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Use of low level laser therapy to control neuropathic pain: A systematic review

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ABSTRACT

Neuropathic pain can be defined as pain initiated or caused by a primary lesion or dysfunction in the central or peripheral nervous system. The low level laser therapy (LLLT) has gained great prominence as a treatment in this type of pain; however, the application parameters are still controversial in the literature. This study aimed to review the literature on the use of LLLT in neuropathic pain with the goal of establishing a "therapeutic window" for the effective use of this treatment. We analyzed 14 articles, 10 in experimental animals and 4 in humans. The results are presented in three tables, the first being for comparison of the studies' application parameters, the second showing the average and median parameters experimental studies and third showing the clinical studies embodiment. The experimental studies revealed better results for LLLT and infrared laser powers above 70 mW. Clinical studies are inconclusive as to the application parameters, due to the discrepancy; however all demonstrate the effectiveness of LLLT. According to the data presented, it was concluded that LLLT has positive effects on the control of analgesia for neuropathic pain, but further studies with high scientific rigor are needed in order to define treatment protocols that optimize the action LLLT in neuropathic pain.

1. Introduction

Science describes pain as an evolutionary reaction whose main function is the communication of the bodily structural and functional damage through information concerning location and intensity of harmful and potentially damaging stimuli [1]. Lesion in the central or peripheral nervous system triggers a special type of pain, which is characterized by the absence of nociception, and this type of pain is named neuropathic pain [2]. Whereas the physiological or nociceptive pain is fundamental for the preservation of one's integrity because it warns for the occurrence of lesions in several bodily tissues, the neuropathic pain is maladaptive and is an important cause of permanent disability, especially when it is chronic [3].

According to the international Association for the Study of Pain (IASP), neuropathic pain can be defined as "pain caused by a lesion or disease of the somatosensory system" (www.iasp-pain.org/resources/pain definition). This definition replaces that appeared in the Classification of Chronic Pain published by IASP in 1994, which defined neuropathic pain as the pain triggered or caused by a lesion or primary dysfunction of the nervous system, or may occur due to peripheral nerve lesion (amputation), infection (post herpetic neuralgia), nerve compression (accidents, surgeries, tumor), infarction, metabolic (diabetic neuralgia) or could even be idiopathic [4]. Neuropathic pain is classified according to its intrinsic cause or by the location of the nervous lesion - central or peripheral - but the physiopathology and its biological mechanisms are not yet fully understood [5,6]. In order to better understand the human neuropathic syndrome, a great variety of experimental models has been developed, among which partial or total nerve transection, perineural inflammation, experimental diabetes and chronic sciatic nerve compression [7–12].

Nowadays, painkillers are the most commonly used techniques to treat. However, they have shown only 30% effectiveness in patients with neuropathic pain [13–15]. Therefore, several researchers have been seeking for alternative treatments, other than pharmacological, for the treatment of this type of pain, such as anesthetics and neurosurgical procedures, psychotherapy and physiotherapeutic resources [16–19].

Among the physiotherapy resources, LLLT has been widely used in investigations on tissue regeneration and pain reduction. This therapy has been highlighted due to its low cost, to the fact that it is non- invasive and that it presents few contraindications as well as rare side effects [20–23]. LLLT has effects on the reduction of fibrinogen levels, reduction of the edema and the quantity of inflammatory cells, which suggests analgesia by the reduction of the inflammatory process [23,24]. During the inflammatory process, LLLT acts modulating chemical mediators, vasodilation, increase on protein and cortisol synthesis [23,25], besides producing an increase in the synthesis of endorphins [26,27].

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The first work found in the literature that approaches LLLT for the control of neuropathic pain was described by Gustafsson et al., (2003) [28]. In this study, the authors used 532 nm laser, with 70 mW power and energy densities of 263 J/cm^2, 656 J/cm^2 and 1312 J/cm^2. Other works such as the one by Cidral-Filho et al., (2012) [29] approached LLLT for the treatment of neuropathic pain with much lower energy density values than the ones used by Gustafsson et al., (2003) [28]. They used the energy densities of 1 J/cm^2, 2.5 J/cm^2 and 4 J/cm^2. In both studies LLLT was effective and applied energy. The literature shows many studies in which LLLT is used in the treatment of neuropathic pain using energy densities ranging from 1 J/cm^2 to 1312 J/cm^2, and, in most studies, the results are positive despite the discrepant energy densities as well as other parameters, such as power and total energy, which also had divergent values. Therefore, it was necessary to perform a systematic review with the purpose of establishing a "therapeutic window" for the treatment of neuropathic pain with LLLT, aiming a more effective treatment and a better understanding of the mechanism of action of this therapeutic resource.

