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The Efficacy of Low-Power Lasers in Tissue Repair and Pain Control: A Meta-Analysis Study

CHUKUKA S. ENWEMEKA, P.T., Ph.D., FACSM,[1,2] JASON C. PARKER, MSPT,[2]
DAVID S. DOWDY, MSPT,[2] ERIN E. HARKNESS, MSPT,[2] LEIF E. SANFORD, MSPT,[2]
and LYNDA D. WOODRUFF, P.T., Ph.D.[3]

ABSTRACT

Objective: **We used statistical meta-analysis to determine the overall treatment effects of laser phototherapy on tissue repair and pain relief.** ***Background Data:*** **Low-power laser devices were first used as a form of therapy more than 30 years ago. However, their efficacy in reducing pain or promoting tissue repair remains questionable.** ***Methods:*** **Following a literature search, studies meeting our inclusion criteria were identified and coded. Then, the effect size of laser treatment, that is, Cohen's *d*, was calculated from each study using standard meta-analysis procedures.** ***Results:*** **Thirty-four peer-reviewed papers on tissue repair met our inclusion criteria and were used to calculate 46 treatment effect sizes. Nine peer-reviewed papers on pain control met the inclusion criteria and were used to calculate nine effect sizes. Meta-analysis revealed a positive effect of laser phototherapy on tissue repair ($d = +1.81$; $n = 46$) and pain control ($d = +1.11$; $n = 9$). The positive effect of treatment on specific indices of tissue repair was evident in the treatment effect sizes determined as follows: collagen formation ($d = +2.78$), rate of healing ($d = +1.57$), tensile strength ($d = +2.13$), time needed for wound closure ($d = +0.76$), tensile stress ($d = +2.65$), number and rate of degranulation of mast cells ($d = +1.87$), and flap survival ($d = +1.95$). Further, analysis revealed the positive effects of various wavelengths of laser light on tissue repair, with 632.8 nm having the highest treatment effect ($d = +2.44$) and 780 nm the least ($d = 0.60$). The overall treatment effect for pain control was positive as well ($d = +1.11$). The fail-safe number—that is, the number of studies in which laser phototherapy has negative or no effect—needed to nullify the overall outcome of this analysis was 370 for tissue repair and 41 for pain control.** ***Conclusions:*** **These findings mandate the conclusion that laser phototherapy is a highly effective therapeutic armamentarium for tissue repair and pain relief.**

INTRODUCTION

MORE THAN 30 YEARS have elapsed since Endre Mester[1–3] first demonstrated that imperceptible amounts of laser light—so innocuous and so low in intensity that some have likened it to weak sunlight—could relieve pain and promote tissue repair. For as many years, the therapeutic value of these low-power lasers, generally, ≤500 mW in average power, has remained controversial, with several studies supporting the original notion that they promote tissue repair processes in experimental animals.[4–32] and human wounds and ulcers,[8,33–38] and other studies[39–46] suggesting the contrary.

A close examination of well-controlled *in vitro* and *in vivo* laboratory experiments suggests that low-intensity lasers enhance wound healing by promoting cell proliferation,[8,28–30,41–44] accelerating the formation of granulation tissue, promoting collagen synthesis,[3–13,47–61] fostering the formation of type I and type III procollagen specific pools of mRNA,[62] increasing ATP synthesis within the mitochondria, activating lymphocytes, and increasing their abilities to bind pathogens.[10,52] This trend is not so clear when clinical reports on tissue repair are examined, as a dichotomy appears between studies demonstrating beneficial effects and those reporting no effects whatsoever.[10,33–46]

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[1] School of Health Professions, Behavioral and Life Sciences, New York Institute of Technology, Old Westbury, New York.
[2] Department of Physical Therapy and Rehabilitation Sciences, University of Kansas Medical Center, Kansas City, Kansas.
[3] Department of Physical Therapy, North Georgia College & State University, Dahlonega, Georgia.

