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REVIEW ARTICLE

Low-level laser therapy in the treatment of pressure ulcers: systematic review

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Abstract The aim of this study was to evaluate the effects of low-level laser therapy (LLT) in pressure ulcers (PU) in humans through a systematic review of randomized studies. The search includes the databases MEDLINE, PEDro, Cochrane CENTRAL, and Lilacs, as well a manual search until May, 2016. This included randomized clinical trials of LLT compared with other interventions, different types of LLT, LLT placebo, or control in the treatment of PU. The outcomes evaluated were the ulcer area, healing rate, and overall healing rate. The risk of bias was evaluated using the tool of the Cochrane Collaboration, and the results were analyzed descriptively. From the 386 articles identified, only four studies were included, with two LLT used with single wavelength (1: 904 nm vs. control and 2: 940 nm vs. 808 nm vs. 658 nm vs. placebo) and two LLT used to probe cluster. One study compared to different single wavelengths showed a significant 71% reduction of the PU and an improved healing rate in which 47% of PU healed completely after 1 month of therapy with the use of LLT with a wavelength of 658 nm compared with other lengths. The other analyzed wavelengths were not significant in the assessed outcomes. Significant results were observed in the use of LLT with a 658 nm wavelength, and no evidence was found for use of wavelengths above that for the treatment of PU. Therefore, we also found no evidence in the laser used to probe the cluster.

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Keywords Lasers · Skin ulcer · Pressure ulcers · Review

The prevalence of pressure ulcers (PU) in hospitals is high, ranging from 2.7 to 29.5%. Tetraplegic patients (60%) and seniors with femoral neck fractures (66%) have the higher rates of this complication followed by critical patients (33%) [1]. Besides the high prevalence, PU also features significant costs to the health system. The treatment cost in the USA is estimated at $ 2000 to $ 25,000 per individual per year [2]. In Brazil, an assessment found the average cost of treatment for PU grade III in a neurosurgical clinic in 2005, and the estimated value was R$ 180.00 per day. This value included only industrialized dressings and medication [3].

Besides the high cost, PU is a gateway to infections, prevents patients' recovery, and increases the duration of nursing care [4]. They also need long-term care, which limits the individual's functionality [5]. All these factors contribute to increased morbidity and mortality rates, creating significant consequences for the individual and for the health care institution. Therefore, treating PU is important to minimize the costs and the risks of complications to the patients.

Among the methods of non-pharmacological treatment, the American College of Physicians [6] describes, among other adjunctive therapies, the use of light therapy and low-level laser therapy (LLT). Light therapy consists of the application of energy from the infrared, visible, or ultraviolet spectrum to the wound site to promote healing. Some studies showed that this therapy reduced the ulcer surface area compared with sham treatment or usual care but showed no improvement in complete wound healing [7, 8]. On the other hand, LLT consists of amplified light of low radiation power capable of promoting biochemical, bioelectric, and bioenergetic effects

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resulting in stimulation of microcirculation, analgesia, anti-inflammatory and anti-edematous effects, and healing [9]. The use of LLT turns on a spreading range of growth [10], increasing epithelial cell motility [11], and collagen standing [12], which is directly connected to the healing of PU. These insights depend on the kind of protocol (wavelength, energy amount, frequency, and power) used. However, there is lack of evidence to support their effectiveness.

Animal studies have shown the beneficial effect of the treatment of PU with LLT [13]. In humans, few experimental studies were found, and they present a large variety of protocols insufficient to produce conclusive results. For example, the study by Taradaj et al. can be mentioned, which compared different wavelengths of LLT and the placebo effect; only one wavelength showed significant results [14]. Due to the existence of conflicting evidence in the literature, the need for a systematic review on the subject is justified. Thus, the aim of this study was to evaluate the effects of LLT compared to those of another types of laser, another type of intervention, placebo, or control group in the treatment of PU in humans through a systematic review of randomized controlled trials (RCTs).

Methods

Protocol and registration

The planning for this review was based on the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA recommendations). This systematic review was recorded in PROSPERO under number CRD42016036648.

