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The Efficacy of Laser Therapy in Wound Repair: A Meta-Analysis of the Literature

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ABSTRACT

Objective: **We determined the overall effects of laser therapy on tissue healing by aggregating the literature and subjecting studies meeting the inclusion and exclusion criteria to statistical meta-analysis.** ***Background Data:*** **Low-level laser therapy (LLLT) devices have been in use since the mid sixties, but their therapeutic value remains doubtful, as the literature seems replete with conflicting findings.** ***Materials and Methods:*** **Pertinent original research papers were gathered from library sources, online databases and secondary sources. The papers were screened and coded; those meeting every inclusion and exclusion criterion were subjected to meta-analysis, using Cohen's *d.* statistic to determine the treatment effect size of each study.** ***Results:*** **Twenty-four studies with 31 effect sizes met the stringent inclusion and exclusion criteria. The overall mean effect of laser therapy on wound healing was highly significant (d = +2.22). Sub-analyses of the data revealed significant positive effects on wound healing in animal experiments (d = +1.97) as well as human clinical studies (d = +0.54). The analysis further revealed significant positive effects on specific indices of healing, for example, acceleration of inflammation (d = +4.45); augmentation of collagen synthesis (d = +1.80); increased tensile strength (d = +2.37), reduced healing time (d = +3.24); and diminution of wound size (d = +0.55). The Fail-Safe number associated with the overall effect of laser therapy was 509; a high number representing the number of additional studies—in which laser therapy has negative or no effect on wound healing—required to negate the overall large effect size of +2.22. The corresponding Fail-Safe number for clinical studies was 22.** ***Conclusion:*** **We conclude that laser therapy is an effective tool for promoting wound repair.**

INTRODUCTION

To many clinicians and scientists, the idea that low-power laser light (so low in intensity that some have compared its power to dull sunlight) can be therapeutic enough to relieve pain and promote tissue repair in collagenous tissues seems preposterous. Yet, reports abound which indicate that these lasers, that is, lasers with ≤500 mW average power, promote the repair processes of skin, ligaments, tendons, bone, and cartilage in experimental animals,[1–28] as well as wounds and ulcers of a wide range of etiologies in humans.[7,29–34] The availability of other studies[35–42] that suggest the contrary, that is, that low-intensity lasers and other monochromatic light sources are not effective in promoting tissue repair, further complicates the matter, creating the present scenario in which low-intensity lasers are viewed with doubt and cynicism.

There is little disagreement that a majority of animal experiments suggest that low-intensity lasers enhance wound healing by promoting cell proliferation,[1,7,43–53] accelerating collagen synthesis and promoting the formation of granulation tissue,[2–6,55–60] fostering the formation of type I and type III procollagen specific pools of mRNA,[58] increasing ATP synthesis within the mitochondria, activating lymphocytes, and increasing their ability to bind pathogens.[7,61–66] In contrast, clinical reports concerning the effects of low-intensity lasers remain, at least prima facae, contradictory, with some studies reporting

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beneficial effects on tissue repair and others showing no effect whatsoever.[7,29–42,67–76] 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 concerning the true effects of laser therapy on tissue repair. Consequently, the purpose of this study was to aggregate the literature, and subject every study meeting every inclusion and exclusion criteria to statistical meta-analysis, in order to determine objectively the overall effects of laser therapy on tissue repair processes. A secondary goal was to elucidate information that might be helpful to clinicians and researchers in developing effective treatment guidelines.

In this study laser therapy or laser is used operationally to treat with monochromatic light devices, including low-power lasers, light-emitting diodes, and superluminous diodes.

MATERIALS AND METHODS

Subjects and design

Original research papers, investigating the effects of laser therapy on tissue healing, were gathered and used for this study. 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 "laser therapy," laser biostimulation," "soft laser," laser photostimulation," "biostimulation," "photostimulation," "light therapy," "laser therapy and wound healing," and "biostimulation and wound healing." 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: We included studies that met the following criteria:

- The type of laser and precise wavelength were defined.
- Laser or other light source is clearly identified as the independent variable.
- At least one index of wound healing, that is, collagen content, healing time—defined as the total amount of time that treatment was performed to achieve full healing of tissues—reduction in wound area, tensile strength, acceleration of inflammation, and prevention of dermal necrosis was identified as the dependent 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), size of the area treated, and mode of treatment (contact or non-contact mode).
- The condition treated, for example, bed sores, venous ulcers, diabetic ulcers, or surgical wounds, was clearly stated.

Exclusion criteria: Studies excluded from this analysis include:

- *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,[77] that is, treatment effect, could not be calculated using one of the statistical formulas detailed below.
- Studies reported in languages that we could not interpret.

