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Low level light therapy/ photobiomodulation for diabetic peripheral neuropathy: protocol of a systematic review and meta-analysis

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ABSTRACT

Introduction Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes that strongly impact the patients' quality of life and working ability. Evidence indicated that low level light therapy (LLLT)/photobiomodulation might be effective for neuropathy. However, the effect of LLLT for DPN is not clear. The objective of this systematic review and meta-analysis is to determine the effects and safety of LLLT/ photobiomodulation for DPN, in comparison with other methods such as sham light, no treatment, other active treatment and LLLT as an additional treatment compared with another treatment alone.

Methods and analysis We will search eight databases from their inception to the date before the review submission. Randomised controlled trials (RCTs) will be included. Two reviewers will independently extract data using a structured data extraction method and assess the risk of bias in the included studies. Data will be synthesised using standardised mean difference or risk ratio with 95% CIs for continuous and dichotomous data, respectively. The primary outcome will be change in pain and secondary outcomes will include global symptom improvement, functional impairment and disability, impairment of sensation, quality of life, nerve conduction, and adverse events. Sensitivity and subgroup analysis will be employed to explore the influence of possible clinical and methodological characteristics. Publication bias will be assessed using funnel plot. We will conduct meta-analysis with RevMan V.5.4 and evaluate quality of the evidence using GRADE approach.

Ethics and dissemination This study does not require ethics approval. Our findings will be disseminated in the peer-reviewed publications.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The systematic review method in the protocol follows standard methodological procedures recommended in the Cochrane Handbook in terms of literature searching and screening, data collecting, risk of bias assessing and data synthesis.
⇒ The reporting of the protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
⇒ This study will search eight databases and two trial registries without language restrictions.
⇒ The main expected limitations are variations in light treatments and in outcome measures that may introduce heterogeneity or imprecision, which will influence the reliability of the evidence.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes and affects nearly 50% of adults with diabetes during their lifetime.[1] DPN strongly impacts the patients' quality of life and capacity for work. It leads to foot ulcer in 50% diabetes, and even cause lower limb amputation.[1] People with type 2 diabetes suffered higher risk of DPN than type 1.[1] DPN is recognised by damage to peripheral nerves, commonly occuring in the lower limbs and occasionally affecting the hands. However, up to 50% of patients never experience symptoms, thus, diagnosis can only be made in accidental examination or until foot ulcers appear. For patients who have already experienced symptoms, numbness, dryness, burning pain, needle-like pain and some other abnormal sensations are most frequently mentioned.[2]

Significant risk factors for DPN include diabetes duration, age and glycosylated haemoglobin.[3 4] Some other factors, including hypertension, hyperlipidaemia and obesity, may also play a role at varying degrees.[5]

Other than improving glycaemic control, there is no specific treatment for the underlying nerve damage. Enhanced glucose control can effectively prevent DPN in type 1 diabetes, whereas the evidence for the effect of glycaemic control is not strong in type 2 diabetes.[6] Furthermore, enhanced glucose control can increase the risk of

severe hypoglycaemic episodes.[6] Some symptomatic therapies, such as pregabalin, duloxetine or gabapentin, are recommended as first-line pharmacological treatment for relieving painful symptoms. Tricyclic antidepressants, venlafaxine, carbamazepine, opioids and topical capsaicin are also probably effective in relieving pain.[7 8] However, these drugs are accompanied with a variety of adverse events, such as dry mouth, sedation, dizziness, confusion, orthostatic hypotension, headache, nausea, constipation, diarrhoea, etc.[9]