Similar inconsistencies seem evident in the use of low-power lasers for pain control. Whereas some have shown rapid pain relief in a variety of clinical conditions,[63–66] others have demonstrated that, regardless of etiology or wavelength, low-power lasers are of little or no therapeutic value for pain control.[67–70] Given the multitude of variables involved in treatments with laser therapy devices, that is, wavelength, power, power density, energy, energy density, treatment duration, treatment intervention time post-injury, and method of application (contact mode versus non-contact mode), a traditional review of the literature does not leave one with a clear impression of the true effects of low-power lasers on tissue repair or pain control.

Consequently, the purpose of this study was to aggregate the literature, and subject every study meeting the inclusion and exclusion criteria to statistical meta-analysis, in order to test the hypothesis that laser therapy has a significant positive effect on tissue repair and pain relief. Our null hypothesis was that there would be no significant effect of laser therapy on tissue repair and pain control. A secondary goal was to elucidate information that might be helpful to clinicians and researchers in developing effective treatment guidelines.

Meta-analysis is a statistical analysis of a large collection of results from a number of individual studies with the overall goal of determining the overall effect of treatment.[71] Each data point used in the analysis is obtained from an individual study rather than from an individual subject, as is typically done in a traditional research study. Whole studies are treated as subjects, and their primary findings used as data points. Therefore, the procedure permits a quantitative review, statistical analysis, and synthesis of the research literature—not just a traditional review, which can be subjective or prone to bias.

MATERIALS AND METHODS

Subjects

Subjects were primary studies published within the last 30 years in which laser therapy—also known as soft laser, cold laser, low-intensity laser, low-power laser, or low-level laser therapy (LLLT)—was used as treatment for tissue repair or pain control. The papers were sought and obtained from library sources and online data bases, including Medline, Index Medicus, Excerpta Medica, Citation Index for Nursing and Allied Health Literature (CINAHL), and Psychology Information (PsycInfo). Search terms used include "phototherapy," "laser phototherapy," "laser therapy," "laser biostimulation," "soft laser," "laser photostimulation," "biostimulation," "photostimulation," "light therapy," "laser therapy and wound healing," "biostimulation and wound healing," "pain," "pain control," and "pain management." Additional secondary sources of information include papers cited by authors whose articles were obtained from the aforementioned sources, Internet Web pages, and pertinent papers published in journals that were not found from any of the above data bases.

Inclusion criteria

Articles were included in the meta-analysis if they met the following criteria:

- Study was published in a referred professional or scientific journal.
- Study entailed *in vivo* determination of tissue repair (i.e., *in vivo* human and animal studies)
- The effect of laser treatment on pain control was performed on human subjects.
- Low power laser, defined as lasers with ≤500 mW average power was used for treatment, i.e., as the independent variable.
- The authors either stated or we were able to determine the following treatment parameters: power, power density, energy, energy density, number of treatments given, duration of each treatment, frequency of treatment, beam and spot size, dose (expressed in J/cm^2 or in similar units), size of the area treated, and mode of treatment (contact or non-contact mode).
- The condition treated (e.g., bed sores, venous ulcers, diabetic ulcers, surgical wounds) was clearly stated.
- The wavelength and type of laser used were defined.

Exclusion criteria

Articles were excluded based on the following criteria:

- *In vitro* studies involving cells and tissues, not whole animals
- Case reports and single case studies, regardless of etiology
- Studies with data from which Cohen's *d* statistic or treatment effect could not be calculated using one of the statistical formulas detailed below
- Studies reported in languages that we could not translate into English

Data coding and pilot reliability study

In strict compliance with the seven steps advocated for accurate and reliable coding of data,[71] data coding and a reliability study were conducted as follows. A coding form was developed and used to list the essential parameters and other pertinent information obtained from each primary study as detailed in Table 1. The initial coding form, which contained 13 variables, was adapted from those suggested by Basford,[72] and used to organize data, compare studies, and ascertain their overall quality as suggested by Wolf.[71] Then, after coding, data were obtained from those studies meeting every inclusion criteria and used to establish a data pool. Since four investigators served as raters, a pilot study was undertaken to determine inter-rater reliability of the four raters (i.e., the level of agreement among raters as they calculated the treatment effect sizes—Cohen's *d*—from each study).

