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Artigo

THE THERAPEUTIC EFFECTS OF LIGHT-EMITTING DIODE IN WOUND HEALING – SYSTEMATIC REVIEW

EFEITOS TERAPÊUTICOS DO DIODO EMISSOR DE LUZ NA CICATRIZAÇÃO CUTÂNEA – REVISÃO SISTEMÁTICA

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ABSTRACT - The used of phototherapy with Light-Emitting Diode (LED) in clinical treatments as biostimulation methods for tissue repair isn't established. **Objective:** To assess the therapeutic effects of phototherapy with LED in wound healing. **Methods:** A search and a selection of randomized clinical trials published in the last 10 years in the main data basis were performed. The studies were selected, summarized and evaluated on their methodological quality and level of evidence. **Results:** Most of the studies evaluated the reduction of the wounds through photographs. Some papers also evaluated

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Temas em Saúde
Volume 19, Número 5
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João Pessoa, 2019

the granulation tissue, erythema, hyperemia, swelling and pain before and after the treatment. Such studies showed a large diversity of parameters: wavelength varied between 400 and 956nm, dose from 3 to 6 J/cm^2, frequency of application from twice a day to once a week, among others. Control groups received at least the conventional treatment (cleaning of lesions and bandaged) and/or treatment with the equipment turned off. The majority of the studies were classified with a high quality by the PEDro scale and there was a positive evidence for the role of LED in wound healing, by providing a faster and safer repair of the skin. **Limitations:** The use of the meta-analysis as a quantitative statistic tool use was not possible because of some limitations of the selected articles. **Conclusion:** This first systematic review will help the improvement of the knowledge on the subject, contribute to new research strategies and facilitate evidence based practice.

Keywords: Phototherapy; Laser Therapy; Low-Level; Wound healing; Skin ulcer.

RESUMO - O uso clínico da fototerapia por Light-Emitting Diode (LEDs) como método bioestimulador para o reparo tecidual ainda não está bem estabelecido. **OBJETIVO:** Avaliar a atuação de LED's na cicatrização cutânea. **MÉTODO:** Foi realizada busca e seleção de ensaios clínicos randomizados publicados nos últimos 10 anos nas principais bases de dados. Os estudos selecionados foram sumarizados e submetidos às avaliações sobre a qualidade metodológica e níveis de evidencias. **RESULTADOS:** A maioria destes estudos avaliou a cicatrização cutânea por imagens, verificando o fechamento das lesões. Alguns trabalhos verificaram também o tecido de granulação, o eritema, a hiperemia, o edema e a dor antes e após o tratamento. Estes estudos apresentaram grande diversidade de parâmetros: comprimento de onda variou entre 400 a 956nm, a dose entre 3 e 6 J/cm^2, a quantidade de aplicações de duas vezes ao dia a uma vez por semana, dentre outros. Os grupos controles receberam pelo menos o tratamento convencional (higienização da lesão e curativo) e/ou tratamento com o aparelho desligado. A maioria dos estudos foi classificado como de alta qualidade pela Escala PEDro e verificou-se evidencia positiva da atuação de LED's na cicatrização cutânea, contribuindo para o reparo cutâneo mais rápido e seguro. **LIMITAÇÕES DO ESTUDO:** Algumas limitações entre os artigos selecionados inviabilizaram o uso da metanálise como ferramenta estatística quantitativa. **CONCLUSÃO:** Esta primeira revisão sistemática

Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

servirá para ampliar o conhecimento sobre o assunto, contribuir para novas estratégias de pesquisa e favorecer a prática baseada em evidências.

Palavras-chaves: Fototerapia; Terapia a Laser; Cicatrização; Pele.

INTRODUCTION

The skin, also known as cutis or integument, is the largest organ of the human body with the role of maintaining body homeostasis (BARBUL, 1990; WERNER, 2003). Such function is damaged after a skin lesion and for its reestablishment a process of healing initiates (BARBUL, 1990). This is a multifactorial, complex process with the involvement of numerous cellular types (WERNER, 2003).

Over the last few years, phototherapy with coherent lights (LASER – Light Amplification by Stimulated Emission of Radiation) and incoherent ones (LED – light emission diodes) has been highlighted as biostimulation methods for tissue repair and have been used in clinical treatments or as a increment of other therapies (CAETANO, 2009; MINATEL, 2009; CHAVES, 2014).

