

A Meta-analysis of the Efficacy of Phototherapy in Tissue Repair

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Abstract

Objective: The effect of phototherapy on tissue repair was determined by aggregating the literature and using statistical meta-analysis to analyze pertinent studies published between 2000 and 2007. **Background Data:** Phototherapy has been used for more than 40 y; however, its efficacy on tissue repair remains contentious. **Method:** Related original studies were gathered from every available source. The papers were then screened and coded; those meeting pre-established inclusion criterion were subjected to meta-analysis, using Cohen's d statistic to determine treatment effect size. **Results:** Seventy effect sizes were computed from the 23 papers that met the inclusion criteria. The overall mean effect obtained was highly significant, $d = +1.94$ (95% confidence interval = 0.58–2.50). Further analyses revealed a similarly positive effect of phototherapy on tissue repair in experimental animal studies, $d = +2.60$, and a small to moderately positive effect in human cases of tissue repair, $d = +0.34$. The fail-safe number associated with the overall effect was 869; i.e., the number of additional studies in which phototherapy has negative or no effect on wound healing needed to negate the overall large effect size of +1.94. The corresponding fail-safe numbers for experimental animal and human tissue repair studies were 612 and 64, respectively. **Conclusion:** These findings indicate that phototherapy is a highly effective form of treatment for tissue repair, with stronger supporting evidence resulting from experimental animal studies than human studies.

Introduction

IT HAS BEEN MORE THAN 40 y since laser phototherapy was first shown to heal wounds and ulcers,^{1–3} but its efficacy as a clinical tool remains contentious. Abundant evidence indicates that phototherapy promotes the repair processes of skin,^{4–6} ligament,⁷ tendon,⁸ bone,^{9–11} and cartilage¹² in laboratory animal wounds and human ulcers.^{13–16} Moreover, the underlying mechanisms of action are now clearer as an increasing number of studies continue to demonstrate that phototherapy promotes fibroblast proliferation,¹⁷ collagen synthesis,^{17–19} and the cellular and subcellular processes needed to augment the formation of type I and type III procollagen pools of mRNA,²⁰ ATP synthesis, and lymphocytic action.²¹ Whereas the positive healing effects of phototherapy in experimental laboratory studies is rarely contested, its effect in human cases of ulcers and wounds is not as clear. The majority of clinical studies that indicate that phototherapy promotes tissue repair lack adequate experimental controls.^{22–27} Moreover, the wide range of variables that must

be accounted for in clinical practice, such as wavelength, power, power density, energy, energy density, treatment duration, treatment intervention time post-injury, and mode of treatment, further complicate the situation, making it difficult to compare one study to another.

Meta-analysis is a powerful statistical procedure for combining the results of two or more related studies in order to determine an overall treatment effect.²⁸ The resulting effect size of treatment yields a robust estimate of the true treatment effect compared to those derived from individual studies, thereby permitting a better overview of the topic than would have been realized either by simply reviewing the literature, conducting a systematic review, or relying on the outcome of multiple studies. Moreover, the procedure permits statistical testing of overall factors or effect sizes, inherently offering higher statistical power to detect true treatment effect, thereby fostering generalization to the population.²⁹ These qualities render meta-analysis of the literature an objective quantitative review that can eliminate subjective assessment, thus resolving most of the

controversies concerning the value of phototherapy in clinical practice.

There have been previous attempts to perform a meta-analysis of the phototherapy literature.^{30–32} One of the earliest analyses³⁰ examined papers dating back to 1948 and found four eligible reports that met their inclusion criteria. An analysis of the papers showed no beneficial effect of phototherapy on healing of venous leg ulcers.³⁰ However, based on comprehensive analyses of papers published during the 30 y period before year 2000, Enwemeka et al.³¹ and Woodruff et al.³² demonstrated significant positive treatment effects in the areas of tissue repair and pain relief. The large volume of papers published since 2000, coupled with the significant advancements in technology—in particular, the shift from laser technology to light emitting diodes and the sophisticated level of contemporary research reports—suggest a need to re-analyze the literature. Consequently, we aggregated peer-reviewed papers published from January 2000 to December 2007 and subjected those meeting our pre-established inclusion criteria to statistical meta-analysis. Our aims were to test the null hypothesis that phototherapy has no significant positive effect on tissue repair and to determine if the current literature supports the use of phototherapy for tissue repair.