Reliability study and data coding: To determine the presence or absence of our inclusion or exclusion criteria in each study reliably, 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. Then, a pilot study was conducted to ascertain the level of agreement among raters as they calculated the treatment effect sizes, that is, Cohen's d, from each study. The analysis was continued when 90% agreement was achieved among raters. Thereafter, studies included in the meta-analysis were coded by one of the investigators using the nineteen parameters on the coding form. Thus, the overall result of each study was transformed into a standardized effect size statistic using Cohen's d formula.[77]

Data analysis

Calculation of Cohen's d: Treatment effect sizes were calculated using the formulae for determining Cohen's d.[77] According to Wolf,[77] Cohen's d may be defined as the standardized difference between the means of the experimental group and the comparison group divided by a standard deviation of the comparison group. This definition and Cohen's classification of effect sizes were applied to each study included in our meta-analysis. According to Cohen, the values of 0.2, 0.5, and 0.8 indicate a small, medium, and large average effect size, respectively.

Conceptually Cohen's statistic may be expressed as follows:

$$d = \frac{|x_1 - x_2|}{SD_{comparison}}$$

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 $SD_{comparison}$ is the standard deviation of the comparison group.

If means or standard deviations were not reported and percentages were reported in a study, then, the following t formula was used:

$$t = \frac{P_2 - P_1}{\sqrt{\left\{\frac{(P_2)(1 - P_2)}{N_2} + \frac{(P_1)(1 - P_1)}{N_1}\right\}}}$$

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.

Once a t-value was calculated, then it was converted to d as follows:

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

TABLE 1. ESSENTIAL LASER TREATMENT PARAMETERS SOUGHT FROM EACH STUDY

Subjects	Power
Condition being treated	Power density
Independent variable	Dosage
Dependent variable	Energy density
Type of laser	Number of treatments
Wavelength	Frequency of treatments
Beam	Duration of treatments
Spot size	Area of the wound
Distance from area	Outcome

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

The effect size (d) was assigned a positive or negative value depending on the outcome of the study. For example, positive values were assigned to experiments whose results were positive, that is, indicated that laser therapy promotes wound healing. Negative values were assigned to experiments that showed negative effects of laser therapy, that is, that laser therapy had no effect or retarded wound healing. After calculating the treatment effect size of each study independently, the mean overall effect size was calculated by summing all the effect sizes and dividing by the total number of effect sizes using the following formula[77]:

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

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

Multiple effect sizes were calculated in several studies. In order to avoid violating the assumption of independence, no more than two effect sizes were taken from each study.

Calculation of fail-safe number: Given the likelihood that we did not obtain every study that ever examined the effects of lasers on wound healing, a fail-safe number (N_{fs}) was calculated. 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. The following formula was used to calculate the fail-safe number:

$$N_{fs} = \frac{N(\bar{d} - d_c)}{d_c}$$

where N_{fs} is the fail-safe number (N) value; N = the number of studies in the meta-analysis; and $\bar{d}$ = the average effect size of all studies, and d_c = the criterion value.

Sub-analysis of effect sizes: The data obtained were grouped into categories to permit further sub-analysis of the overall treatment effects of laser therapy on each outcome parameter. The outcome categories used were: collagen content, healing time (i.e., the total amount of time that treatment was performed to achieve full healing of tissue), reduction in wound area, tensile strength, acceleration of inflammation, and prevention of dermal necrosis. Furthermore, the data were analyzed to compare the overall effects of the different types of lasers, as well as the relative effects of treatment in animal and human experiments.

RESULTS

The overall effect of laser therapy on tissue repair

Our literature search revealed hundreds of studies that examined the effects of laser therapy on tissue repair, but the final set of papers from which treatment effect sizes could be calculated was just 24. These 24 publications had 31 computable effect sizes. Insufficient data with which to calculate treatment effect size and/or inadequate reporting of treatment parameters were the major reasons that so many studies were not included in the meta-analysis. In addition, there were several studies in which data were only summarized in the form of graphs and illustrations from which it was not possible to extrapolate the data needed to compute Cohen's d.

The overall mean treatment effect size (Cohen's d), determined from the 24 studies was +2.22, indicating that laser therapy is highly effective in promoting wound healing. The fail safe number (N_{fs}) associated with this finding was 509, meaning that 509 additional studies in which laser therapy had little or no effect on tissue repair, would be needed to negate the large treatment effect of this meta-analysis. When animal and human clinical studies were analyzed separately, our sub-analysis revealed an overall treatment effect size of +1.97 and +0.54, respectively, indicating that laser therapy strongly promotes healing in experimental animal models and moderately so in humans. Given the overwhelming interest in the clinical effects of laser therapy on wound healing in humans, we sub-analyzed the fail-safe number for human studies, using the same set criterion value of 0.10. The fail-safe number (N_{fs}) associated with this sub-analysis was 22 additional human studies in which laser therapy had little or no effect on tissue repair. This number corresponds with the moderate healing effect of +0.54 previously determined from the diverse clinical studies analyzed.