The pilot study was conducted as follows. Twelve articles were randomly selected from the pool of papers. Then, each paper was coded independently by each of the four raters. A limit of ≥80% agreement was set as an acceptable inter-rater reliability. Raters were continually trained on new sets of data and retested for reliability until an acceptable level of agreement was attained. The analysis was continued when 88% agreement was achieved among raters.

Determination of effect size

Treatment effect sizes were determined by calculating Cohen's *d*.[71] Cohen's *d* has been defined as the standardized

TABLE 1. ESSENTIAL TREATMENT PARAMETERS SOUGHT FROM EACH STUDY

Experimental subjects
Condition treated
Independent variable
Dependent variable(s)
Type of laser used
Laser wavelength
Beam
Spot size
Distance from surface area treated
Power
Power density
Dosage
Energy density
Number of treatments
Frequency of treatments
Duration of treatments
Area of the wound
Outcome

difference between the means of the experimental group and the comparison group divided by a standard deviation of the comparison group,[71] as expressed in the following equation:

$$d = \frac{|x_1 - x_2|}{\mathrm{SD}_{\mathrm{comparison}}}$$

where d is the effect size, x_1 is the mean of the laser treated group, x_2 is the mean of the comparison group, and $\mathrm{SD}_{\mathrm{comparison}}$ is the standard deviation of the comparison group.

According to Cohen, the values of 0.2, 0.5, and 0.8 indicate a small, medium, and large average effect size, respectively. Where means or standard deviations were not reported but data were presented as percentages, the following t formula was used as the first step toward obtaining d:

$$t = \frac{P_2 - P_1}{\left[\frac{(P_2)(1 - P_2)}{N_2} + \frac{(P_1)(1 - P_1)}{N_1}\right]^{1/2}}$$

where P_2 is the population of the laser group, P_1 is the population of the comparison group, N_2 is the number of subjects in the laser group, and N_1 is the number of subjects in the comparison group.

The t-value obtained was then converted to d as follows:

$$d = \frac{2t}{\sqrt{df}}$$

where d = effect size; t = t-value, and df = the degrees of freedom.

The effect size (d) was assigned a positive or negative value depending on the outcome of the study. Thus, positive values were assigned to experiments whose results were positive—i.e., studies indicating that laser therapy promotes tissue repair or pain control; while negative values were assigned to experiments that showed negative effects.

Subsequently, the mean overall effect size was calculated by summing all the effect sizes obtained independently from each study and dividing by the total number of effect sizes using the following formula[71]:

$$d_{\mathrm{average}} = \frac{\Sigma d}{N}$$

where d_{average} = mean effect size, Σd = the sum of the effect sizes, and N = the total number of effect sizes calculated and used.

To avoid violating the assumption of independence, not more than two effect sizes were taken from studies in which multiple effect sizes were calculated. A 95% confidence interval was then calculated using the following formula:

$$95\%\ \mathrm{CI} = x \pm (1.96)s_x$$

where x = mean effect size, and s_x = standard error of the mean effect size.

Calculation of fail-safe number

Given the likelihood of not including every available study in our meta-analysis, a Fail Safe number (N_{fs}) was calculated to determine the number of studies confirming the null hypothesis that would be needed to reverse the outcome of our study.[71] The N_{fs} reveals the number of additional studies with effect sizes below a set criterion value that would have to be included in the meta-analysis in order to change the outcome of the study. We used 0.10 as the criterion, a number that is remarkably lower than the small effect size of 0.2 suggested by Cohen, statistical significance was set at 0.05, and the fail-safe number was calculated as follows:

$$N_{\mathrm{fs.05}} = N(d - d_c)/d_c$$

where N = the number of studies in the meta-analysis; d = the average effect size for the studies synthesized; d_c = the criterion value selected that d would equal when some knowable number of hypothetical studies ($N_{\mathrm{fs.05}}$) were added to the meta-analysis. For this study, $d_c = 0.2$, to reflect the value of a small effect size.