Methods

Subjects and design

Original research papers investigating the effects of phototherapy on tissue repair that were published from January 2000 to December 2007 were aggregated, coded, and used in this study. The articles were obtained from libraries and online sources, including Medline, PubMed, OVID, and Citation Index to Nursing and Allied Health Literature (CINAHL). The terminologies that were used to identify these articles included “laser therapy,” “low level laser therapy,” “photobiomodulation,” “light therapy,” “phototherapy,” “wound healing,” “tissue repair,” and “healing.” Secondary sources included papers cited by articles already retrieved, internet web pages, commercial search engines, and papers published in journals that were not available in the aforementioned databases.

Studies were included in the meta-analysis if they met the following criteria: 1) article published between January 2000 and December 2007, 2) *in vivo* study involving humans or experimental animals, 3) article either stated or permitted our computing the following variables: power, power density, energy density, number of treatments given, duration of each treatment, frequency of treatment, beam spot size, dose, size of the area treated, and contact or noncontact mode of treatment, 4) the condition treated was clearly stated, and 5) the wavelength and light source were defined. Studies were eliminated if any of the following exclusion criteria applied: 1) study was conducted *in vitro*, 2) article was a case study, 3) the outcome measure had no direct relationship with tissue repair, 4) Cohen’s *d* statistic could not be calculated from the data provided, or 5) members of the research team were unable to translate the article into English to compute Cohen’s *d*.

Pilot reliability study and data coding

A coding form with a list of relevant parameters and related information was developed as shown in Table 1. Then,

TABLE 1. PARAMETERS USED FOR CODING EACH STUDY

1. Experimental Subjects
2. Condition Treated
3. Independent variable(s)
4. Dependent variable(s)
5. Source of Light
6. Wavelength
7. Spot size
8. Applicator Distance from surface
9. Dosage
10. Power (W)
11. Power density (W/cm ²)
12. Energy density (J/cm ²)
13. Number of treatments
14. Frequency of treatments
15. Duration of treatments
16. Wound area
17. Outcome of study (positive or negative)

data were obtained from studies that met the inclusion criteria and used to establish a data pool. To ensure data accuracy, our six raters were first trained. Then a pilot study was conducted to determine the level of agreement among them as they ascertained the presence or absence of the parameters detailed in Table 1 and as they calculated the treatment effect sizes (i.e., Cohen’s *d*) from an initial set of 10 randomly selected studies. Raters were retrained with new sets of articles and retested for reliability until at least 90% agreement was attained.

Determination of effect size

Effect size was calculated using the formulae for computing Cohen’s *d* statistic.^{20,28} Cohen’s *d* is defined as the difference between the means of the experimental group and the comparison group divided by the standard deviation of the comparison group:

$$d = \frac{x_1 - x_2}{SD_{\text{comparison}}} \quad (1)$$

where *d* stands for the effect size, x_1 is the mean of the treated group, x_2 is the mean of the comparison group, and $SD_{\text{comparison}}$ is the standard deviation of the comparison group.

When means and standard deviations were not reported but data was presented as percentages, a *d*-value was calculated by first finding the associated *t*-value with the following formula:

$$t = \frac{P_2 - P_1}{\sqrt{\frac{P_2(1-P_2)}{N_2} + \frac{P_1(1-P_1)}{N_1}}} \quad (2)$$

where P_2 is the percent change of the treatment group, P_1 is the percent change of the comparison group, N_2 is the number of subjects in the treated group, and N_1 is the number of subjects in the comparison group.