Eligibility criteria

The included RCT had patients with PU (any grade rating), and the LLT was performed and compared with other interventions: different types of LLT, LLT placebo, or control group (without conducting intervention). The area of healing rate and the overall healing rate were evaluated as well. Pilot studies and articles with incomplete data were not included.

Search strategy

The following electronic databases were researched: MEDLINE (accessed through PubMed), Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), Physiotherapy Evidence Database (PEDro), and Lilacs. In addition, a search of the published studies of references on the subject was carried out. The search was conducted in May 2016 and consisted of the following MeSH terms added to their synonymous terms: "Pressure Ulcer" and lasers as shown in Table 1. There was no language restriction in the search.

Study selection

The titles and abstracts of all articles were identified by the search strategy and evaluated by two researchers. All the abstracts that did not provide sufficient information concerning the inclusion and exclusion criteria were selected to evaluate the full article. In the second phase, the same reviewers independently evaluated the full articles and made their selection in accordance with the eligibility criteria. Disagreements between reviewers were resolved by consensus.

Data extraction

Data extraction was performed using a standardized form by two reviewers independently. The primary outcome was the area of the ulcer assessed in mm^2 or cm^2. We also analyzed the outcome healing rates of ulcer in percentage or average and total healing rate (amount or percentage of PU that completely healed).

Assessment of risk of bias

The assessment of methodological quality was performed by two researchers using the Cochrane Collaboration tool that evaluates the following items: generation of randomization sequence, blinding of allocation, blinding of the therapist, the patient and the assessors of outcomes, analysis by intention to treat, and description of losses and exclusions. Studies without a clear description of these features were considered unclear.

Data analysis

Data analysis was performed with a qualitative design. It was impossible to perform meta-analysis, because clinical differences were detected in the selected studies among the participants in each study and between the methodologies used. Moreover, the intervention protocol of each study ranged in relation to the type of LLT parameters and application frequency. This difference caused a significant clinical heterogeneity, preventing a quantitative analysis.

Results

Study selection and study characteristics

The initial search identified 386 articles, of which 22 were recovered for detailed analysis. Of this total, 18 were

Table 1 Search strategy used in PubMed

Step	Search terms
#1	"Pressure Ulcer" [Mesh] OR "pressure ulcer" OR "Pressure Ulcers" OR "Ulcer, Pressure" OR "Ulcers, Pressure" OR "Bedsore" OR "Bedsores" OR "Pressure Sore" OR "Pressure Sores" OR "Sore, Pressure" OR "Sores, Pressure" OR "Bed Sores" OR "Bed Sore" OR "Sore, Bed" OR "Sores, Bed" OR "Decubitus Ulcer" OR "Decubitus Ulcers" OR "Ulcer, Decubitus" OR "Ulcers, Decubitus" OR "Pressure Ulcer Healing" OR "ulcer healing"
#2	"Lasers" [Mesh] OR Laser OR lasers OR "Q-Switched Lasers" OR "Laser, Q-Switched" OR "Lasers, QSwitched" OR "Q Switched Lasers" OR "Q-Switched Laser" OR "Pulsed Lasers" OR "Laser, Pulsed" OR "Lasers, Pulsed" OR "Pulsed Laser" OR "Continuous Wave Lasers" OR "Continuous Wave Laser" OR "Laser, Continuous Wave" OR "Lasers, Continuous Wave" OR "laser therapy" OR "Laser Irradiation" OR "low-level laser therapy" OR "laser treatment" OR phototherapy OR "laser phototherapy"
#3	#1 AND #2

excluded because they did not report the outcome of interest, lacked data, or had incomplete data, leaving four articles which were included in the analysis. The selected studies totaled 210 patients. Among the four articles included, two used LLT with a single wavelength: Lucas et al. [15] used 904 nm wavelength with a dose of 1 J/cm^2 compared with a group that performed usual care, and Taradaj et al. [14] compared four groups, where each one used a different wavelength (940 nm, 808 nm, 658 nm, and LLT placebo); however, they all used a dose of 4 J/cm^2. Two studies used LLT with probe cluster that allows propagate different types of diode and wavelengths simultaneously. Nussbaum et al. [16] conducted a comparison between a LLT group with probe cluster with center wavelength of 820 nm surrounded by ten outputs of 950 nm, ten outputs of 880 nm, and ten outputs of 660 nm and dressing; another group that received ultrasound application associated with ultraviolet light and dressing; and a group which received only the dressing application. Taly et al. [17] compared LLT clusters with central source of 820 nm surrounded by five outputs of 940 nm, ten outputs of 880 nm, ten outputs of 870 nm, ten outputs of 950 nm, and ten outputs 650 nm plus dressing; and placebo plus dressing. Figure 1 shows the flowchart of the selected studies and Table 2 summarizes the characteristics of these studies.