RESULTS

Effect of laser therapy on tissue repair

Of the hundreds of studies found in the literature, only 34 tissue repair studies with 46 computable effect sizes, and nine pain control papers with nine effect sizes, met the inclusion criteria. The major flaws found in most reports were inadequate reporting of laser parameters and insufficient data with which to calculate treatment effect size. In some instances data were simply illustrated, making it impossible to calculate Cohen's d.

As summarized in Table 2, the overall mean effect size d for tissue repair was +1.81; (SD = 2.26; median = 0.88; 95% confidence interval = 1.16 to 2.46), indicating that laser therapy is highly effective in promoting tissue repair. The fail safe num-

TABLE 2. TREATMENT EFFECT OF LASER PHOTOTHERAPY ON VARIOUS INDICES OF TISSUE REPAIR

Dependent variable	*Effect size*	n *of effect sizes*
Flap survival	+1.95	2
Collagen formation	+2.78	7
Rate of healing	+1.57	14
Tensile strength	+2.13	7
Tensile stress	+2.65	2
Decreased dermal necrosis	+5.85	1
IL-6 formation	+0.86	1
Wound closure	+0.76	6
Mast cell no.	+1.87	3
Percentage degranulation	+0.26	3
Overall effect size	+1.81	46

ber (N_{fs}) associated with this finding was 370, meaning that 370 additional studies in which laser therapy had neutral or negative effect on tissue repair, would be needed to nullify the large treatment effect obtained. Further analysis revealed that laser therapy promotes collagen formation ($d = +2.78$), tensile strength ($d = +2.13$), rate of healing ($d = +1.57$), and wound closure ($d = +0.76$) during tissue repair.

Similarly, there was an overall positive effect of laser therapy on pain relief, $d = +1.11$ (SD = 1.02; median = +0.79; 95% confidence interval = +0.44 to +1.78). The corresponding fail-safe number associated with this finding was 41 (i.e., the number neutral or negative studies needed to nullify this significant treatment effect for pain control).

Effect of wavelength on treatment effect sizes

The limited number of studies meeting our inclusion and exclusion criteria significantly hampered our ability to pinpoint the effect of specific wavelengths on treatment. Within this limitation, the few studies available for sub-analysis revealed significant positive effects of various wavelengths of light for tissue repair. Light of 780-nm wavelength had the least significant treatment effect (d = +0.60), while 632.8-nm wavelength had the most (d = +2.44). The so-called cluster probe, with multiple wavelengths of light, had a high treatment effect of +1.95 (Table 3). For pain relief, the wavelength with the most significant treatment effect was 830 nm (d = 1.60), but only four studies meeting the inclusion criteria were available for this analysis.

TABLE 3. EFFECT OF WAVELENGTH ON TREATMENT EFFECT SIZES

Wavelength	*Effect size*	n *of studies*	n *of effect sizes*
514 nm	+1.89	4	5
632.8 nm	+2.44	14	19
780 nm	+0.60	3	4
820 nm	+1.00	2	4
830 nm	+0.61	4	4
904 nm	+1.09	6	8
Cluster	+1.95	3	4

DISCUSSION

In meta-analysis, it is generally accepted that a treatment effect value of 0.2 denotes a small effect size, 0.4, a medium effect size, and a value of 0.8 or greater represents a large effect of treatment.[71] Thus, our finding that laser therapy has overall mean treatment effect sizes of 1.81 and 1.11 for tissue repair and pain control respectively, evince a high level of efficacy for both conditions regardless of etiology.