2. Materials and Methods

A systematic review of the literature was carried out after a bibliographical search on the database Medilane/PubMed, Lilacs, Embase, Scielo, Scopus and active search lists of bibliographical references of articles selected up to April 2016. The search was carried out according to the orientations in PRISMA [32] (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). The database search was performed using the following terminology for laboratory tests: low level laser therapy and chronic nerve lesion and neuropathic pain and pain. For the clinical studies, the terminologies used were: low level laser therapy or laser therapy and neuropathic pain and clinical studies.

2.1. Inclusion Criteria

We selected full articles published in national and international periodicals, in English, Spanish and Portuguese, from the first publication on the subject until April 2016, which addressed the use of low intensity laser therapy in controlling neuropathic pain.

2.2. Study Type

We selected randomized clinical trials and experimental studies published in complete articles that used low level laser therapy as the main resource for the treatment of neuropathic pain.

2.3. Type of Participants

We included only those studies that reported results on people suffering from neuropathy and results experimental studies in an experimental model of neuropathic pain in rodents.

2.4. Intervention Type

We selected studies investigating the action of low level laser therapy as primary treatment resource for neuropathic pain.

2.5. Types of Reported Results

We included studies that investigated variables related neuropathic pain.

Clinical articles included in this review had their methodological quality assessed by the PEDro scale Physiotherapy Evidence Database.

Due to the heterogeneity of the primary studies, it was not possible to perform a meta-analysis. In order to compare the effect size (ES) of each MT technique, standardized mean difference was calculated for each comparison group separately, considering the values before and after intervention. They were further classified as small (<0.20), moderate (around 0.50) or large (>0.80), according to Cohen's criteria.

3. Results

We identified 34 works in the search for clinical studies (PubMed: 11; Lilacs: 5; Scopus 18), and for the laboratory studies we found 218 works (PubMed: 111; Lilacs: 50; Scopus 55, Scielo:1; whereas 1 study has been found by active search in bibliographical references), totaling 252 studies. After removing duplicated studies, the count was of 192 and after excluding articles whose title and abstract did not match with the proposal of this review, the final count was of 15 articles (Fig. 1).

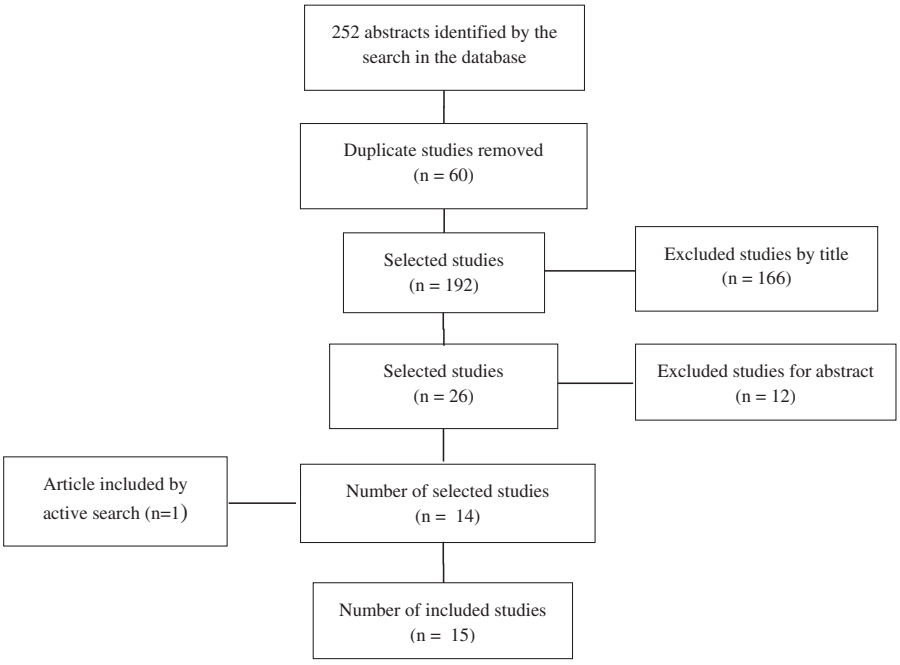

Fig. 1. Flow diagram of the different phases of the systematic review recommended by PRISMA [32].