Non-pharmacological therapy, such as low level light therapy (LLLT), has also been used to treat DPN due to its function in alleviating pain[10] and improving lower limbs sensation.[11 12] LLLT, also known as photobiomodulation, has been in use from its invention in 1960s. The light used in LLLT is mainly in the red (wavelength of 600–700 nm) and near-infrared (NIR, wavelength of 780–1100 nm) region.[13 14] The red and NIR light is mostly absorbed by the mitochondrial enzyme (ie, cytochrome-c-oxidase), the key chromophore in the cellular response to LLLT, to increase ATP production, modulation of reactive oxygen species (ROS) and the induction of transcription factors.[13–15] The mid-IR including carbon dioxide laser at wavelength of 10.6 μm and broad band IR source in the 10–50 μm range are also reported as effective LLLT light. Mid-IR light is considered to be absorbed by water in some nanostructured form possibly present in biological membranes.[13] On the tissue level, LLLT has been used to inhibit pain and pathological conditions associated with the nervous system. It exerts potent anti-inflammatory effects in the peripheral nervous system and promotes functional recovery and regeneration of peripheral nerves after injury, also in DPN.[14 16] The effect of LLLT depends on the type of light, irradiation mode, power density and the properties of irradiated tissue.[13]

Although two systematic reviews[17 18] have evaluated the effects of LLLT/photobiomudulation for DPN, they both included only a small number of studies in published in English language. Furthermore, one[17] of them only provided qualitative description of the included studies. With some new and larger-sample size RCTs[19–22] published, it is important to conduct an updated systematic review and meta-analysis of LLLT for DPN.

Objective

The objective of this review is to determine the benefit and harm of LLLT/photobiomodulation in comparison to sham light, no treatment, other active treatment or as an additional treatment compared with another treatment alone in patients with DPN. The benefit will include its effect in relieving pain and global symptoms and improving nerve function as well as quality of life.

METHODS AND ANALYSIS

We will use standard methodological procedures following the Cochrane Handbook. The planned start date of the study is July 2021 and end date of the study is December 2022.

Eligibility criteria for included studies

Types of studies

We will include randomised controlled trials assessing the benefits and harms of LLLT/photobiomodulation for DPN. Trials with randomisation of interventions taking place within individuals to different body parts (eg, to the two legs) will also be included.

Types of population

We will include participants of any age and sex, with either form of diabetes, that were diagnosed as DPN. Although many light therapies are focused on DPN patients with type 2 diabetes, there are also studies involving patients with type 1 diabetes. We believe the mechanisms of DPN from both types of diabetes are similar. Thus, we include patients with either form of diabetes.

Types of intervention

LLLT/photobiomodulation uses non-ionising forms of light sources, including lasers, LEDs and broadband light, in the visible and IR spectrum.[23] The commonly used lights in DPN treatment may include red (wavelength of 780–1100 nm), NIR (wavelength of 780–1100 nm), mid-IR (eg, 10.6 μm) and broad band IR light in the 10–50 μm.[13] We will compare true LLLT versus sham LLLT, LLLT versus no specific treatment, LLLT versus other specific treatment, or LLLT plus another treatment (usually conventional treatment) versus another treatment only. In order to eliminate confounding effects, we will only include RCTs that used the same cointervention in each group.

Types of outcome measures

Main outcome

The main outcome will be change in pain measured using a validated scale including Visual Analogue Scale, Numeric Rating Scale, Likert scale or Verbal Description Scale, etc.

Additional outcomes

1. Global symptom improvement measured by a validated instrument such as Neuropathy Symptom Score, Neuropathy Total Symptom Score or Total Neuropathy Score.[24–26] The DPN examintion scales such as Michigan Neuropathy Screening Instrument, Michigan Diabetic Neuropathy Score and Toronto Clinical Scoring System will not be considered as validated instruments in evaluating DPN symtoms. Where this continuous outcome was not available, the primary outcome will be an improvement of 30% or more in a validated clinical global symptom score.[27]
2. Change in functional impairment and disability by Neuropathy Impairment Score or Neuropathy Defects Score in the lower limbs.
3. Change in impairment of sensation in quantitative sensory testing (eg, vibration perception threshold,

thermal threshold and Semmes-Weinstein Monofilaments).