That only 34 tissue repair studies and nine pain control studies met our inclusion criteria is proof that the literature—in particular, earlier studies—are replete with data from which not much can be deciphered. Hence it is not surprising that in the absence of objective statistical analysis, previous attempts to review the literature resulted in reports, which suggest that no conclusions can be drawn on the exact effects of therapeutic lasers.[39–44] Our findings that insufficient reporting of treatment parameters, inconsistencies in terminology, inadequate and/or inexplicable reporting of data or treatment outcome, and occasionally, lack of hardcore data are the major flaws of the literature, are well supported by previous studies.[9,73]

Further support for this assertion can be seen in the large standard deviation associated with our overall finding and the large 95% confidence interval, both of which suggest a high degree of variability within the computed effect sizes. Treatment methods, outcome measures, and subjects differed markedly from one study to the next. Despite the large standard deviation and 95% confidence interval, the large fail-safe number obtained for each of the two conditions relative to the number of studies used for this meta-analysis, buttress the large treatment effect size and strengthens the conclusion that laser therapy promotes tissue repair and pain relief. The high variability of computed effect sizes reflects the variances in the treatment parameters used from one study to the next.

Our effort to pinpoint the wavelength of light that is most beneficial for each of the two conditions was severely limited by the number of studies that met our inclusion criteria, and the fewer number of studies in each sub-category of wavelength. Therefore, our result, which indicates that 780- and 632-nm wavelengths, respectively, have the least and most significant treatment effects on tissue repair should be interpreted with great caution. It may be used as a guide or starting point for well-designed studies aimed at comparing the effects of various wavelengths.

Our results show that many indices of tissue repair are positively affected by laser treatment. The process of tissue repair may be subdivided into three major phases: (1) inflammation, (2) cell proliferation—i.e., proliferation of fibroblasts, keratinocytes, chondrocytes, osteoblasts—along with collagen synthesis, and (3) tissue maturation. Our sub-analysis reveals that all three phases of tissue repair are positively affected by laser treatment. As shown in Table 2, there is a positive effect of laser treatment on known aspects of inflammation such as mast cell proliferation and degranulation, as well as the cell proliferation-promoting activities of the multifunctional cytokine, Interleukin-6.[74]

Similarly, the computed effect size for collagen synthesis and the rate of wound closure indicates that laser therapy promotes the cell proliferation/collagen synthesis phase of tissue repair. Its positive effect on tensile strength and tensile stress of the repaired tissue, similarly suggests that the process of remodeling is accelerated (Table 1). Although the low number of studies used in each sub-analysis suggests caution in relying heavily on this aspect of our results, these findings support experimental animal and clinical reports, which indicate that laser therapy promotes wound healing by accelerating collagen synthesis,[3–13,47–61] inflammation,[10,47,48] and healing time and strength acquisition.[7,10,12,15–21,75–79] Furthermore, the sub-analysis is consistent with previous reports that have demonstrated elevation of several metabolic indices of tissue healing, including ATP synthesis,[80–83] and fibroblast proliferation,[10,12,84,85] as well as increases in the biomechanical indices of tissue healing.[2,7,75–79]

Our meta-analysis was limited to papers published in the English literature. Given the large number of papers published in other languages, a determined effort should be made to include such studies in future meta-analysis of the literature. Such effort could yield a larger pool of studies that permit the sub-analysis of a large pool of data from which far-reaching conclusions on the specific effects of wavelength and treatment parameters on various indices of tissue repair and pain control can be drawn. Nonetheless, it is pertinent to note that the relatively few foreign language papers we examined had such limited information that it was impossible to include them in the present study.

CONCLUSION

Our meta-analyses warrant the conclusions that laser therapy is a highly effective modality for tissue repair, and pain control. Wavelength may influence the outcome of treatment.

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Address reprint requests to:
Dr. Chukuka S. Enwemeka
School of Health Professions, Behavioral and Life Sciences
New York Institute of Technology
Old Westbury, NY 11568-8000

E-mail: Enwemeka@nyit.edu