Table 1
Trial characteristics and dosage in laboratory trials and clinical with significant LLLT modulation of neuropathic pain.

Study	λ	Output power	Cross-sectional area of the beam	Application technique	Energy density	Energy per point	Number of irradiated points	Total power	Total application (sessions)	Results
Gustafsson et al., 2003 [28]	532 nm	70 mW	0.032	Exact	262 J/cm^2 656 J/cm^2 1312 J/cm^2	8,4 J 21 J 42 J	1	8.4 J 21 J 42 J	1	+
Zinman et al., 2004 [31]	905 nm	60 mW	1 cm^2	Exact	9 J/cm^2	9 J	2	18 J	8	–
Ali-Asgarzadeh et al., 2011 [32]	980 nm	200 mW	[a]	Exact	[a]	10 J	8	80 J	12	+
Bertolini et al., 2011 [33]	830 nm	30 mW	0.11	Exact	4 J/cm^2 8 J/cm^2	0,42 J 0,88	1	0.42 J 0.88 J	5	+
Khamseh et al., 2011 [34]	808 nm 905 nm	25 mW	1 cm^2	Exact	10 J/cm^2	10 J	10	100 J	10	+
Yan et al., 2011 [35]	650 nm 808 nm	35 mW 450 mW	[a]	Exact	[a]	1.05 J 13.5 J	4	4.2 J 54 J	1	+ +
Cidral-Filho et al., 2012 [29]	950 nm	80 mW	1 cm^2	Exact	2.5 J/cm^2 1 J/cm^2 4 J/cm^2	2.5 J 1 J 4 J	1 1 1	2.5 J 1 J 4 J	14	+
Hsieh et al., 2012 [36]	660 nm	30 mW	0.2 cm^2	Exact	9 J/cm^2	1.8 J	4	7.2 J	7	+
Ribas et al., 2012 [37]	830 nm	70 mW	0.028 cm^2	Exact	8 J/cm^2 15 J/cm^2	0.21 J 0.42 J	1 1	0.21 J 0.42 J	9	+
Bashiri et al., 2013 [38]	780 nm	[a]	[a]	Exact	2.5 J/cm^2	[a]	[a]	[a]	8	+
Jameie et al., 2013 [18]	980 nm	70 mW	0.24	Exact	4 J/cm^2	0.91 J	2	1.82 J	14	+
Coradini et al., 2014 [39]	830 nm	30 mW	0.11	Exact	8 J/cm^2	0.87 J	2	1.74 J	2	+
Masoumipoor et al., 2014 [19]	660 nm 980 nm	100 mW 70 mW	0.24	Exact	4 J/cm^2 4 J/cm^2	0.9 J 0.91 J	3	2.7 J 2.73 J	14	+ +

+: Positive LLLT in controlling neuropathic pain. −: Negative results of LLLT in controlling neuropathic pain.
[a] Data not available in the study or data without the possibility of calculation.

From the 15 selected studies, 10 have used animals as experimental models (9 in rodents and 1 in falcon) and 5 involved humans. Among the articles that used animal models, one was excluded as it used an experimental model that is not frequently used in the literature (falcon) and, among the works that involved humans, one was excluded as it was published in Serbian and therefore did not meet the inclusion criteria of studies in English, Portuguese or Spanish.

Table 1 shows the 13 articles included in this study, with description of the main parameters for the LLLT application. In order to make the table, some parameters have been calculated from existing data intending to facilitate the data comparison.

As for the type of laser used for the neuropathic pain, one study used green laser (532 nm), 4 studies used red laser (650 nm to 670 nm) and 11 studies used infrared laser (780 nm a 980 nm). Besides this, the analyzed studies have used several different power values, ranging from 25 mW to 450 mW. The most commonly used power value was of 70 mW, which coincides with the median found in Table 2.

From the data analysis shown in Table 1, it was possible to establish the average and median of some parameters, such as power, energy density, energy per point and total energy. Table 2 shows these parameters, with their minimum and maximum values for each experimental study.

Table 2
Mean and median power, fluency, power and total energy per point of experimental studies analyzed.

