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SYSTEMATIC REVIEW

A Non-Invasive Technique of Low Dosage Laser Treatment on Post Herpetic Neuralgia: A Systematic Review and Meta-Analysis

Sathya Siva[1,*], Prathap Suganthirababu[2], V Surya Prakash[3], Vignesh Srinivasan[4], J Titus[5], Kishoremoy Das[4], Priyadharshini[1], Dhanusia[1], Santhana Lakshmi[1], Vanitha[1]

[1] *Tutor, Research Scholar, Saveetha College of Physiotherapy, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India*

[2] *Principal, Saveetha College of Physiotherapy, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India*

[3] *Clinical Physiotherapist, Lakshmi Physiotherapy and Rehabilitation Clinic, Kallakurichi district, Tamil Nadu, India*

[4] *Assistant Professor, Saveetha College of Physiotherapy, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India*

[5] *Clinical Physiotherapist, Dr Mehta's Hospital Velappanchwadi, Chennai, 600077, Tamil Nadu, India*

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[*] *Corresponding author.*
Sathya Siva
sathyasivakannan@gmail.com

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ABSTRACT

Introduction: Post herpetic neuralgia (PHN) is a chronic neuropathic pain condition that persists for months or even years following the resolution of herpes zoster (HZ) rash. The biological effects of Low-Level Laser Therapy (LLLT) on pain and tissue repair are multifaceted and complex. **Methods:** The research followed PRISMA guidelines and utilized search terms such as "postherpetic neuralgia OR PHN, pain, low level laser therapy OR LLLT, varicella-zoster virus OR VZV, herpes zoster OR HZ, Systematic review and Meta-analysis, Randomized controlled trial " across Scopus, ScienceDirect, and Web of Science, Embase, Cochrane Library databases. Studies meeting eligibility criteria were included, and a forest plot analysis was obtained using a random-effects model with standardized mean difference (SMD) of 95% confidence interval which was calculated based on visual analogue scale (VAS) outcomes from selected studies. **Results:** Four eligible studies were identified and subjected to both qualitative and quantitative evaluations. The pooled standardized mean difference data (SMD = -6.39, CI = -11.06 to -1.72, p = 0.007) indicate that LLLT significantly reduces pain associated with PHN compared to conventional treatments. **Conclusion:** This systematic review and meta-analysis demonstrate that LLLT technology is more effective in reducing pain associated with PHN than conventional treatments. Importantly, there is no evidence suggesting adverse effects of LLLT treatment for PHN.

Keywords: Low-Level Laser Therapy; Randomized controlled trial; Herpes Zoster; Systematic review and Meta-analysis

INTRODUCTION

LLLT, also known as photo biomodulation therapy, involves the use of low-power lasers or light-emitting diodes to alter cellular function. It is used to reduce inflammation, enhance tissue repair, and modulate pain perception.

Post herpetic neuralgia (PHN) is a persistent neuropathic pain condition that can occur after an episode of herpes zoster (HZ), commonly known as shingles (Painful Rash). HZ is caused by the reactivation of the varicella-zoster virus (VZV). After the initial infection, the virus remains dormant in nerve cells. Factors like aging or immunocompromised states can lead to its reactivation, resulting in HZ.

PHN is characterized by prolonged pain and abnormal sensations that persist for 120 days or more after the initial HZ rash. Pathophysiology of PHN involves damage to both peripheral and central nerve systems. This damage leads to spontaneous nerve firing and increased sensitivity to stimuli, contributing to the chronic pain experienced by PHN patients. HZ typically manifests as a painful rash localized to one dermatome (area of skin supplied by a single nerve root). The rash progresses from erythematous maculopapular lesions to vesicles, pustules, and eventually scabs. PHN manifests as ongoing pain and discomfort in

the affected area long after the rash has resolved. PHN significantly impacts quality of life due to chronic pain. It can lead to exhaustion, depression, sleep disturbances, appetite loss, weight loss, and cognitive decline in some cases [1,2].

Treatment strategies for PHN include prevention through vaccination, prompt treatment of acute HZ to reduce the likelihood of PHN, and multimodal approaches involving drugs and interventions to manage PHN symptoms effectively [1–3].

LLLT is a therapeutic approach used for inflammation and pain reduction, functional restoration, and stimulation of healing. It works by triggering various cellular responses in the skin, such as improved blood circulation, release of nitric oxide, increased ATP production, and activation of stem cells for tissue repair. Beyond pain relief, LLLT has been shown to improve functional outcomes in PHN patients. This includes improvements in range of motion, sensory function, and overall quality of life. Studies are being conducted to evaluate its effectiveness in alleviating PHN symptoms. PHN is a challenging condition characterized by persistent pain following an episode of HZ. Understanding its pathophysiology and employing effective treatment strategies, including emerging therapies like LLLT, are crucial for improving outcomes and quality of life for affected individuals [4].