Risk of bias

In relation to the four studies, 75% described a random generation sequence presenting the lowest risk of bias for this feature [14, 15, 17], but only 25% described if there was allocation concealment, setting a high risk of bias [14]. Still, 25% reported the blinding of patients and assessors on outcomes, presenting a high risk of bias for these features [14, 17]. All studies presented descriptions of losses and exclusions (low risks of bias), and 50% used the principle of analysis by intention to treat for statistical analysis (moderate risk of bias) [15, 17].

Effects of intervention

Pressure ulcer area

Among the selected studies, only those using a single wavelength rated this outcome. Lucas et al. [15] compared two groups: one that applied the LLT with a wavelength of 904 nm and dressing, and another group that just applied the dressing, with the area of the PU assessed before and after 6 weeks of treatment. The intervention group showed a 22% reduction of the PU, with 41% in the control group, but found no significant difference between the groups. In contrast, Taradaj et al. [14] randomly divided the patients into four groups: three groups used different wavelengths each (940, 808, and 658 nm) associated with the dressing, and a placebo group associated with the dressing. The authors found that the group that used laser length wave of 658 nm showed a significant reduction of 71% in the PU area after 1 month of therapy, against 28.3% in the other groups ($p = 0.011$). The groups using wavelengths of 940 and 808 nm showed no significant difference compared to placebo.

Healing rate

The two studies using LLT with probe cluster assessed this outcome. Nussbaum et al. [16] conducted a comparison between a LLT group with probe cluster with center wavelength of 820 nm surrounded by ten outputs of 950 nm, ten outputs of 880 nm, and ten outputs of 660 nm and dressing; another group that received ultrasound application associated with ultraviolet light and dressing, and a group which received only the dressing application. After 22 weeks of intervention, the percentage of weekly healing of the LLT group was 23.7%, and in the ultrasound/ultraviolet light group, it was 53.5%; in the control group, it was 32.4%. There was no significant difference between the LLT group and ultrasound/ultraviolet light group compared to the control group. In contrast, there was a significant difference in the ultrasound group associated with ultraviolet light when compared to the LLT group. Taly et al. [17] compared LLT clusters with central source of