	Power (mW)	Energy density (J/cm^2)	Point for energy(J)	Energy total (J)
Minimum	30	1	0.42	0.42
Maximum	450	1312	42	80
Mean	105	175.2	6.8	16
Median	70	6	1.4	4.1

For the clinical studies conducted to evaluate the PEDro scale, which punctuates the methodological quality of the articles of zero to ten, zero being the lowest and ten assigned as the highest quality. One of the articles received the highest score in the evaluation and the lowest value was three (Table 3).

The total number of participants in the clinical study was 130. In all studies the participants were 18 years and older; and there was no gender restriction; however all studies showed predominance of women. The patients did not use any analgesic medication and had been diagnosed with diabetic polyneuropathy and had therefore history of neuropathic pain. In all clinical studies, LLLT was applied with infrared laser. Three of the clinical studies used visual analogue scale (VAS) as evaluate method and they achieved relief of pain in all studies with two weeks of treatment. The values of energy density used in the study were very close to each other; however the power applied was discrepant (Table 4).

3.1. Effect of LLLT in Neuropathic Pain Control

The quality of evidence for LLLT technique according to GRADE approach is presented in Tables 5–7. Tables 5 and 6 present evidence of works in animal models and Table 7 shows the level of evidence for clinical studies.

The evidence synthesis showed moderate, for both clinical studies and for experimental studies, demonstrating the efficacy of LLLT in controlling the neuropathic pain [30].

4. Discussion

This review shows that LLLT is very effective in the control of neuropathic pain, although the parameters do not follow a specific standard over the different studies analyzed.

Table 1 shows that the researched literature presents several studies that used lasers with different wavelengths and found significant

Table 3
Methodological evaluation of studies with technical specifications by Pedro scale.

Study	Specified eligibility	Randomisation of participants in groups	Distribution of participants was blind	All groups had a similar prognosis	All subjects participated in a blinded fashion	All physiotherapists participated blindly	All evaluators participated blindly	There were 85% of the participants on the outcome of at least one result	Analysis of results by "intention to treat"	There were inter-group comparisons	There precision and variability measures at least one result	Total score
Khamseh et al., 2011 [34]	1	0	0	1	0	0	0	0	1	0	1	4
Bashiri, 2013 [38]	1	1	1	1	0	1	1	1	1	1	1	9
Zinman et al., 2004 [31]	1	1	1	1	1	1	1	1	1	1	1	10
Ribas et al., 2012 [37]	1	0	0	1	0	0	0	1	0	0	0	3
Ali-Asgarzadeh et al., 2011 [32]	1	1	1	1	0	0	0	0	1	1	1	7

increase in analgesia [28,31,33]. Most studies showed positive results with the application of LLLT in the treatment of neuropathic pain. However, the variables energy density, power and application time were mostly distinct.

Several researchers have been reporting the importance of LLLT in the treatment of pain in patients with diabetic neuropathy as a non-pharmacological alternative, due to the actions of biomodulation and antioxidant effects of laser [40,41].

Bjordal et al., (2006) [42] carried out a review study in which they described three different LLLT mechanism of action in pain. First, through the modulation of the inflammatory process, then through the alteration of excitation and conduction of peripheral nerves and finally through the stimulation and increase in the synthesis of endorphins. New hypothesis on the mechanisms of LLLT, such as systemic effects through the synthesis of nitrous oxide (NOS), cannot be discarded, but up to now these are only experimental possibilities that should be explored.

Alcantara et al., (2013) [41] presented a study demonstrating the action of LLLT in the control of inflammatory mediators in rats that have gone through the ICC (chronic constriction of the sciatic nerve) process, reporting a modulation of the inflammation. This study corroborates the Aimbieri et al., (2006) [43] study that attributed the analgesia generated in their study to the modulation of inflammatory cells.

Bradykinin is a pro-inflammatory neuropeptide, responsible for sensitizing nociceptors, being a key factor in inflammatory pain [44]. Studies using LLLT to reduce pain, found a strong link between the promotion of analgesia and the reduction of bradykinin through the modulation of the inflammatory process [45,46].

Recent studies have attributed the promotion of analgesia generated by LLLT to the increase of β-endorphin expression, this being a secondary action to the effects of the laser. Laakso & Cabot (2005) [47] and Hagiwara et al. (2008) [48] presented experimental studies in which LLLT was used for promotion of analgesia and the output results a significant pain reduction, such loss being associated to the increased expression of β-endorphin in the groups using LLLT as treatment.