4. Change in quality of life by SF-36 (36-item short-form health survey) or NeurQol, etc.
5. Change in nerve conduction function measured by motor or sensory nerve conduction velocity (NCV), sensory nerve action potential or compound muscle action potential.
6. Number of participants experiencing adverse events.
7. Serious adverse events.

The time point of follow-up will be at equal or less than 3 months (closest to 2 months) after randomisation for short term and at more than 3 months (closest to 6 months) after randomisation for long term.

Search methods for identification of studies

We will search, with no time and language restrictions, the following databases for relevant literature: PubMed (MEDLINE), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science, as well as Chinese language databases including China National Knowledge Infrastructure (CNKI), Wanfang, VIP Chinese Science and Technology Journal Database (VIP) and SinoMed. Furthermore, the search will also include the two trial registries ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (https://trialsearch.who.int/). The electronic database search will be supplemented by a manual search of the reference lists of included articles. The search strategy is illustrated in online supplemental appendix 1. The last search date will be the date before the submission of the full review. The studies in Chinese language will be translated by JYW and checked by KC.

Study selection

At least one author (JYW or ZQH) will screen the title and abstract of all records identified by searching. We will obtain the full text of potentially relevant reports and two authors (JYW and ZQH) will independently review the full text to assess its eligibility. We will resolve disagreements by discussion. In case of disagreement, a third author (KC) will make the final decision on the study selection.

Data extraction and management

Two review authors (JYW and ZQH) will independently extract data concerning details of study population, intervention and outcomes using a structured data extraction form and enter it into a Microsoft excel spreadsheet following section 7.7 of Cochrane Handbook.[28] We will consult the other review author (KC) if there is any conflict.

If the publication did not report outcome data or the data were reported ambiguously, we will request the corresponding authors of the study to provide additional information or clarification by email.

Assessment of treatment adequacy

Two experts, who have a clinical or research experience of more than 5 years in LLLT/photobiomodulation therapy or in DPN treatment, and who have previously worked on RCTs or systematic reviews, will independently assess the adequacy of the light therapy and the control therapy in the trials. Five aspects of the light treatment will be assessed for adequacy: (1) selection of light (including wavelength, power density and energy density); (2) choice of irradiation location; (3) total number of sessions; (4) treatment duration and (5) treatment frequency. The validity of the sham intervention will also be assessed using an open-ended question. The experts will be provided with only the part of each publication that describes the light and control procedures, so that their assessments cannot be influenced by the results of the trials. Discrepancies between the two experts will achieve consensus by discussion.

Assessment of risk of bias

Two review authors (JYW and ZQH) independently will assess the risk of bias in the studies that were included in this review according to the criteria described in the section 8.2.3 of Cochrane Handbook for Systematic Reviews of Interventions.[29] We will resolve conflicts by consulting the other review author (KC).

The items involve the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias.

Measures of treatment effect

Mean difference (MD) or standardised mean difference (SMD) with 95% CI will be used for continuous outcome and relative ratios with 95% CI will be used for dichotomous data. Data of studies that are sufficiently similar in terms of their comparisons and outcome measurements will be pooled. The data will be pooled by using random-effects model when studies are heterogeneous on clinical and methodological characteristics, and by using fixed-effect model when they are homogeneous. We will report the data separately if the study cannot be combined. We will use MD for single trial comparisons and for RCTs that used the same instrument to measure the same outcome. For the RCTs that assessed the same outcome by various instruments, we will use SMD. Analyses will be performed by intention to treat, where possible.

Unit of analysis issues

We will also include data from trials with different interventions being applied to different body parts, if the information is available. The analysis will be account for the pairing of parts within individuals in the same way that pairing of intervention periods in the crossover trial.[30] Continuous data from this kind of trial will be analysed using one of the two approaches: use the results from paired analyses if reported in the original article; treat the study as a parallel trial and pool the interventional parts and compare these to the pooled control parts. Dichotomous outcomes for this kind of trial require more

complicated analysis methods and we will consult with a statistician.[31]

Dealing with missing data
For the missing data, we will contact the original author. If we fail to obtain the missing data, we will discuss the potential impact of the dropout for the conclusion of the review.