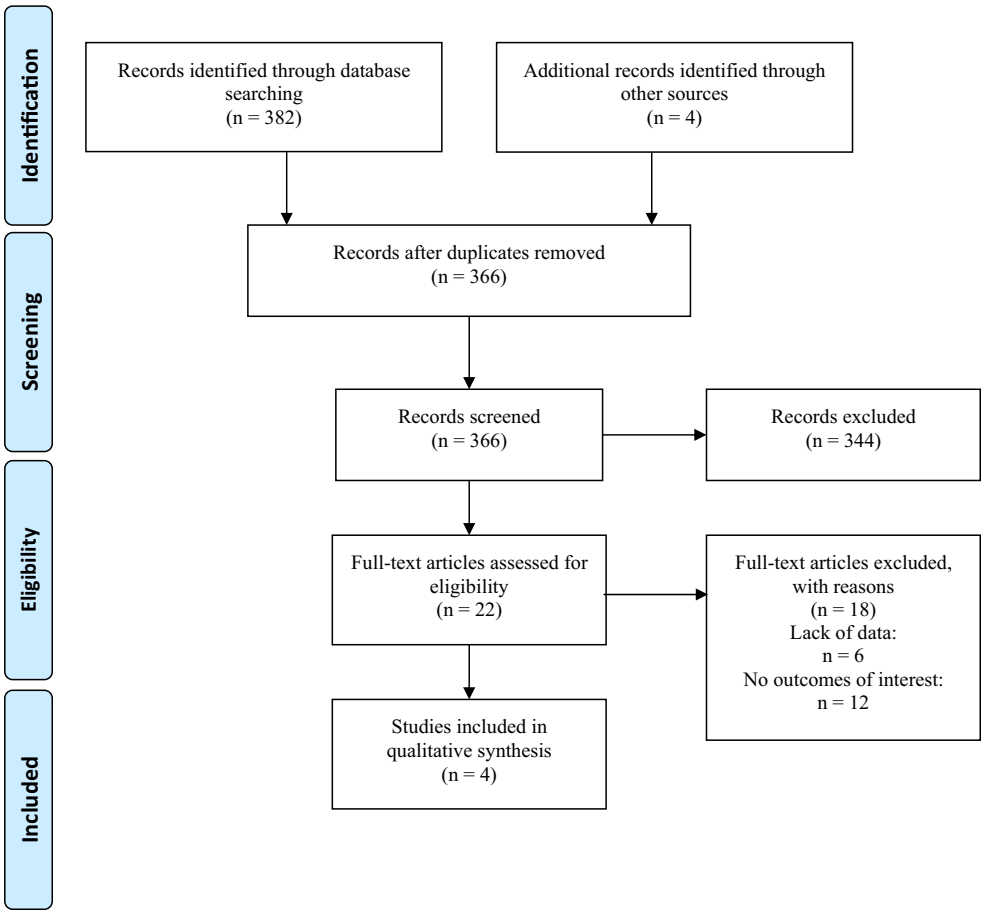

Fig. 1 Flowchart of the included studies

820 nm surrounded by five outputs of 940 nm, ten outputs of 880 nm, ten outputs of 870 nm, ten outputs of 950 nm, and ten outputs 650 nm plus dressing; and a placebo group plus dressing. This study also assessed the average rate of healing of weeks required for healing the PU, and the results were an average of 2.4 ± 2.1 weeks for healing the PU in the LLT group and 1.8 ± 2.1 weeks for healing in the control group, with no significant difference between the groups.

Total healing rate

Lucas et al. [15] assessed the overall healing rate of PU after 6 weeks of treatment. In the LLT group, 50% (18/36) of the PU healed completely; in the control group, 35% (15/43). This difference between the groups was not significant. In the study by Taradaj et al. [14], the percentage of completely healed ulcers was assessed 1 and 3 months after treatment. In the period after a month, 11.1% (2/18) of the PU healed in the 940-nm, 808-nm, and placebo groups, versus 47% (8/17) of the PU healed in the 658-nm group. This showed significant differences between the groups ($p \leq 0.001$). After 3 months, the percentage in the 940-nm, 808-nm, and placebo groups was of 16.7%, against 58.6% of the 658-nm group—so, the results found in the LLT 658-nm group were significant when compared to the other groups. Taly et al. [17] found that 51.4% (18/35) of the PU in the intervention group healed completely, against 48.2% (14/29) of the PU in the control group; therefore, there was no significant difference between the groups.

Discussion

In this study, a systematic review was conducted to assess the effect of LLT treatment of PU. Significant results were observed with the use of LLT with a wavelength of 658 nm and a dose of 4 J/cm^2 in the evaluated outcomes, and no evidence was found with single wavelengths above this. Furthermore, no significant difference was found when LLT was used with a probe cluster on PU.

The wavelength is one of the important parameters in the use of LLT, and may have contributed to the heterogeneous results found, because this is one of the determining factors in the laser interaction with tissue. Laser light produces some effects when absorbed by the tissue, and this light energy is converted into thermal and biochemical energy. Although, the

