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Is Low-Level Laser Therapy (LLLT) effective in reducing pain and ulcer size in diabetic patients with foot ulcers?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2017
Abstract

OBJECTIVE: The objective of this selective EBM review is to determine whether or not Low-level laser therapy (LLLT) is an effective therapy in reducing pain and ulcer size in diabetic patients with foot ulcers.


DATA SOURCES: The studies compare the effectiveness of LLLT versus conventional wound treatment in reducing pain and ulcer size in diabetic patients with foot ulcers. All studies were found using PubMed and CINAHL Plus.

OUTCOMES MEASURED: Pain as perceived by the patient, measured by visual analog for pain scale or by brief pain inventory questionnaire prior to treatment and following treatment. Ulcer size was measured by researchers in square centimeters (cm²) or square millimeters (mm²).

RESULTS: Two of the randomized control trials suggested that the use of LLLT was significant in pain reduction of foot ulcers in diabetic foot patients. All three randomized control trials suggested that LLLT was statistically significant in the reduction ulcer size compared to conventional ulcer treatment.

CONCLUSIONS: All three studies showed that there was a decrease in ulcer size and two studies showed that there was a reduction in pain when using LLLT to treat patients with diabetic foot ulcers, proving that it is an effective treatment option. However, further studies with larger sample sizes that examine LLLT with uniform modalities and methods of application will be needed to reinforce the conclusion that Low-Level Laser Therapy is an effective and reliable therapeutic option in treating diabetic patients with foot ulcers.

KEYWORDS: Low-Level Laser Therapy, Foot ulcer
Introduction

Diabetes mellitus a condition characterized by abnormal hyperglycemia due to either a defect in metabolism caused by a deficiency of insulin secretion, or tissue sensitivity with resistance to insulin. It can be broken up into two categories: type I diabetes mellitus is an autoimmune condition that is distinguished by the destruction of pancreatic beta islet cells resulting in the absence of insulin secretion; type II diabetes mellitus is due to tissue sensitivity and resistance to insulin, predominantly due to genetic and environmental factors. Obesity is the most important environmental factor causing insulin resistance.\(^1\)

There are approximately 30.3 million people in the United States that have diabetes mellitus, a majority of which have type II.\(^1\) A number of complications are associated with Diabetes Mellitus, many of which can result in increased morbidity and mortality. Foot ulcers are one of the most common complication found in diabetics, and it has been found that gangrene of the foot from ulceration and peripheral vascular disease is 30 times greater in diabetic patients compared to age matched controls.\(^1\) The pathophysiology of foot ulcers in diabetics is not completely understood, but it is thought to be a combination of multiple factors including neuropathy, ischemia and infections.\(^2\) In 2014, the Centers for Disease Control and Prevention found that 7.2 million US adults were discharged from hospitals with diabetes, and of that number 108,000 were discharged as a result of a lower-extremity amputation. This correlates to approximately 5 per 1,000 people with diabetes.\(^3\) According to the American Diabetes Association, the total estimated medical costs of diagnosed diabetic patients in 2017 was $327 billion, a figure which included both medical costs and a reduction in productivity.\(^4\) With the staggering statistics of those affected by diabetes and its complications, as well as the financial
implications, alternative treatments to diabetes and the associated sequelae has received much interest and controversy.

Diabetic foot ulcers typically present as ulcerations or eschar that are most commonly found on high-pressure areas or areas exposed to repetitive stress, often at the metatarsal heads. The cause of foot ulcers is thought to be attributed to a combination or peripheral neuropathy, poor blood circulation and increased susceptibility to infections. Foot ulcers can go unnoticed and grow very large due to the neuropathy and poor wound healing connected with diabetes, which can lead to infections and ultimately gangrene and amputations if not caught early.