Assessment of heterogeneity
We will use I^2 statistic to assess statistical heterogeneity. If the I^2 value is greater than 50%, we will conduct subgroups to explore the sources of heterogeneity.

Reporting bias
We will make a funnel plot to assess publication bias if the number of studies is more than 10.

Sensitivity analysis
We will perform sensitivity analysis excluding the trials with high risk of bias when data are adequate. For pooled analyses with continuous data, we will consider analyses based on change scores to be the primary analysis, and analyses based on post-treatment scores to be sensitivity analysis.

Subgroup analysis
If we find sufficient number of RCTs, we will perform subgroup analyses according to:
1. Type of diabetes (type 1 or type 2 diabetes mellitus).
2. Type of light (red, IR or other).
3. Dosage of light treatment: including power density, energy density, as well as duration and frequency of the treatment according to the assessment results of treatment adequacy by the experts.

Confidence in cumulative evidence
We will use GRADE (Grades of Recommendations Assessment, Development and Evaluation) system to assess the confidence of our evidence considering five criteria: study limitations, consistency of effect, imprecision, indirectness and publication bias. We will conduct the assessment in accordance with section 14.2 of the Cochrane Handbook[32] using GRADEpro software.

Patient and public involvement
No patient involved.

DISCUSSION
Evidences for LLLT/photobiomudulation in treating DPN are deficient so far. A 2017 systematic review focused on using IR light for DPN.[18] A more recent systematic review from 2019 studied LLLT for painful diabetic neuropathy.[17] Both reviews included only six studies each. Among the six studies included the 2019 review, three were non-RCTs, thus the 2019 review only narratively described the results of the individual study without conducting any meta-analysis or assessing the risk of bias of the included studies. In addition, the conclusions of the two reviews were inconsistent with each other. The 2017 review showed limited evidence of IR phototherapy resulting in short-term improvement of tactile sensitivity, but not in neuropathic pain relief. In contrast, the 2019 review concluded LLLT is associated with a positive effect in relieving neuropathic pain.

Compared with previous reviews, we will update the search to date to include more recent studies and will expand our search scope to Chinese language databases to collect more evidences. Furthermore, we will include more types of lights, not focusing only on IR lights as in the 2017 review, since other than IR light, visible lights are also used in clinic for DPN. In terms of the outcomes, the 2017 review[18] investigated plantar tactile sensitivity and pain; the 2019 review[17] focused on pain and NCV. In additional to the aforementioned outcomes, we will also be concerned about global symptom improvement, functional impairment and disability, quality of life, as well as adverse events due to the therapy. Compared with the 2017 review[18] which performed subgroup analysis according to the type of comparison and length of follow-up, we will carry out subgroup analysis focusing more on the differences in the populations and intervention characteristics (eg, type of diabetes, type of light and dosage of therapy) according to the suggestion in the Cochrane Handbook.[33]

There are some expected limitations in this review. First, the heterogeneity in light treatment including different types of light, irradiation modes, power densities and sites of irradiation, may result in important heterogeneity in pooled results. Second, the global symptom outcome is usually assessed with composite measures and the measures vary among studies. This may introduce heterogeneity and render pooled estimates difficult to explain. Last, the variations in electrophysiological measures and quantitative sensory testing among studies may result in only a limited number of studies that can be pooled for a certain outcome. This may influence the reliability of the evidence.

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Competing interests XS and KC have had a patent issued for a type of laser therapy apparatus simulating the infrared radiation spectrum of traditional Chinese moxibustion (China Invention Patent ZL 200910056991.4; issued 1 December 2010).

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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