Consistent with Figure 1, the distribution of the calculated effect sizes was trimodal, with all three peaks occurring above zero, and with the largest peak between zero and 1.5; again showing an overall positive effect of laser therapy on wound healing. Treatment effect sizes ranged from −0.33 to +9.10; mean ± SD = 2.22 ± 2.86. The associated 95% confidence interval was calculated as −3.41 to +7.81, reflecting the wide variability in the parameters of treatment used in these studies (Table 2).

In order to verify the accuracy and dependability of the overall effect size and its implications, we examined the data points that were used to calculate the effect size and determined whether extremely large effect sizes skewed the data. An analysis of the trimodal frequency distribution curve revealed no obvious differences between the studies in the positively skewed cluster and the rest of the data. Moreover, the median was found to be +0.95, signifying that more than half of the effect sizes were greater than or equal to +1.00.

Furthermore, 15 studies, which examined the effects of laser therapy on wound healing in experimental animal models and

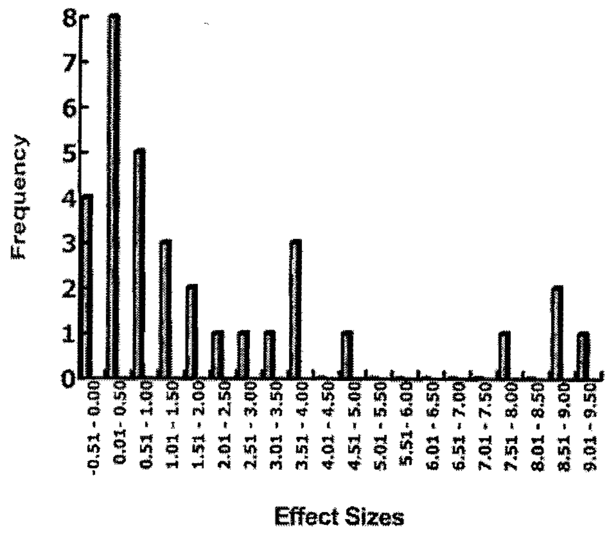

FIG. 1. Frequency distribution of effect sizes.

humans but were excluded from this meta-analysis because the data needed to calculate effect size narrowly missed our stringent inclusion and exclusion criteria, i.e., data were either insufficient or presented in graphs from which effect sizes could not be derived, were closely examined after the meta analysis. Of these studies, 12 reported positive outcomes and three reported negative outcomes. Moreover, four were human studies and 11 were animal studies. All the human studies showed positive outcomes favoring the use of therapeutic lasers on wounds. Thus, it appears that if these studies were included in the meta-analysis, the overall treatment effect size reported here would have been higher than +2.22.

TABLE 2. RANGE OF LASER THERAPY PARAMETERS USED IN THE LITERATURE

Parameter	*Range*
Type of beam	Continuous to pulsed; pulse density ranged from 200 nsec to 260 msec; pulse frequency varied from 2.5 to 20,000 Hz
Spot size	1 mm^2 to 3.90 cm^2
Distance from area Treated	0 to 10 cm (where 0 = direct contact)
Power	0.2 μW to 13 W
Power density	1 mW/cm^2 to 1.2 W/cm^2
Energy	Reported only in two studies as 1J[50,65]
Energy density	76.4 mJ/cm^2 to 140 J/cm^2
Number of treatments	1–36
Frequency of treatment	Twice per week, to daily
Duration of treatment	20 sec to 30 min
Size of wounds treated	0.39 to 16 cm^2

TABLE 3. TREATMENT EFFECTS OF LASER THERAPY ON INDICES OF TISSUE REPAIR

Variable	*Effect size*
Collagen content	+1.80
Time to heal	+3.24
Area reduction	+0.55
Tensile strength	+2.37
Acceleration of inflammation	+4.45
Prevention of dermal necrosis	+4.00

Sub-analyses of effect sizes

Further sub-analyses of our data showed a positive influence of laser therapy on several indices of tissue repair, including reduction of skin necrosis, acceleration of inflammation, wound tensile strength, reduction of wound sizes, healing time, and total collagen content (Table 3). Similarly, as shown in Table 4, there were notable differences in the treatment effects of the different lasers used in the literature. In this analysis, Krypton laser had the highest treatment effect size (+4.29), and Gallium Arsenide laser, the least (+0.63).