Scientific evidence suggests that both LASER and LED therapy produce similar effects of wound healing, which reinforces the idea that the therapeutic effect of phototherapy depends on photon absorption by cromophores on the target tissue. According to the literature, the use of phototherapy usually increases local circulation, cellular proliferation and the synthesis of collagen (MINATEL, 2009; PRINDEZE, 2012; CHAVES, 2014).

Photobiostimulation activates a mechanism through the mitochondria, which starts producing signaling cells that promote a cascade of intracellular reactions. At cellular level, photobyological responses are the activation of genes of transcription factors, enzymes and pathways related to the increment in metabolism. In a simply manner, cells absorb photons and transform them into adenosine triphosphate (ATP), which will be used in metabolic processes, synthesis of deoxyribonucleic Acid (DNA), ribonucleic Acid (RNA), proteins, enzymes and other products required for tissue repair and to restore homeostasis (KARU, 1988; KARU, 1999).

Despite the use of phototherapy with LED for the treatment of skin wounds is more recent, studies executed in animals and humans have already shown a high healing potential (SMITH, 2005; MINATEL, 2009). It is known so far that such phototherapy

Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

may induce faster healing because it modulates the inflammatory process and the synthesis of collagen, through photobiostimulation of the cells involved in skin repair (KARU, 1999; PRINDEZE, 2012; CHAVES, 2014).

With such a complicacy for the healing process, its importance for the maintenance of body homeostasis and the recent use of LED in the treatment of wounds, we consider that there is a need to aggregate scientific evidence on its effects in tissue repair, to certify its safety and effective clinical use. The aim of this systematic review is to evaluate the therapeutic effects of phototherapy with LED in wound healing.

METHODS

Two independent review authors perfomed a search, between January and March, 2015, of papers published in the last ten years on the data basis Cochrane, Lilacs, Medline, SciELO, Pubmed, Scopus, Web of Science and PEDro. The following descriptors from Mesh/Decs were used as strategy for the search: Phototherapy, "wound healing" and "skin ulcer", and the word "Light emitting diodo". The Boolean operators "OR" and "AND" were used and the search expressions resulted were: (phototherapy or "Light emitting diodo") and ("wound healing" or "skin ulcer").

Studies were selected through the following inclusion criteria: to be published in English or Portuguese over the last ten years, fully available, human clinical trials, presence of a control group, with or without randomization, containing description of the parameters of the equipment used for the treatment, outcomes regarding the healing process characteristics and statistical analysis of the data. Studies including the use of LED associated with other forms of phototherapy (e.g., LASER) were excluded. Discordance between research author for the inclusion was solved by a consensus between them, considering the criteria for inclusion and exclusion.

Data from the studies was summarized in a uniformed descriptive table, based on the following topics: Authors, Characteristics of the sample, Outcomes, Methodological design, Intervention, Results and Conclusions.

Studies were also submitted to an evaluation of their methodological quality according to the PEDro (Physiotherapy Evidence Database) scale. It contains 11 items, each one scores 1 point, except for the first item which does not score. Total score ranges from 0 (zero) to 10 (ten). The PEDro assessment was performed independently by both research authors, since moderate levels of reliability have been observed between

Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

examiners, when assessing the presence or absence of the qualifiers of the scale (MAHER, 2003).

Studies selected were classified as high quality when five or more criteria were positive, according to the PEDro scale, which reliability for the total score is enough for systematic reviews on Physiotherapy clinical trials, according to the Delphi list (MAHER, 2000). For the final classification of the studies, differences were discussed until an agreement was achieved between the authors.

After the quality assessment, papers were evaluated on their levels of scientific evidence for the efficacy of the treatment. Such system, named levels of evidence, classifies the effectiveness of an intervention into four levels (strong, mild, limited or conflicted and no evidence) considering their quality, results and the number of studies that applied the same intervention (Table 1) (VERHAGEN, 2001).