The *t*-value calculated was then converted to a *d*-value using the following formula^{28,29,31,32}:

$$d = \frac{2t}{\sqrt{df}} \quad (3)$$

where d is the effect size, t is the t -value, and df is the degrees of freedom. The degrees of freedom was determined with the formula²⁹:

$$df = N_1 + N_2 - 2 \tag{4}$$

where N_1 and N_2 are the numbers of subjects treated in the comparison group and the treated group, respectively.

The overall mean effect size was calculated by summing the d -values obtained independently from each study and then divided by the total number of d -values as follows:

$$d_{\text{average}} = \frac{\sum d}{N} \tag{5}$$

where d_{average} is the mean effect size, $\sum d$ is the sum of the effect sizes, and N is the total number of d -values used.

Grubb's extreme studentized deviation (ESD) test for critical outliers

Grubb's test³³ for critical outliers was performed on the pool of calculated d -values using the following formula:

$$z = \frac{(d_{\text{average}} - d)}{SD} \tag{6}$$

where z is the z -score for each individual d -value, d_{average} is the mean effect size, and SD is the standard deviation of d_{average} .

The z -score was then compared to a critical z -value obtained from Grubb's critical- z table.³³

In further analysis, the effect sizes obtained from studies with repeated measurements of the same outcome variable were averaged to minimize undue influence of any one study on the overall effect size.³⁴ For example, if wound sizes were measured on the same subjects at five different time intervals in a particular study, the d -values obtained were averaged to yield one d -value instead of five.³⁴ The overall d -value obtained was considered small, medium, or large in accordance with previously published guidelines.^{29,34,35} According to Cohen,²⁹ the values of 0.2, 0.5, and 0.8 indicate a small, medium, and large average effect size respectively.

Calculation of the fail-safe number

Considering the likelihood that our meta-analysis did not include every pertinent article, we computed the fail-safe number (N_{fs}) associated with the overall d -value obtained. From a statistical point of view, this is the number of non-

significant studies that would be necessary to reduce the effect size resulting from this analysis to a nonsignificant value. Practically, it is the number of additional studies with effect sizes below our set criterion value that would have to be included in the meta-analysis in order to negate the outcome of this study. A set criterion value of 0.05 was used, statistical significance was set to 0.05, and the N_{fs} was calculated with the following formula:

$$N_{fs.05} = \frac{N(d - d_c)}{d_c} \tag{7}$$

where N is the number of studies in the meta-analysis, d is the average effect size for the studies used, and d_c is the criterion value selected. For this meta-analysis d_c was set to 0.05, the value of a nonsignificant small effect size.

The data were further analyzed to separately determine the effect of phototherapy on tissue repair in experimental animal studies and clinical human cases.

Results

Overview

Twenty-three of the 104 peer-reviewed papers identified met the inclusion criteria (Appendix 1). Twenty-three other papers were excluded from the analysis outright because they were either case studies, descriptive nonexperimental studies, review papers, or relied on outcome measures that did not reflect tissue repair. Another set of 58 papers were experimental and quasi-experimental studies, but they were excluded from the analysis mostly because they lacked the relevant numerical data needed to compute treatment effect sizes (Appendix 2). In many instances, results were illustrated graphically without numerical data. An analysis of the 58 studies revealed that 54 of them (93.1%) reported that phototherapy significantly promotes tissue repair; only four did not (Table 2).

