such as low cost, apparent safety, no associated adverse effects and the possibility to submit a diversified population to this care in any health organisation or even at the patient's home.

5 I CONCLUSION

The studies analysed emphasise the evidence of additional O_2 usage in wound care, since it reduces hypoxia and it allows triggering mechanisms which are essential in the healing process.

As far as the 11 articles included in this review are concerned, study design and methods used range considerably, making direct comparison difficult. Although the current results indicate this therapy's potential, randomised-controlled clinical trials are necessary

in order to increase the strength of evidence of its effectiveness and to establish ideal parameters for its usage in the different types of wounds, since the therapy's frequency and duration must depend on the wound aetiology, its response to treatment and the patient's tolerance.

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