Conventional methods of treating diabetic foot ulcers are based on standard wound treatment including debridement, slough excision, saline solution irrigation and betadine solution dressings coupled with effective blood glucose control. Systemic antibiotics have also been used based on culture and sensitivities in the presence of co-existing infections. Other treatment options include contact case immobilization or in the incidence of gangrene or severe ulceration, amputation has been indicated.

Low-Level Laser Therapy (LLLT) is a new alternative approach to treating diabetic foot ulcers that is still being investigated for the efficacy of its use. Although the mechanism of action for the Low-Level Laser is not completely understood, it is believed that the non-thermal laser stimulates photoreceptors at a cellular level to increase the production of adenosine triphosphate (ATP) from mitochondria, resulting in increased cellular oxygen utilization, anti-inflammatory effects and increased blood circulation to the area. The utilization of Low-Level Laser Therapy (LLLT) is still being researched in many different medical conditions to further understand its efficacy.
Objective

The objective of this selective evidence-based medicine review is to determine whether Low-Level Laser Therapy (LLLT) is an effective therapy in reducing pain and ulcer size in diabetic patients with foot ulcers.

Methods

The studies selected for this systematic review included three randomized control trials (RCTs) that investigated the use of LLLT in diabetic adults with foot ulcers or ulcers on the distal third of the lower leg. All three of the articles included were published in peer reviewed journals and found using the following databases: PubMed and CINAHL Plus. The keywords used to search relevant articles were chosen using the keywords “Low-Level Laser Therapy” and “foot ulcers.” The articles were selected based on their relevance to one another, the clinical question and if patient-oriented evidence that matters (POEMs) were incorporated. Articles were excluded if they were published greater than ten years ago or were not randomized control trials. Significance of the results was determined through evaluation of the calculated p-value, mean change from baseline, as well as number needed to treat (NNT). Safety precautions for each of the studies included proper eyewear for patients and researchers during the application of the Low-Level Laser Therapy. Additional inclusion and exclusion criteria can be found in Table 1, as well as specific demographics for each of the individual studies.

The studies were selected based on their population, intervention used and comparison between articles. In all three of the studies the Low-Level Laser treatment was administered by researchers, with two studies using the following laser modalities: continuous wave, visible beam, 658 nm, 30 mW power for 80 seconds; the other study used a handheld diode laser (660 nm) for 60 seconds.\textsuperscript{2,6,7}
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age (years)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvalho, (2016)</td>
<td>RCT</td>
<td>32</td>
<td>40-70 yrs</td>
<td>Type II Diabetes Mellitus pts with fasting blood glucose values between 150-350 mg/dL with an ulcer on the foot or on medial or distal third of the leg measuring between 1-5 cm.</td>
<td>Fasting blood glucose values greater than 350 mg/dL and ulcers greater than 5 cm in length</td>
<td>0</td>
<td>LLLT via a handheld 30 mW power Laser delivering a fluence of ~4J/cm² VS. daily ulcer cleaning and dressing application by the patient</td>
</tr>
<tr>
<td>Fietosa, (2015)</td>
<td>RCT</td>
<td>16</td>
<td>N/A*</td>
<td>Non-controlled Type II Diabetic patients with ulcers on the lower limb</td>
<td>N/A*</td>
<td>N/A*</td>
<td>LLLT via a handheld 30 mW power Laser delivering a fluence of ~4J/cm² held approximately 1 mm perpendicular to the wound VS. daily Saline Solution 0.9% irrigation</td>
</tr>
<tr>
<td>Mathur, (2017)</td>
<td>RCT</td>
<td>30</td>
<td>20-75 yrs</td>
<td>Treatment avg: 49 yrs Control avg: 49 yrs</td>
<td>Type II Diabetes Mellitus patients with Meggitt-Wagner grade I DFUs of at least 6-week duration</td>
<td>0</td>
<td>LLLT via a handheld diode laser held 1 ft above ulcer surface delivering a fluence of ~3J/cm² VS. daily wet saline or betadine dressings, antibiotic treatment, contact cast immobilization and slough excision</td>
</tr>
</tbody>
</table>

*N/A – Not Reported in study.*
In two of the studies, the control group received daily cleansing and dressings for ulcers, while Carvalho et al. instructed its participants to perform self-cleansing on a daily basis.\textsuperscript{2,6,7} Two of the RCTs used measured clinical outcomes in patients following 30 days of treatment, while the Mathur et al. measured clinical outcomes after 2 weeks of treatment.\textsuperscript{2,6,7} Ulcer size and pain assessments were analyzed before and after the treatment to be used in comparison between the control and experimental groups.