Furthermore, 38 were strictly experimental animal studies and 22 were human studies—two of these studies had both animals and humans as subjects; hence there are a total of 58 studies in Table 2 instead of 60. Thirty-six (94.72%) of the experimental animal studies showed significant positive effect of phototherapy on tissue repair, while 20 (90.9%) of the clinical human studies showed phototherapy to be effective in promoting tissue repair (Table 2). In contrast, a lower percentage of the papers used in our meta-analysis—17 of the 23 studies (73.9%)—showed that phototherapy has a positive healing effect on tissues; 6 (26.1%) did not. These

TABLE 2. REVIEW OUTCOME OF EXCLUDED EXPERIMENTAL/QUASI-EXPERIMENTAL STUDIES

Category	No. of papers	No. (%) of papers with positive results	No (%) of papers with negative results
Included studies	23	17 (73.9)	6 (26.1)
Excluded animal studies	38 ^a	36 (94.7)	2 (5.3)
Excluded human studies	22 ^a	20 (90.9)	2 (9.1)
Total no. of excluded studies	58	54 (93.1)	4 (6.9)
Total (included and excluded studies)	81	71 (87.7)	10 (12.3)

^aTwo of the studies (Appendix 2; Whelan et al., 2001 [reference 58] and Simunovic et al.²⁷) involved both animals and humans; hence there were 38 and 22 respectively; total being 58 instead of 60.

TABLE 3. OUTCOME OF STATISTICAL META-ANALYSIS

<i>Analysis</i>	<i>No. of papers</i>	<i>N of effect size</i>	<i>Cohen's d</i>	<i>95% CI</i>	<i>Fail-safe N (0.05 criterion)</i>	<i>Fail safe N (0.10 criterion)</i>
Overall	23	70	1.94 (2.23 ^a)	0.58–2.50	869 (1008 ^a)	423 (490 ^a)
Human studies	11	20	0.34	–0.25 to 0.94	64	26
Animal studies	12	50	2.60	1.34–3.31	612	300

^aValue obtained without removing the lone outlying *d*-value from the analysis.

findings clearly show that there was no bias in excluding certain papers from the analysis. Overall, of the 81 relevant studies found in the literature (i.e., 23 included studies plus 58 excluded papers), 71 (87.7%) showed that phototherapy significantly promotes tissue repair and 10 (12.3%) did not.

Effect of phototherapy on tissue repair

A total of 106 treatment effect sizes were originally computed from the 23 studies included in the analysis. Seventy effect sizes were obtained when multiple *d*-values from the same study were averaged to account for repeated measurements of the same variable over time as detailed in Table 3 above. The overall mean effect size obtained from the 70 computable effect sizes was +2.23; 95% confidence interval (CI)=1.31–3.15. The fail-safe number associated with this result was 1008; meaning that an additional 1008 studies—in which phototherapy has neutral or negative effect on tissue repair—would be needed to negate the outcome of the analysis (Table 3).

To permit a comparison of our result with those of Enwemeka et al.³¹ and Woodruff et al.³² who used 0.10 as their set criteria, the fail-safe number was recalculated with 0.10 as the set criterion, instead of the commonly used 0.05. The resulting fail-safe number was 490; a high number that again confirms that the likelihood of overturning the significant treatment effect size obtained is minute. Grubb's ESD test for critical outliers identified one high outlying *d*-value. When this outlier was removed from the analysis, the overall mean treatment effect remained significantly high ($d = +1.94$; 95% CI = 0.58–2.50; $N_{fs} = 869$ using 0.05 as criterion or $N_{fs} = 423$ with 0.10 as the set criterion).

Effect of phototherapy on clinical cases of tissue repair

Thirty-one effect sizes were originally computed from the 11 human studies in the analysis; 20 were obtained when the effect sizes derived from repeated measurements of the same variable were averaged. The overall mean effect size was +0.34 (95% CI = –0.25 to 0.94), indicating that phototherapy has a small to moderate positive effect on clinical cases of tissue repair (Table 3). The fail-safe number associated with this result was 64 ($N_{fs} = 26$ when 0.10 was used as the set criterion).

Effect of phototherapy on tissue repair in experimental animal-studies

Seventy-five computable effect sizes were initially calculated from the 12 animal studies included in the analysis. These yielded 50 effect sizes when the effect sizes obtained

from repeated measurement of the same variable over time were averaged. The overall mean effect size obtained, after removing the lone outlying high effect size, was +2.60 (95% CI = 1.34–3.31); indicating that phototherapy has a strong positive treatment effect on tissue repair (Table 3). The fail-safe number associated with this finding was 612 ($N_{fs} = 300$, if 0.10 is used as set criterion).