METHODS

Protocol

PRISMA Guidelines (preferred reporting items for systematic reviews and meta-analyses) were used to conduct a systematic review and meta-analyses, and the findings are subsequently registered to (PROSPERO ID: CRD42023480702) [5].

Pico Criteria

To obtain the research question, PICO criteria were used.

Population: Postherpetic neuralgia population.

Intervention: Low Level Laser Therapy

Comparison: Low Level Laser Therapy versus conventional therapy.

Outcomes: Pain

Research Questions

How beneficial is LLLT for postherpetic neuralgia in comparison to conventional therapy?

Objectives

- The primary objective of the research is to evaluate LLLT efficacy in treating postherpetic pain.
- The secondary objective of the research is to evaluate the efficacy of LLLT vs traditional PHN therapy.

Search Strategy, Selection Criteria, and Screening Process

The study of research articles was carried out by three researchers (Author 1,2,3) independently, including the LLLT intervention on postherpetic neuralgia symptoms until the end of December 2023, tracing the articles that were released from 1991 until 2023. The Scopus, ScienceDirect, and Web of Science, Embase, Cochrane Library databases were routinely searched for papers. The following search terms ”postherpetic neuralgia (OR) PTN, pain, low level laser therapy (OR) LLLT, varicella-zoster virus (OR) VZV, herpes zoster (OR) HZ, Systematic review and Meta-analysis, Randomized controlled trial ” were used to search for open access papers in the database. A researcher (Author 4) has screened for the eligible record independently.

The eligible studies were randomized controlled trial and double-blind crossover trial studies. Articles published years between 1991 to 2023 with post herpetic neuralgia symptom only were considered. Both children and adults were included. The study has filtered the open-access and full text articles and excluded the systematic review and meta-analysis. However, reference sections were screened for more relevant literature (Figure 1).

Total number of participants ”n”, study design, study location, outcome measures, interventions and outcome details have been extracted from each article independently by researchers (Table 1) (Author 1,2,4)

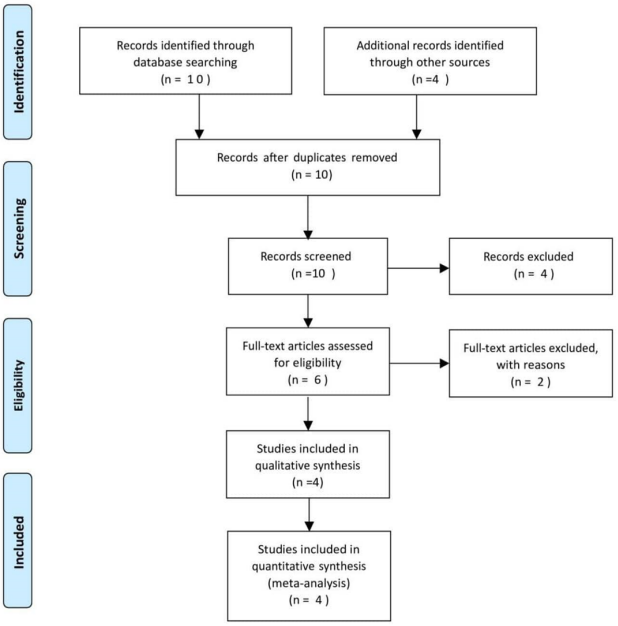


Fig. 1: PRISMA flow chart

QUALITATIVE EVALUATION

The Cochrane risk of bias approach was applied for qualitative assessment in the articles that were selected for the purpose of investigation (Figure 2). Some of the strategies used to evaluate bias included creating a random sequence, selective reporting, concealing the allocation, additional sources of bias such as inadequate outcome of data, blinding staff and participants, and blinding outcome evaluation. The reviewer's assessments of High, Low, and Unclear risk of bias are assessed based on each specific article selected for the study by researcher (author 5) (Figure 3).