**Outcomes measured**

The primary outcome measured in all three studies was the change from baseline in ulcer size measured by researchers, and in Feitosa et al. and Carvalho et al. pain as perceived by the patient was a secondary measured outcome. Feitosa et al. used a Visual Analog Scale for Pain to numerically scale the patients perceived pain, with zero indicating the absence of pain and ten indicating maximum pain.\textsuperscript{7} Carvalho et al. used the Brief Pain Inventory and the Visual Analog Scale for Pain to assess pain, with reported pain on a scale of zero to ten, ten being maximum amount of pain and zero indicating the absence of pain.\textsuperscript{6} Ulcer size was measured in size square centimeters (cm\textsuperscript{2})\textsuperscript{6,7} and square millimeters (mm\textsuperscript{2}).\textsuperscript{2} In all three of the RCTs, Image J Software was the measurement tool utilized. This tool uses the circumscription of the ulcer area to measure in square centimeters or square millimeters.\textsuperscript{2,6,7}

**Results**

In the study conducted by Carvalho et al. 32 participants were selected based on their demographics and meeting certain inclusion criteria. The eligibility of participants was based upon the criteria as follows: Type II Diabetes Mellitus patients between 40-70 years old with fasting blood glucose levels between 150-350 mg/dL with an ulcer on the foot or in the medial or distal third of the leg, measuring between 1 and 5 cm in length.\textsuperscript{6} Of the 32 eligible participants,
all 32 completed the 30-day program. Initially, each individual was evaluated by an angiologist to evaluate the ulcer clinically, as well as Doppler ultrasound and ankle-brachial index (ABI). The purpose of the use of the Doppler ultrasound and ABI was to assess the peripheral vascularization of each individual patient. The participants were randomly distributed into four different groups: the control group, Low-Level Laser Therapy group (LLLT), Essential Fatty Acids (EFA) and LLLT with EFA (LEFA) group. The control group was instructed to clean ulcers and apply dressings on a daily basis without assistance from researchers. Each participant of the LLLT group received 12 treatments of phototherapy, each for 80 seconds following an initial cleanse of the ulcer with 0.9% saline solution. Assessments were made before and after 30 days to compare results.

Following 30 days of treatment, there was a reduction in total ulcer area for the LLLT group (-5.59 cm²) compared to the control group, which showed a significant increase in total ulcer area (+5.88 cm²). The findings were statistically significant with a 95% confidence interval (CI) and p-value of 0.00428. There was also a significant decrease in pain for the LLLT group (-4.20) compared to the control group, which had an increase in pain (+0.40) compared to initial evaluation. The results suggest that the use of LLLT showed statistically significant decreases in pain and total ulcer area compared to daily cleansing and dressing application. The study by Carvalho et al. also included results of the use of Calendula officinalis alone compared to Calendula officinalis along with LLLT, however those results are not included in this systematic review.