RESULTS

To perform this systematic review was not necessary the approval of the Ethics Committee. An initial number of 1262 articles were found in the electronic data basis, as described in Figure 1. After a filtering by the year of publishing, idiom and clinical trials, 612 remained. From these, titles and abstracts were read, the doubles excluded, such as the trials that applied phototherapy with LASER or the associated use of LED to other forms of phototherapy, and 42 remained. After the reading of these papers, 10 articles were selected according to the inclusion criteria and their information is reunited in Table 2. Article scores in each item of the PEDro scale is shown in Table 3.

DISCUSSION

Because our research was limited to a period of ten years, a few random clinical trials were found, an average of one per year. Size of the samples varied among papers, however none of them presented an n<5. Usually all the studies were concerned about criteria for inclusion and equality between groups, which turns the results more reliable. Only one study has not described the detailed characteristics of the participants (OH, 2015).

Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

Artigo

When considering the outcomes assessed, most of the studies evaluated wound healing through pictures by verifying their reduction. Some studies also verified the granulation tissue (MINATEL, 2009), erythema (OH, 2015), hyperemia (DE OLIVEIRA, 2014) and swelling (OH, 2015). Three papers assessed the pain before and after treatment through scales and questionnaires (DE OLIVEIRA, 2014; CHAVES, 2012; PARK, 2013). The intensity of the pain reported by the patients in the treated groups reduced significantly after the treatment. One study assessed the inflammatory activity through cytokine dosage (SIQUEIRA, 2015). It is important to remind that more clinical trials that evaluate the role of the LED in the physiopathology of the healing process at a deeper cellular level are required.

The parameters used in the intervention showed variety. The wavelength ranged from 400 to 956nm. The majority of the studies used wavelength around 600nm (visible red light) (CAETANO, 2009; MINATEL, 2009; DEHLIN, 2007; LANDAU, 2011; SCHUBERT, 2011; OH, 2015; DE OLIVEIRA, 2014; SIQUEIRA, 2015), five studies used the wavelength of 800nm (infrared) (CAETANO, 2009; MINATEL, 2009; LANDAU, 2011; CHAVES, 2012; PARK, 2013), two of them used 956nm (infrared) (DEHLIN, 2007; SCHUBERT, 2011) and five studies combined more than one wavelength in the same treatment (DEHLIN, 2007; CAETANO, 2009; MINATEL, 2009; LANDAU, 2011; SCHUBERT, 2011). None of the studies compared the treatment between one wavelength and treatments that used the combination of more than one wavelength.

When comparing the fluence, half of the studies used 3, 4 or 6 J/cm^2 (CAETANO, 2009; MINATEL, 2009; DE OLIVEIRA, 2014; CHAVES, 2012; SIQUEIRA, 2015) while the rest of them did not inform it. Three articles used the pulsed mode (DEHLIN, 2007; SCHUBERT, 2011; CHAVES, 2012). The time of application ranged from 30 seconds (CAETANO, 2009; MINATEL, 2009), 79 seconds (CHAVES, 2012) 152 seconds (DE OLIVEIRA, 2014), 2 minutes and 40 seconds (SIQUEIRA, 2015), 4 minutes (LANDAU, 2011), 9 minutos (DEHLIN, 2007; SCHUBERT, 2011), 10 minutes (PARK, 2013) to 15 minutes (OH, 2015). Some studies did not inform the accurate distance between the equipment and the wound area during the treatment (CHAVES, 2012; PARK, 2013; OH, 2015). Two studies used a distance of 2 cm (LANDAU, 2011; SIQUEIRA, 2015), other two studies used a distance of 3 cm (DEHLIN, 2007; SCHUBERT, 2011) and three applied the equipment in contact with the skin (CAETANO, 2009; MINATEL, 2009; DE OLIVEIRA, 2014). To use the equipment in direct contact with the skin, a transparent piece of plastic was positioned between them

Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

(CAETANO, 2009; MINATEL, 2009; DE OLIVEIRA, 2014). Frequency of the applications ranged among the studies: twice a day (LANDAU, 2011), once a week (SIQUEIRA, 2015), twice a week (CAETANO, 2009; MINATEL, 2009; CHAVES, 2012; PARK, 2013), daily (DEHLIN, 2007; OH, 2015; SCHUBERT, 2011) or every other day (DE OLIVEIRA, 2014).

The participants of the control groups received appropriate conventional treatment (cleaning of lesions and bandaged) and/or treatment with the equipment turned off.