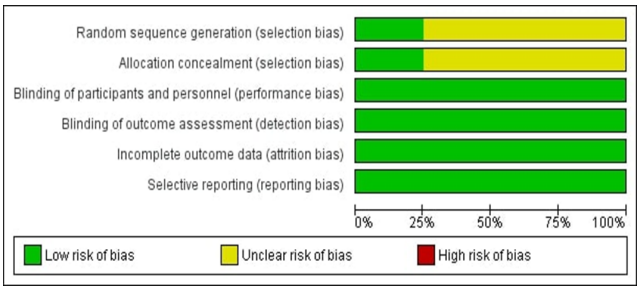


Fig. 2: Percentage of studies included that are associated with a bias risk

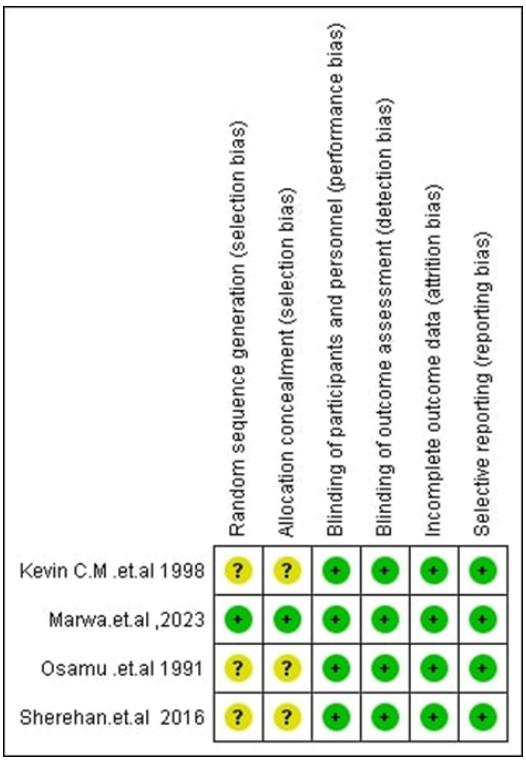


Fig. 3: Overview of risk of bias for included studies

STATISTICAL ANALYSIS

We pooled the continuous VAS data from each trial to generate a standardized mean difference (SMD) with a 95% confidence interval (CI) using a random-effects model. The heterogeneity between the studies was investigated using the I-squared statistical test, ranging from 0% to 100% and with a P value less than 0.05 as significant. Using RevMan software, a forest plot was generated to produce the quantitative analysis (Graph 1) by the researcher (Author 1).

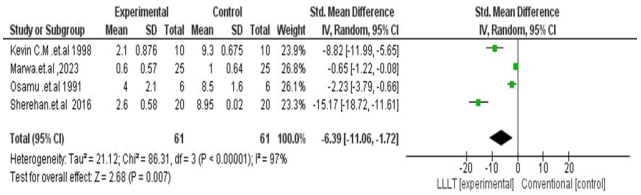
RESULTS

Characteristics of included studies

Evidently four of the studies that meet the eligibility criteria, two of which were conducted in Egypt and the other two from Japan and UK. The methods of studies were randomized controlled trials and double-blind crossover trials which have been described. Each of the four studies has undergone qualitative and quantitative analyses. Two randomized controlled trials (RCTs) comparing the PLACEBO LASER and LLLT were conducted to treat postherpatic neuralgia (SMD = -15.17; 95% CI = -18.72 to -11.61).When comparing TENS with conventional medical care and LLLT with conventional medical care (SMD = -0.65, 95% CI = -1.22 to -0.08) The effects of LLLT and PLACEBO treatment were compared in two studies using a double blind cross-over trials (SMD = -2.23; 95% CI = -3.79 to -0.66).and comparing the LLLT group to the control group (SMD = -15.17; 95% CI = -18.72 to -11.61) (Graph 1).

Meta-Analysis

Based on a meta-analysis of the overall VAS outcome measure with standardized mean difference (SMD), 95% confidence interval (CI) using a random-effects model (Graph 1) all of four articles validate the findings that LLLT functions significantly to reduce pain on post-herpetic neuralgia (SMD = -6.39, CI = -11.06 to -1.72 , p = 0.007) when compared to conventional treatment. The heterogeneity test result showed a significant difference in heterogeneity (I^2 = 97%; P $\leq$ 0.00001).