Regarding the change of excitement and nerve conduction generated by LLLT, literature presents inconclusive results since there is insufficient evidence to affirm that this change is related to the promotion of analgesia. It is believed that induction of analgesia is more strongly linked to the specific inhibition of type C and delta fibers [46,49].

Masoumipoor et al., (2014) [19] and Yan et al., (2011) [35] presented comparative studies between lasers with different wavelengths in neuropathic pain. Both compared infrared laser with red laser. However, in both studies, the different wavelengths presented positive results as for the increase in analgesia. Nevertheless, when compared among themselves, the results were controversial. Masoumipoor et al., (2014) [19] reported that the red laser had better results while Yan et al., (2011) [35] found better results with the infrared laser. However, in both studies, the group which presented better results had used higher power, which led to the association of increase of analgesia with the power used in the application.

In the studies by Gustafsson et al., (2003) [28] and Cidral-Filho et al., (2012) [29] using LLLT in neuropathic pain in animal models, both compared different energy densities and fixed the other parameters. Both studies showed that higher energy densities presented more significant results. However, Cidral-Filho et al., (2012) [29] compared three different energy densities, 1 J/cm^2, 2.5 J/cm^2 and 4 J/cm^2, and showed that the energy densities 2.5 J/cm^2 and 4 J/cm^2 presented positive results without significant differences, stating that due to the lower application time, the use of energy density of 2.5 J/cm^2 would be more adequate.

In the same work, Gustafsson et al., (2003) [28], it was possible to observe a great discrepancy related to the values of energy density used in LLLT when compared to the other studies. The values of energy density found were of 263 J/cm^2, 656 J/cm^2 and 1312 J/cm^2. However, such high energy densities have been used due to particularities of the laser equipment used in the study, which was a Nd:YAG with a fiber

Table 4
LLLT in neuropathic pain: characteristics for trials measuring effects within two weeks.

Study	Laser type	Energy density	Energy	Number attendees	Treatment	VAS (before)	VAS (after)
Khamseh et al., 2011 [34]	Infra-red	10 J/cm^2	10 J	17	Two weeks	[a]	[a]
Bashiri et al., 2013 [38]	Infra-red	2,5 J/cm^2	[a]	60	Two weeks	8.17	6.2
Zinman et al., 2004 [31]	Infra-red	9 J/cm^2	9 J	50	Two weeks	7.1	5.8
Ribas et al., 2012 [37]	Infra-red	8 J/cm^2 15 J/cm^2	0.21 J 0.42 J	3	Two weeks	8.3	2.3
Ali-Asgarzadeh et al., 2011 [32]	Infra-red	[a]	10 J	12	Two weeks	9.53	5.8

[a] Data not available in the study.

Table 5
Summary off indings: LLLT red versus placebo in model experimental.

Low level laser therapy - in model experimental									
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Manual therapy (n)	Comparison (n)	Statistics	GRADE level of evidence
LLLT red protocol X control/Sham									
Neuropathic					Hsieh et al., 2012 [36]	20	20	$p < 0.001$	
Pain					Masoumipoor et al., 2014 [19]	20	10	$p < 0.001$	
					Yan et al., 2011 [35]	20	10	$p < 0.05$	
					Gustafsson et al., 2003 [28]	15	5	$p < 0.05$	
	Serious	No	No	Serious	No				MODERATE

of 200 to 220 μm in diameter. Most lasers, as the ones used in the studies in this review, used a fiber of 600 to 650 μm in diameter, which justifies the use of high energy densities in the work of Gustafsson et al., (2003) [28].

Among the four clinical studies that used application of infrared laser as a resource for treating neuropathic pain, only the study by Zinman et al., (2004) [31], did not present significant results. This study used LLLT with wavelength of 950 nm in 50 patients with diabetic polyneuropathy, who were placed in a control group and in a treated group. When the treated group was compared to the control group, no statistically significant improvement was observed, thus highlighting the importance of including placebo/control groups in clinical researches. However, when the pain before and after treatment were compared, a significant decrease in VAS in the treated group was found. Although most clinical studies showed significant results as for the LLLT for the treatment of the neuropathic pain, the number of studies is very scarce, which evidences the need of further studies so that the action of LLLT for the treatment of

Table 6
Summary off indings: LLLT infrared versus placebo in model experimental.