Table 2 Characteristics of included studies

Study, year	Patients (*n*)	PU type	Age (mean ± SD)	Intervention	Comparison	Outcomes evaluated	Results
Single laser wavelength							
Lucas et al. 2003 [15]	Group I: 39	Grade 3	Group I: 81.3 ± 9.6	Laser GaAs, 904 nm, 830 Hz, 1 J/cm^2, 5 times a week, 6 weeks, daily dressing, guidelines, and change of decubitus.	Daily dressing, guidance and exchange of decubitus.	Area and full healing of PU after 6 weeks. Used as an evaluation the Polaroid camera image.	Average mm^2 area before/after the control group: 338 ± 386/200 ± 384. LLT Group: 246 ± 264/194 ± 444. 15/43 wounds of laser group and 18/36 wounds of control group reached the size 0. There was no significant difference between the groups ($p = 0.59$).
	Group C:47		Group C: 83.5 ± 8.9	Group 1: GaAlAs laser, 904 nm, 20 Hz, 50 mW, 4 J/cm^2, 5 times a week for 1 month, daily dressing and guidance.			
Taradaj et al. 2013 [14]	Group I: 53 Group C: 18	Grades 2 and 3 Group 2: 70.1 Group 3: 68.9 Group C: 66.2	Group 1: 69.2	Group 2: laser GaAlAs, 808 nm, 50 mW, 20 Hz, 4 J/cm^2, 5 times a week for 1 month. Daily dressing and guidance. Group 3: laser GaAlAs, 658 nm, 50 mW, 20 Hz, 4 J/cm^2, 5 times a week for 1 month. Daily dressing and guidance.	Placebo laser, 5 times a week for 1 month. Daily dressing and guidance.	PU area cm^2 1 month after therapy. PU percentage that healed completely after 1 month of therapy. PU percentage that healed completely after 3 months of the end of the study. PU evaluation by infrared camera.	Area in cm^2 before/after a month: group 1:30.23 ± 29.17/19.23 ± 23-.88 ($p = 0.005$). Group 2: 34.88 ± 36.12/21.07 ± 26.0-2 ($p = 0.005$). Group 3: 32.87 ± 31.33/8.42 ± 14.23 ($p = 0.001$). Group C: 30.89 ± 31.83/20.07 ± 27.2-3 ($p = 0.005$). Significant result only in group 3 (laser 658 nm) compared to the other groups. Percentage of complete healing after 1 month: Groups 1, 2, and C: 11.1% vs. Group 3: $p = 47\%$ (0.001). Total healing percentage after 3 months: Groups 1, 2, and C: 16.7% vs. group 3: 58.8% ($p = 0.001$).
Laser with probe cluster							
Nussbaum et al. 1994 [17]	Group 1: 6 Group 2: 6 Group C: 6	Uninformed	Group 1: 42 Group 2: 42.2 Group C: 36	Group 1: central laser 820 nm surrounded by 30 outputs with different power, 15 mW, 4 J/cm^2, for 35 s, 3 times per week, daily dressing and orientations.	Daily dressing and guidance.	Healing rate. PU perimeter was designed in a transparency and the depth was evaluated by placing a disposable tape measure in the deepest part of the PU.	Average healing rate: group 1: 23.7%. Group 2: 53.5%. Control group: 32.4% were no significant differences in the ultrasound group/UV light compared to LLT.

Table 2 (continued)

Study, year	Patients (*n*)	PU type	Age (mean ± SD)	Intervention	Comparison	Outcomes evaluated	Results
				Group 2: Ultrasound 3 MHz, intensity 0.2, 5 min by 5 cm^2 and UV 250 nm, 95% emission, 2.5 cm away. Alternated days 5 times a week.			There was no difference in the two intervention groups compared to the control.
Taly et al. 2004 [16]	$N = 35$	Grades 2, 3, and 4	31.7 ± 1.2[a]	Laser 20 Hz, 4.5 J/cm^2 820 nm central surrounded by 45 outputs with different power for 60 s of exposure 10 cm^2 each, 3 times a week until healing or 14 applications. Daily dressing and guidance	Placebo laser 3 times a week until healing or 14 applications. Daily dressing and guidance.	Total healing percentage. Healing rate. Photography at the beginning, at the end and 14 days after.	Total healing rate: 18/35 in LLT group and 14/29 in the control group healed completely ($p = 0.802$). Average of 2.4 ± 2.1 weeks for healing in group I and 1.8 ± 2.1 for healing in group C ($p = 0.330$).

