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RESEARCH

Evaluating laser photobiomodulation for chemotherapy-induced peripheral neuropathy: a randomised phase II trial

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Abstract

Purpose This study aims to evaluate the efficacy and safety of laser photobiomodulation (PBM) for treatment of established chemotherapy-induced peripheral neuropathy (CIPN) in cancer survivors.

Methods We conducted a randomised phase II, non-comparative, sham-controlled, single-blinded clinical trial in 44 cancer survivors reporting CIPN symptoms at least 3 months following completion of neurotoxic chemotherapy. Participants were randomised 2:1 to either PBM laser or sham control delivered twice weekly for 12 sessions. Assessments were conducted at baseline, the end of intervention (6 weeks), and 6 weeks post intervention (12 weeks). Participants completed neuropathy, quality of life and function questionnaires, and a clinical neurological assessment. The primary outcome was proportion of participants with CIPN response, defined as either symptom resolution or reduction of minimally clinically important difference.

Results In the laser and control groups, CIPN response rates were − 48% and 53% at 6 weeks and 45% and 33% at 12 weeks, respectively. The null hypothesis that the true response rate is 5% in the laser arm was rejected at both 6 and 12 weeks ($p < 0.001$ for both). Compared to baseline, patient-reported CIPN improved in both laser and control groups after the intervention. At 12 weeks, improvement was sustained in the laser group and approaching baseline in the control group. Clinical signs, quality of life, and function remained stable in both groups. Low-grade "side-effects" were observed in both arms.

Conclusion PBM may offer clinically meaningful symptom benefit in cancer survivors with established CIPN with improvement potentially continuing beyond completion of the intervention. A larger study is warranted to evaluate this further.

Keywords Chemotherapy-induced peripheral neuropathy · Photobiomodulation · Laser therapy · Survivorship · Neurotoxicity · Patient-reported outcomes

Introduction

Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and potentially disabling toxicity of several commonly used chemotherapy agents including platinum compounds, taxanes, vinca alkaloids, and some targeted agents [1]. CIPN is a predominantly sensory neuropathy affecting the extremities; patients report numbness, tingling, pain, and/or burning in their hands and feet. In a systematic review of patients with any cancer type, prevalence of CIPN was 68.1%, 60%, and 30% at 1, 3, and > 6 months following chemotherapy respectively [2]. Once established, CIPN may persist, with a recent systematic review indicating a quarter of patients treated with oxaliplatin for colorectal cancer have symptoms of CIPN 3 years after chemotherapy [3]. Due to the protracted symptom burden, disability, and an increased risk of falls in cancer survivors, CIPN is associated with reduced quality of life [4, 5].

There are no proven preventative strategies and few evidence-based treatment options for CIPN. Marginal symptom benefits have been shown in randomised trials of moderate

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intensity exercise [6], and duloxetine for painful peripheral neuropathy [7]. The mainstay of CIPN management involves reducing exposure to the causative chemotherapy before irreversible impairment occurs, which has implications for treatment delivery and efficacy [8].

The hypothesised mechanism of CIPN varies depending on the causative agent. Oxaliplatin compounds accumulate in the dorsal root ganglion of peripheral nerves, and form DNA adducts which disrupt sodium channel function and lead to hypersensitivity [9]. The mechanism of action for paclitaxel is microtubule disruption, with CIPN developing due to mitochondrial damage to neurons, production of reactive oxygen species, and impaired transport of cellular components required for metabolism. Altered expression and function of sodium and potassium ion channels lead to neuronal hyperexcitability, with overall loss of epidermal neuronal fibres in the longer term [10, 11]. Regardless of the agent, common multifactorial processes implicated in CIPN pathogenesis include microtubule disruption, oxidative stress, myelin, mitochondrial and DNA damage, and altered ion channel dysregulation. A common outcome is the release of pro-inflammatory cytokines mediated by glial cells, causing hyperexcitability and sensitisation of peripheral neurons via altered cellular function and dysregulation of ion channels [12]. Axonal degeneration is the ultimate result of neuroinflammation and persistent dysregulation of ion homeostasis [13, 14].

Photobiomodulation

Photobiomodulation (PBM) is the therapeutic use of non-ionising laser light for its anti-inflammatory and regenerative effects. PBM is the currently used MeSH term encompassing a developing field with several synonyms in research literature (low-level laser therapy, light therapy, low-power laser, photobiostimulation, laser therapy). The 'low level' definition differentiates the laser power from surgical lasers used for purposes such as ablation, cutting, and coagulation [15].

Biological effects

Photons from laser light applied to tissues is hypothesised to increase cellular function and regeneration through the production of mitochondrial products adenosine triphosphate (ATP) and adenine nucleotides (NADH) [15]. Preclinical evidence suggests that PBM can modulate the inflammatory response by inducing nuclear factor kappa B (NF-kB), with implications for wound healing and neural regeneration [16].

Animal studies have recognised that laser suppresses nociceptor Aδ and C fibre action potentials implicated in the transmission of pain, while sparing motor fibres. This provides the basis for a model to use PBM to treat neuropathy [17]. Peripheral nerves are responsible for communicating pain, touch and vibration via action potentials to the central nervous system. The cell bodies of neurons are within the dorsal nerve root ganglion but the axons extend to the epidermis, within the penetration depth of a light source applied to the skin [18]. PBM was found to induce analgesia in a rat model and decrease the release of pro-inflammatory neuropeptides IL-1 and TNF-α, suggesting its possible mechanism of action [19].