Low level laser therapy - in model experimental									
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Manual therapy (n)	Comparison (n)	Statistics	GRADE level of evidence
LLLT infrared protocol X control/Sham									
Neuropathic					Bertolini et al., 2011 [33]	12	6	$p < 0.05$	
pain					Cidral-Filho et al., 2012 [29]	8	8	$p < 0.05$	
					Jameie et al., 2013 [18]	30	10	$p < 0.001$	
					Masoumipoor et al., 2014 [19]	20	10	$p < 0.01$	
					Yan et al., 2011 [35]	20	10	$p < 0.05$	
					Coradini et al., 2014 [39]	6	6	$p < 0.05$	
	Serious	No	No	Serious	No				MODERATE

Table 7
Summary off indings: LLLT infrared versus placebo in model experimental.

Low level laser therapy - in clinical									
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Manual therapy (n)	Comparison (n)	Effect size	GRADE level of evidence
LLLT infrared protocol × control/Sham									
Neuropathic					Ali-Asgarzadeh et al., 2011 [32]	15	15	−0,753	
pain					Bashiri et al., 2013 [38]	30	30	−0,377	
					Zinman et al., 2004 [31]	25	25	0,101	
	No	Serious	No	Serious	No				MODERATE

neuropathic pain can be effectively recognized as an alternative treatment. Due to short time of treatment and the small size of the sample, we could not detect a significant result. In addition, it is believed that the action of LLLT is related to the small diameter fibers and it is difficult to evaluate them accurately.

In this review, a great difficulty to compare the studies was found due to a lack of detailed laser and energy density parameters in some of the studies reviewed it is difficult to suggest possible efficacious treatment protocols.

When applied in a manner that is not adequate, according to each case, high energy densities may cause damage to the tissue, as described by Hawkins e Abrahamse (2005) [50]. On the other hand, studies such as the one by Núñez et al., (2004) [51], which used HeNe laser with energy density of 1 J/cm^2 and power of 10 mW, did not find any biological alteration on the irradiate tissue due to the low energy density of the LLLT.

In a review study carried out by Bjordal et al. (2006) [42] on the use of infrared lasers for the management of neuropathic pain, the authors concluded that the positive effects could be observed with up to 1.8 J per point, and the energy should be about or higher than 5 J.

It is believed that the existence of a "therapeutic window" can generate an effective photo stimulation, based on those described in Arnold Shultz Law, which predicts the existence of a "dose–response" able to inhibit or stimulate biological processes [52–55]. For this law is assumed that the energy density (J/cm^2) is strongly related to the efficiency of laser radiation, supported by studies KARU (1989) [52] which describe the energy density responsible for regulating or speed up the transport of electrons the mitochondrial respiratory chain. But currently, the literature has shown that the action of laser radiation is interrelated with the energy (J) which is "offered" to the tissue while energy density is the total power transmitted by a laser beam not necessarily what reach the body, making it necessary to calculate both the energy and power density, considering the other parameters such as power (mW) and time (*sec*), so that LLLT is applied effectively [54].

Thus, it is possible to observe that LLLT can be effective for the treatment of neuropathic pain, and suggested the use of a laser infrared wavelength (780 nm to 905 nm) due to the majority of studies using this wavelength and present significant results when compared to other types of laser. Regarding power, we found significant results between 30 mW–450 mW, and the power of 70 mW the most used with effective results. Since the power density for experimental studies, showed significant responses to the range of 1 J/cm^2–15 J/cm^2, and energy densities found above this range but with a particular type of laser. About energy (J) for both clinical study and experimental, found a large discrepancy, however all doses used to demonstrate efficacy for the promotion of analgesia, and for the experimental studies 042 J - 42 J, while for clinical study could not find a "therapeutic window" because of the labor shortage in the area.

5. Conclusion

With this review, it is possible to conclude that the use of LLLT in the treatment of neuropathic pain has positive effects in the control of analgesia. Besides, it was possible to establish effective parameters for the treatment of this type of pain. However, further studies are necessary, with higher scientific rigor, especially as for the description of all parameters of LLLT, thus aiming the comparison among results and therefore defining protocols of treatment that optimize the action of LLLT in the treatment of neuropathic pain.

Disclosure Statement

There are no competing financial interests.

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