PU pressure ulcer, *laser GaAs* gallium arsenide laser, *laser GaAlAs* gallium aluminum arsenide laser, *laser with probe cluster* laser with multiple wavelengths, *LLT* low-level laser therapy, *group I* group intervention, *group C* control group, *UV* ultraviolet

[a] Values expressed as mean ± SD

greater the length of the emitted wave, the greater the depth range, which results in less absorption by the more superficial tissues. Furthermore, they are slightly absorbed by hemoglobin and water, allowing deeper penetration. In contrast, shorter wavelengths have a more superficial action, because they are more absorbed by these tissues [18, 19].

This is consistent with the results observed in this review in the study published by Taradaj et al. [14], which found beneficial results in the area and the PU rate of healing only in the group using a wavelength of 658 nm, which was not observed in the groups using longer wavelengths, although all used the same energy dose (4 J/cm^2). Because it is a shorter wavelength (658 nm), the effect of LLT was more absorbed in the most superficial part of the skin, where the PU are located, since this study included PU grades 2 and 3. In contrast, the study by Lucas [15], using GaAs laser with wavelength of 904 nm, did not find any beneficial effects of the LLT treatment on PU. The results of this article demonstrated the ineffectiveness of this type of laser treatment for grade 3 ulcers, probably because the wavelength exceeds the fabric layer where the wound is, since this length acts mainly at the bone, tendon, and muscle level [20].

Studies justify the use of LLT with a probe cluster with the intention of joining the effects of laser therapy in more damaged areas, with the benefit of different wavelengths [21, 22]. Taly et al. [17] and Nussbaum et al. [16] used the laser with probe cluster, and the results from the studies showed that the interaction between different lengths in a single probe did not cause significant effects on PU.

Another important factor of the laser parameters is the energy dose. This parameter is displayed in J/cm^2 and represents how much energy was delivered to the tissue by cm^2 [23, 24]. Nussbaum et al. [16], Taly et al. [17], and Taradaj et al. [14] used 4 J/cm^2, while Lucas et al. [15] used 1 J/cm^2. It is noteworthy that even the articles of Nussbaum et al. [16], Taly et al. [17], and Taradaj et al. [14] use the same dose of energy, but it was not enough to show positive results in all studies, leading us to believe that the wavelength is perhaps one of the key parameters to be established.

None of the studies included in this review presented all the items analyzed in the assessment of risk of bias. The study by Taly et al. [17] showed better methodological quality compared to the other studies, with a clear description of the patient and assessor's blinding, description of losses and exclusions, and analysis by intention to treat and generating random sequence. Despite this, the results presented by the study were not significant, indicating that the methodological quality did not influence the results of this study. Taradaj et al. [14] also presented the items observed in the study by Taly et al. [17], but did not use the principle of analysis by intention to treat. The study results presented by Taradaj et al. [14], however, were significant, and the techniques used in both studies

were different, indicating that the method of applying the LLT influenced the results more than the methodological quality. Lucas et al. [15] and Nussbaum et al. [16] showed no clear description of most of the items evaluated, and the results were not significant for the LLT technique applied; also, the technique was different between the two studies, so it is not possible to assess whether the low methodological quality influenced the lack of significant results in these two studies.

Study limitations and strengths of the review

Although it was not possible to perform a meta-analysis, this study presented two methodological strong points: firstly, a specific research question was formulated, and secondly, there was a significant bibliographic search, comprehensive and systematic, with explicit and reproducible eligibility criteria, without language restriction, performed by two independent reviewers. The selected studies were methodologically limited because none of them presented all the items noted in the assessment of risk of bias. Due to the small number of studies, which included a limited number of patients, it is not possible to present a definite conclusion about this issue. Furthermore, the parameters used in each study differed greatly from each other, which resulted in inconclusive results regarding the effect of the therapy.

Conclusion

Through this systematic review, significant results were observed for the use of LLT with a wavelength of 658 nm, and no evidence was found with a single wavelength greater than this. Furthermore, no significant difference was found in the use of LLT with the probe cluster on PU. Regarding non-significant studies on patients, there is insufficient scientific evidence to ensure the effectiveness of the LLT treatment on PU, and studies with higher methodological quality should be performed, using parameters similar to those which have found significant results in this review.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Role of funding source The study did not have funding source.

Ethical approval and informed consent Since this study is a systematic review, it was not necessary to have an approval from the ethics committee and informed consent.

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