Graph 1: **Comparing outcomes of VAS with LLLT and conventional treatment**

Table 1: Characteristics of included studies

Authors	Study Design	Samples	Study Location	Intervention	Outcome	Parameters	Results
Sherehan et al[6]	RCT	N=40	Egypt	1.Group A: LLLT 2.Group B: PLACEBO LASER	1.VAS 2.Neuropathic Pain Scales.	GaAIAs diode laser 1/week for 3 months 5 min in each point 4-points 1-point: L5-S1 over the erector spinae motor point 2-point: Gluteus Maximus 3-point: Mid-point b/w ischial tuberosity and greater trochanter & back upper thigh. 4-point: upper to popliteal crease. Duration: 20 min	Highly significant decrease in mean value of VAS and NPS on LLLT group compared to Placebo group.
Marwa et al.,[7]	RCT	N=50	Egypt	1.Group A: LLLT + Traditional Medical Treatment 2.Group B: TENS + Traditional Medical Treatment	1.VAS 2.Electronic Algometer.	LASER: LLLT Chattanooga low level laser therapy with 850nm laser irradiation Energy density: 3.6j/cm2 for 1 min Time session/ 20 min 3 times/week. TENS: ITO physiotherapy rehabilitation ES-5200 units Frequency: 70Hz Time session / 20 minutes Repetition of 3 times / week for 4 weeks	LLLT and TENS are clinically significant for reduction of pain. but LASER is more effective.
Osamu et al.,[8]	Double Blind Cross Over Trail.	N= 63	Japan	1.Group A: placebo treatment 2.Group B: LLLT.	1.Visual Linear Analog Scale	GaAIAs diode laser. Continuous mode. 60Mw 830nm near infrared spectrum (model MLD-2001, Mochida, Japan). Power density is 1.2 W/cm2 to 3 w/cm^2 10-20 min per session 10 sec on each point 2 to 3 times a week for OP & 4 to 6 times a week for IP.	LLLT by GaAIAs diode laser was effective for the PHN.
Kevin et al.,[9]	Double Blind Cross Over Trail.	N=20	UK	1.Group A: LLLT 2.Group B: control	Visual Linear Analog Scale	Model: Oh-Lase 3D1 (Japan Medical Laser Laboratory, Tokyo, Japan) GaAIAs diode laser. Continuous mode. 60Mw 3w/cm^2 45J/cm^2	Significant reduction of PHN pain in LLLT group.

DISCUSSION

While the exact physiological pathways of LLLT in treating PHN remain unclear, studies suggest that it may increase local blood flow and induce analgesia through mechanisms such as vasodilation and modulation of pain-modulating chemicals. This increased blood flow, observed through laser Doppler blood flow measurements, correlates with improved clinical outcomes in PHN patients. Numerous studies, including those by Moore et al.,[9] and Kemmotsu et al.,[8] have demonstrated the effectiveness of LLLT in reducing pain and improving symptoms associated with PHN. For instance, the use of an 830 nm diode laser and GaAlAs diode laser showed significant pain reduction and improvement in neuropathic pain scores (NPS) and Visual Analog Scale (VAS) ratings[10]. Clinical trials and pilot studies have consistently reported substantial pain relief and symptom improvement in PHN patients treated with LLLT. Responses have been positive in both acute and chronic stages of PHN, with some studies indicating LLLT's potential to reduce the incidence of PHN when applied early (within five days of Herpes zoster outbreak)[11–13]. Individual case studies, such as the 15-year-old case mentioned, illustrate dramatic reductions in pain scores and resolution of symptoms following LLLT treatment. These cases underscore the potential for LLLT to provide long-lasting relief and improve quality of life in patients resistant to other treatments. The promising results from these studies suggest that LLLT could play a significant role in managing PHN, potentially reducing reliance on analgesic medications, and improving outcomes for patients, including those with unique circumstances such as PHN in COVID-19 patients[14–22]. In conclusion, while further research is needed to fully elucidate the mechanisms and optimize protocols for LLLT in PHN treatment, current evidence strongly supports its efficacy and safety

as a therapeutic option. LLLT offers a non-invasive, well-tolerated approach that may provide substantial pain relief for PHN patients, representing a valuable addition to the treatment armamentarium for this challenging condition.

LIMITATION AND SUGGESTION

While studies have demonstrated the efficacy of LLLT in reducing pain intensity and improving symptoms in PHN patients, there remains a need to systematically investigate how these improvements translate into broader aspects of quality of life which encompasses physical, psychological, and social well-being, which are all affected by chronic pain conditions like PHN.

CONCLUSION

In conclusion, the systematic review and meta-analysis provide robust evidence supporting LLLT as a beneficial and safe treatment option for reducing pain in patients with post-herpetic neuralgia. Due to the limited number of studies and variations in study design and intervention application, the study offers a high level of heterogeneity. The absence of reported adverse effects underscores its potential as a well-tolerated therapeutic approach. Therefore, it is recommended for clinicians and policymakers considering and integrating LLLT as a first-line treatment for PHN. Continued research and clinical application of LLLT will further elucidate its role in optimizing outcomes and improving quality of life for individuals living with PHN.

Conflict of Interest

No conflict of interest throughout the study duration.

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