Since treatment parameters varied widely, the calculated effect sizes did not correlate with any treatment parameter. Nonetheless, a trend was discernible with respect to energy density. Energy densities from 19 to 24 J/cm^2 were more effective than energy densities at or below 8.25 J/cm^2 and at or above 130 J/cm^2.

DISCUSSION

Overall, our findings show that low power lasers promote wound healing in both experimental models of tissue repair and human cases of wounds and ulcers. This finding is consistent with several reports that indicate that laser therapy accelerates tissue repair processes. To many clinicians and scientists, the notion that imperceptible doses of low-energy laser light can promote healing seems impossible. Yet, there are abundant reports that indicate the low-power lasers do not just advance several of the metabolic processes involved in wound healing,

TABLE 4. TREATMENT EFFECTS OF DIFFERENT TYPES OF LASER THERAPY DEVICES

Type of laser	*Effect size*
Krypton	+4.29
Argon	+3.23
Helium neon	+3.05
Gallium aluminum arsenide	+3.02
Red	+1.25
Carbon dioxide	+0.67
Gallium arsenide	+0.63
Infrared	+0.48

they accelerate healing of recalcitrant and non-healing wounds and ulcers in experimental animal models and humans.

This state of affair seems understandable given the availability of reports suggesting that no conclusions can be drawn concerning the effects of therapeutic lasers on wound healing.[35,36,38,39] One meta-analysis on this subject concluded that laser therapy studies are remarkably flawed and poorly reported.[70] In supporting this assertion, others have attributed this situation to inconsistencies in reporting the treatment parameters and the methods used in several published research studies.[44] These observations are consistent with our experience and our finding that only 24 research publications met our inclusion and exclusion criteria. The major flaws in most studies were inadequate reporting of treatment parameters, inexplicable reporting of actual doses used, and lack of hardcore numerical data.

The large standard deviation associated with our overall finding and the 95% confidence interval suggest a high degree of variability within the computed effect sizes, and provide further support for this assertion, that is, that treatment methods, outcome measures, and subjects differ markedly from one study to the next,[78] a situation which has been declared a major problem with the literature.[70] As shown in Table 4, inconsistent reporting of treatment parameters remains a problem with the current literature, as a consensus on effective treatment parameters remains elusive. Notwithstanding the large standard deviation and the 95% confidence interval, the large fail-safe number and the frequency distribution of effect sizes strongly support the large treatment effect size found in this study. Moreover, the large treatment effect obtained would have been larger, had we not eliminated fifteen studies that almost met our criteria, but lacked the data needed to calculate effect size. Of these, 75% reported positive outcomes, and all the human studies had positive results. Overall, the data indicate that laser therapy promotes wound healing in experimental animal models and human cases, but the outcome of treatment varies with treatment parameter.

In this regard, our results reveal that energy density is the only treatment parameter with predictable dose dependent treatment effects. Five studies with energy densities ranging from 19 to 24 J/cm^2 had the largest average effect size.[16,47–50] This suggests that this range of energy densities has more positive effect than other dose levels, but the variability in the experimental models used in these and other studies suggests the need for a considerable amount of caution in drawing any conclusions from this aspect of our findings. Nonetheless, the range of energy density may serve as a reference starting point for research programs aimed at comparing the effects of various energy densities on tissue repair.

Several indices of tissue repair are positively affected by laser treatment. This finding supports experimental animal and clinical reports that indicate that laser therapy promotes wound healing by accelerating collagen synthesis,[2–6,55,60] inflammation,[7,43,44] healing time and strength acquisition.[2–7,29–34,79–85] This is consistent with previous reports that have demonstrated elevation of several metabolic indices of ATP synthesis,[61–66] fibroblast proliferation,[7,8,55,60] and collagen synthesis,[2,8,10,11,21,59] as well as increases in the biomechanical indices of tissue healing.[2–6,86]

The highest mean treatment effect size was calculated from studies that used cows, followed by rats, pigs, and humans in that order. This finding supports previous studies[15,35] that indicate that the effects of low energy lasers appear to be more prominent in loose skinned animals than pigs and humans.[15,35,51] However, these reports must await further confirmation by well-designed studies comparing the effects of laser therapy on loose-skinned animals, pigs, and humans, under the same experimental conditions.

CONCLUSION

The results of this statistical meta-analysis mandate the following conclusions:

- Laser therapy, also referred to as low-level laser therapy (LLLT), is an effective modality for treating wounds.
- The outcome of treatment varies with treatment parameters (i.e., power, power density, wavelength, beam profile, energy, energy density, number and frequency of treatment, duration of treatment).
- Energy density appears to be the only treatment parameter with predictable dose-dependent treatment effects.

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