Discussion

It is well established that in a meta-analysis a treatment effect value of +0.2 represents a small positive effect size, +0.5, a medium effect size, and +0.8 or greater, a large effect of treatment.^{28,29,34,35} Consequently, the overall treatment effect size of +1.94 indicates that phototherapy is an effective form of treatment for tissue repair. This finding is consistent with the results of previous meta-analysis of papers published during the immediate 30 y before year 2000,^{31,32} even though our study focused specifically on papers published between 2000 and 2007. In their meta-analysis of tissue repair studies published during the 1970s, 1980s, and 1990s, Enwemeka et al.³¹ and Woodruff et al.³² found an overall treatment effect of +1.81 and +2.22, respectively. These results mirror our finding that, overall, the effect size of treatment with phototherapy is +1.94 (+2.23 without removing the outlying *d*-value). However, it should be noted that the effect size obtained in this meta-analysis would have been different, and perhaps higher, had it been possible to include the 58 experimental and quasi-experimental studies that were excluded from this study; since 54 of the papers (93.1%) showed that phototherapy is significantly effective in promoting tissue repair in humans as well as experimental animal studies (Table 2).

It is worth noting that 23 peer-reviewed papers with 70 computable effect sizes met our inclusion criteria and that these numbers compare favorably with those reported in previous studies.^{31,32} Woodruff et al.³² found 24 studies with 31 computable effect sizes while Enwemeka et al.³¹ had 34 studies with 46 computable effect sizes that met their inclusion criteria. The higher number of computable effect sizes in our study reflects the high level of sophistication of papers published since 2000. Most papers measured tissue repair at several time points or used several outcome measures to estimate tissue repair. Even with our adjustment to account for repeated measurements of the same outcome variable, the average number of computed effect sizes per paper remained high. That our study, which covered the 8 y period from 2000 to 2007, had about the same number of peer-reviewed papers as the report of Woodruff et al.,³² which covered papers published over three decades, suggests that more papers with sufficient data necessary to compute effect sizes are being published yearly.

Our subanalyses showed that the mean treatment effect was significantly higher in animal experiments of tissue repair than human cases, being +2.60 for animal studies and +0.34 for human studies. We postulate that the large effect size associated with animal studies relates to the investigator's ability to effectively control extraneous factors and potentially confounding variables in animal experiments compared to human clinical trials. For example, laboratory animals used in the same experiment are often bred and raised in the same manner at the same facility. Moreover, food intake, a major factor that can influence tissue repair, is usually well controlled in animal experiments but not in human studies. Whereas each animal is fed the same diet, in general, diet varies significantly from one patient to another in clinical studies. Other factors such as treatment compliance may play a role as well. Notwithstanding, the astounding difference between the effect size obtained in animal experiments versus human studies suggests a dire need for tighter experimental controls in clinical trials examining the effect of phototherapy on tissue repair.

Regardless, our findings leave no doubt whatsoever that phototherapy promotes tissue repair in general, more so in experimental animal studies than in human cases; even though our study is heavily dependent on papers published in the English language, 58 of which were excluded from the analysis. Of these, 54 (93.1%) of the excluded experimental and quasi-experimental papers clearly showed phototherapy to be significantly effective in promoting tissue repair. Our results are further strengthened by the fact that 71 (87.7%) of the 81 relevant studies found phototherapy to be significantly effective in promoting tissue repair; the proportion of positive reports is even greater (93.1%) when the 23 papers used in this meta-analysis are excluded.

Conclusion

Our results warrant the conclusion that phototherapy is a highly effective form of treatment for tissue repair, with stronger supporting evidence resulting from experimental animal research than human studies.

Disclosure Statement

The authors declare that no competing financial interests exist.

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Appendix 1: Studies Included in The Meta-Analysis

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