This systematic review has limitations such as the diversity of the parameters for the application of the phototherapy with LED among the studies, which did not allow the use of the meta-analysis as a quantitative statistic tool. Also the absence of information about the protocols used and the differences among the statistical analysis of each study (DINNES, 2005).

All of the selected studies observed positive results from the use of LED on wound healing. Treated groups showed a faster healing and reduction of the signs of inflammation in the tissues. None of the studies reported adverse effects after the therapy. Three studies observed advantages on the use of phototherapy with LED: easy application, low cost, painless and good acceptance of the participants (DEHLIN, 2007; LANDAU, 2011; CHAVES, 2012). Most of the studies indicate the need of more clinical trials on the topic.

The majority are of high quality, with a score of 5 or more criteria on the PEDro scale, as described on Table 3. Only one of them received a score bellow five and was considered as low methodological quality (OH, 2015).

The scale of the levels of evidence is qualitative and very used in systematic reviews to synthesize the effectiveness of interventions. On the other hand, the criteria used to evaluate these levels of evidence haven't been totally standardized and the choice of different criteria can lead to different conclusions on the efficacy of interventions (FERREIRA, 2002).

This review used as criteria the methodological quality of the articles in the PEDro scale. It was decided the use of one level of evidence (Cochrane) so that the results found would be consistent. Nine of the ten articles selected are of high methodological quality and showed positive results after the treatment.

It has been considered so far a strong evidence of the role of LED in wound healing, with an effective and safe manner. However, we agree with the authors of the articles that more randomized clinical trials are required; with well established parameters and larger samples, to describe deeper the role of LED in wound healing.

Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

Not only this review will increase the knowledge on this therapeutic, but also it can contribute to generate new research strategies and help the decision making of the therapeutist. It is also important to search for new therapies for wound healing that are well accepted by the patients, easy applied, with minimal side effects and low cost.

CONCLUSION

The results of the articles selected in this systematic review show a positive evidence of LED in wound healing, which can contribute to a faster and safer healing. However, since this is a recent therapy it should be used with caution. This systematic review will help the planning of new research on the topic and can help evidence based practice.

Declaration of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

Artigo

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Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

Artigo

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Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

Artigo

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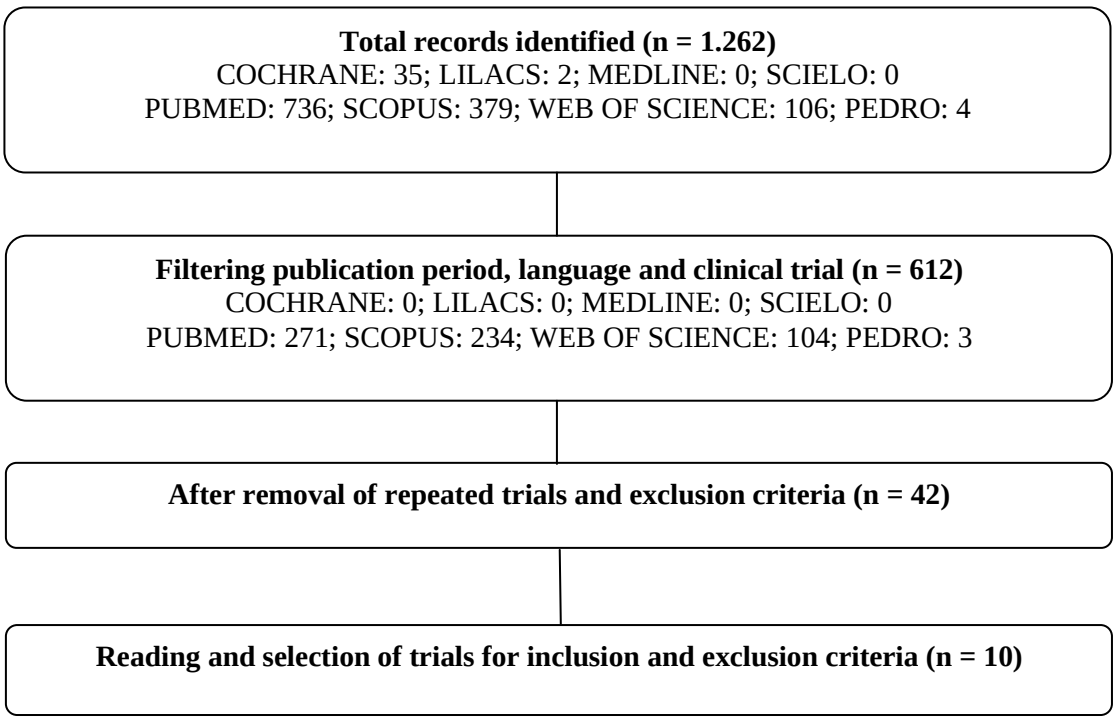
Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