In the study conducted by Feitosa et al. 16 Type II diabetic patients were randomly selected to participate in the trial. Participants were included in the study based on their classification of a non-controlled type II diabetic patient with an ulcer on the lower limb. The
patient age demographics, exclusion criteria and if any patients withdrew was not reported in the study. The 16 participants were randomly divided into two groups of eight, one group designated as the control group and the other receiving the Low-Level Laser Therapy (LLLT). The control group was instructed to strictly use 0.9% saline solution for daily cleansing of ulcers. The LLLT group received daily cleansing with 0.9% saline solution irrigation followed by 80 seconds of laser treatment administered by a researcher. There were 12 treatment procedures administered to the LLLT group, three weekly procedures performed on alternating days. Participants from both the control and LLLT group were evaluated by researchers for ulcer size (cm$^2$) and pain perceived by the patient based on the Visual Analog Scale for Pain. Participants were evaluated on day one as well as 30 days after their respective treatment of the ulcers.

Following 30 days of treatment, there was a statistically significant reduction in ulcer size as well as pain reduction with a p-value of <0.05. The LLLT group showed a reduction in ulcer size of -5.59 cm$^2$, while the control group showed an increase in ulcer size of +5.88 cm$^2$. Using the zero to ten scale for pain the study showed a significant reduction in pain with the LLLT group showing -4.2 points while the control group showed a slight increase of 0.40 points. The increase in ulcer size by the control group indicates a worsening in patients’ health, as evidenced by the example of one participant progressing to a transfemoral amputation following the conclusion of the study. The results of the study imply that LLLT is effective in reducing pain and total ulcer size compared to irrigation with saline solution.

Mathur et al. gathered 30 participants between the ages of 20 and 75 years old to participate in the study. The participants were included based on the diagnosis of Type II Diabetes Mellitus with a Meggitt-Wagner grade 1 foot ulcer present for greater than 6 weeks duration. Patients were excluded if there were clinical signs of ischemia, fasting blood sugar
levels >200 mg/dL, or signs of septicemia. The participants were randomly divided into a control group and a Low-Level Laser Therapy (LLLT) group. All participants in the study were evaluated on days 0, 7 and 15, with no participants excluded or withdrawn from the study. Patients in the control group received conventional wound treatment including daily wet saline or betadine dressing, slough excision, antibiotic treatment and contact cast immobilization as needed. The LLLT group received 60 seconds of laser exposure conducted by the researcher every day for 15 days, as well as after each treatment moist dressing was placed over the ulcer. If necessary as determined by the researcher, slough excision was provided to patients prior to the exposure to the laser treatment.

At the start of the study, the average ulcer size for the control group and the treatment group was measured and then subsequently measured on day 7 and 15. In this systematic review, the mean change from baseline was measured using the average ulcer size on day 0 and day 15. For the control group, the results yielded a decrease in ulcer size of 206 mm², while the LLLT group showed a decrease from baseline in size of 554 mm². This indicates a statistically significant reduction in wound size with a p-value of <0.001. In the LLLT group approximately 75% of patients had a wound reduction of 30-50%, compared to the control group in which approximately 20% of patients had a wound reduction of >20%. With the provided data, the relative benefit increase (RBI) was calculated to be 2.75, the absolute benefit increase (ABI) was 0.55 and the number needed to treat (NNT) was found to be 1.81, rounded up to 2. This data suggests that for every 2 people with diabetic foot ulcers treated with Low-Level Laser Therapy, one more will see a statistically significant reduction in ulcer size when compared to conventional wound treatment.
Table 2 – Analysis of treatment efficacy and statistical significance

<table>
<thead>
<tr>
<th>Study</th>
<th>CER</th>
<th>EER</th>
<th>RBI</th>
<th>ABI</th>
<th>NNT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathur (2017)</td>
<td>20%</td>
<td>(0.20)</td>
<td>75%</td>
<td>(0.75)</td>
<td>275%</td>
<td>(2.75)</td>
</tr>
</tbody>
</table>

All three studies monitored treatment modalities for adverse events as well as provided appropriate safety precautions to participants and researchers. No adverse events were found from the use of the Low-Level Laser Therapy. All three of the studies found statistically significant decreases in ulcer size as indicated by Table 2.