Artigo

FIGURE AND TABLE LEGENDS

Figure 1. Detailed flowchart demonstrating the selection process of the studies



Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

Artigo

Table 1. Evidence Grade

	Level of Evidence
1	Strong: multiples RCTs with high quality and few limitations.
2	Moderate: one RCT with high quality and one or more RCTs with low quality, or multiples RCTs with consistent results.
3	Limited: one RCT (with high or few qualities) or multiples RCTs with inconsistent results.
4	Inadequate: no RCT

* RCT = randomized controlled trials

Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

Artigo

Table 2. Details of the included studies

Authors	Characteristics of the sample	Outcomes	Methodological design	Intervention	Results	Conclusions
Chaves et al	Initial n= 30, final n= 10. Nipple trauma in breastfeeding women. No significant differences between the groups.	Evaluation of nipple lesions and analysis of photographs. Pain intensity was measured by Visual-Analogic Scale.	Randomized, placebo-controlled intervention trial.	**Experimental group:** wavelength of 860 nm; frequency of 100 Hz; average power of 50mW; power density of 50mW/cm^2;total emission area of 1 cm^2; pulsed emission mode with 50% duty cycle; and dose of 4 J/cm^2. Application time was 79 sec, twice a week for a period of 4 weeks. **Control group:** application with the device off. Both groups received general guidelines to prevent trauma during breastfeeding.	A significant difference between experimental and control groups was observed for the healing of nipple lesions. Intensity of pain reduced significantly in the experimental group.	The LED phototherapy successfully accelerated the healing of nipple lesions and reduced the pain intensity in the participants in the experimental group when compared to those in the control group. Advantages: easy to apply, low cost, and acceptance by lactating women.
Landau et al	Initial n= 20, final n= 16 (5 women and 11 men with diabetes and venous ulcers). No significant differences between the groups.	Time for closing the ulcers and the percentage reduction (photographs).	Placebo-controlled double-blinded.	**Treatment group**: received 180mW/cm^2 broadband (400–800 nm) visible light, distance of 2 cm, each time for 4 min/treatment, twice a week for a period of 12 weeks. **Placebo group:** received non-healing fluence of light (10mW/cm^2).	Wounds reduced in 9 out of 10 patients (90%) from the treatment group, whereas in the placebo group only 2 out of 6 patients exhibited reduced ones (33%). Reduction in wound size in the treatment group versus the placebo group was 89% and 54%, respectively.	Broadband (400–800 nm) visible light was an effective modality for the treatment of leg or foot ulcers. Advantages: light treatments are painless, and no adverse effects have ever been reported.

Temas em Saúde
Volume 19, Número 5
ISSN 2447-2131
João Pessoa, 2019

Artigo

Table 3. PEDro Scale score.

	Chaves et al	Landau et al	Minatel et al	Caetano et al	Park et al	Siqueira et al	de Oliveira et al	Oh IY et al	Dehlin et al	Schubert et al
Eligibility criteria specified (item does not score)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Random allocation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Concealed allocation	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Similar groups at baseline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blinding of subjects	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Blinding of therapists	Yes	Yes	Yes	No	No	No	Yes	No	No	No
Blinding of assessors	No	No	No	No	No	No	Yes	No	No	No
Measure of one key outcome obtained for 85% of subjects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intention to treat analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Between group comparisons of at least one key outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Point and variability measures for at least one key outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Total scores	9/10	8/10	9/10	8/10	7/10	8/10	10/10	3/10	8/10	7/10
Methodological quality	**High**	**High**	**High**	**High**	**High**	**High**	**High**	**Low**	**High**	**High**