Table 3 – Change in ulcer size from baseline and statistical significance

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in Ulcer size following LLLT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvalho (2016)</td>
<td>- 5.59 cm²</td>
<td>0.00428</td>
</tr>
<tr>
<td>Mathur (2017)</td>
<td>- 5.54 cm² (554 mm²)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fietosa (2015)</td>
<td>- 5.59 cm²</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Discussion

Diabetic foot ulcers have long been a significant cause of morbidity and mortality as well as a financial burden placed on those affected. Traditional treatment options for diabetic foot ulcers have been stalled by the associated poor neuropathy, poor wound healing and vascular compromise that is linked to diabetes. This three-study systematic review evaluated the efficacy of Low-Level Laser therapy as an adjunct therapy to traditional ulcer treatment resulting in decreased pain and improved healing. As discussed previously, the mechanism of action of Low-Level Laser Therapy is not completely understood, but it is believed to be related to the laser’s stimulation of the photoreceptors in cells which in turn activate the mitochondria to produce adenosine triphosphate (ATP) which increases the cellular oxygen utilization. With increasing oxygen utilization, the blood flow to the area is amplified resulting in improvements to the healing process of the wound. Low-Level Laser Therapy is currently not an approved treatment...
option for diabetic foot ulcers by the FDA, as there are still clinical trials evaluating its effectiveness. Current approved treatment options include standard wound treatment with debridement, irrigation and dressings, as well as other options including off-loading with contact-cast, hyperbaric oxygen therapy, and negative-pressure wound therapy.\textsuperscript{2,8} There were no adverse results from the application of laser treatment, however appropriate safety measures were taken with both researchers and participants wearing protective glasses during treatments. In review of the three-systematic review studies included in this study, Low-Level Laser Therapy has proven to be a viable, safe and effective adjunct treatment option for diabetic foot ulcers.

It is important to note the limitations to the three RCTs evaluated in this selective EBM review. One of the biggest limitations associated with the studies conducted by Mathur et al., Carvalho et al. and Fietosa et al. was the small sample size assessed which was 32, 16 and 30 respectively.\textsuperscript{2,6,7} With larger sample sizes, the validity of the results found could be further strengthened, improving the significance of the findings. A limitation to the results from Carvalho et al. is the control group was instructed to clean ulcers and apply dressings without assistance of researchers, which could skew results due to the potential inconsistent wound treatment between members of the control group.\textsuperscript{6} Another limitation that is important to note is the absence of reporting of blood glucose control in the participants of each of the studies. Uncontrolled blood glucose levels could potentially lead to an increase in complications and further potentiate the poor wound healing associated with diabetes. Uniform modalities and methods of application would be needed in future studies to completely address the most appropriate usage of laser treatment and to establish the most beneficial options for patients.
Despite the limitations addressed, all three RCTs were POEMs and relevant to improving the quality of life of the population addressed. The studies were also valid as evidenced by the presence of p-values, confidence intervals and randomization of the studies.

**Conclusion**

The primary objective of this systematic review was to determine whether Low-Level Laser Therapy (LLLT) was effective in reducing pain and ulcer size in diabetic patients with foot ulcers. After evaluation of the results presented, it is indicated that there was statistically significant reduction in pain and ulcer size in patients treated with Low-Level Laser Therapy. This conclusively suggests LLLT to be effective in reducing pain and ulcer size in diabetic patients with foot ulcers. It is important to note that the use of LLLT is used in adjunct to traditional wound treatment, and the use of LLLT as monotherapy was not addressed.

Although the popularity of LLLT has continuously increased, it is important to continue further research to promote the efficacy of its use. In order to improve future trials, larger sample sizes could increase the validity of the findings and improve statistical significance. Additionally, specific blood glucose parameters could improve the consistency of findings. With improvements in future studies and progressions in clinical research, the outlook of treating diabetic foot ulcers could be drastically improved with the application of Low-Level Laser Therapy, improving the quality of life and decreasing morbidity and mortality for patients affected by diabetic foot ulcers.
Reference List

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