Applications of PBM

Clinical evidence supports the use of PBM for pain and neurodegenerative conditions. Systematic reviews have concluded PBM was beneficial for acute and chronic neck pain [15] and chronic joint disorders [20], but findings should be interpreted cautiously due to the wide range of patients, treatments and trial designs, with variation reported in treatment dose, equipment used, wavelength, and power of the laser. Preliminary clinical evidence suggests PBM may be beneficial for peripheral neuropathy, with small studies suggesting improvement in painful diabetic neuropathy [21, 22] and oxaliplatin-induced neurotoxicity [23]; however, these trials lacked a comparison arm.

In 2019, a systematic review supporting the use of PBM for oral mucositis caused by cancer treatments resulted in its adoption into the recommendations for prevention of oral mucositis by the Multinational Association of Supportive Care in Cancer [24]. A search of ANZCTR shows 20 currently registered PBM studies for other indications including ophthalmologic, dental, neuromuscular pathology, wound healing, and breast cancer lymphoedema [25].

Regarding the tolerability and safety of PBM, studies utilizing lasers in many populations (including children with headache or post-operative nausea) have demonstrated good tolerance and minimal toxicity [26, 27]. While there is a theoretical risk of PBM causing a transformation to malignancy or accelerated tumour growth, follow-up of patient cohorts after PBM have shown improvements in survival and locoregional control [28]. A systematic review of 27 studies evaluating PBM use in oncology supportive care reported equivalent or improved oncological outcomes within the limitations of the follow-up period [29].

Rationale and aims

Given the growing problem of CIPN in cancer survivorship and limited therapeutic options, clinicians and patients are increasingly open to complementary or novel therapies. The use of complementary and novel therapies by people with cancer has prompted the Clinical Oncology Society of Australia to issue a position statement 'The use of complementary and alternative medicine by cancer patients' as a resource for clinicians [30]. In the case of PBM, there is

evidence supporting the safety and tolerability if used within safety recommendations; however, the benefits — particularly pertaining to effectiveness in treating CIPN — are not yet established.

Complementary therapies should be evaluated in appropriately conducted clinical trials to the same standards as other treatment modalities [31]. The purpose of this research is to explore whether PBM can improve CIPN symptoms, building on early clinical data and evidence for use in other clinical contexts.

Objectives

The general objectives of this study were to evaluate the efficacy, feasibility, and safety of PBM for the treatment of established CIPN. The primary objective is to determine the proportion of CIPN responders in the true laser and 'sham' control arms. The secondary objectives are to explore CIPN and quality of life outcomes, and safety of PBM in the study cohort.

Methods

Design

This was a randomised, single-blinded, two-arm, pre-post, non-comparative phase II trial. Participants were randomised in a 2:1 ratio to either the PBM intervention or sham therapy. The study protocol was approved by the Sydney Local Health District Human Research Ethics Committee–Concord Repatriation General Hospital and registered in the Australian New Zealand Clinical Trials Registry (ACTRN12619001672145p).

Participants

Adults with symptoms of CIPN at least 3 months following completion of potentially neurotoxic adjuvant or neoadjuvant chemotherapy were invited to participate. Convenience sampling was used, with potentially eligible patients being referred for the study from local oncologists at their routine clinical follow-up. Participants were included if they answered 'yes' to the question "Do you have numbness, tingling, or pain affecting the hands and/or feet following chemotherapy?" Participants (or with assistance from accompanying carer) were required to have sufficient English proficiency to complete questionnaires, as assessed by an investigator.

Specific exclusion criteria were (1) inability to lie supine for a 30-min period; (2) open wound or ulcer over the treatment area; (3) clinical diagnosis of peripheral neuropathy from another cause (note diabetes without neuropathy was not a specific exclusion); (4) uncontrolled psychiatric illness or cognitive dysfunction that may interfere with the ability to complete assessments; (5) life expectancy less than 3 months; (6) concurrent complementary therapy for neuropathy for the duration of the study.

Study settings

The study was performed at the Survivorship Cottage at Concord Repatriation General Hospital. All participants signed written informed consent prior to commencement.

Interventions

Participants in the intervention arm received PBM twice a week for 6 consecutive weeks, a total of 12 treatments, provided by therapists accredited in laser safety. Patients were treated in a seated position wearing an opaque eye covering for laser safety and treatment blinding. Treatment was administered by Acupak CL Mini Laser, a class 2 M diode continuous laser which delivers 8 mW power at wavelength 658 μm through a 3.2-mm diameter aperture.

During the intervention, the laser was applied to the interdigital spaces of the hands and feet (16 points), and the cutaneous landmarks corresponding to the C6-T1 and L5-S1 nerve roots bilaterally (10 points). Figure 1a illustrates the device, and Fig. 1b illustrates the anatomical locations where it was applied. The initial treatment dose was 1 Joule/point with escalation to 2 Joule/point for subsequent sessions as tolerated. The dose (Joules) is specified by the therapist, and the Acupak device deactivates the laser once the dose has been delivered.

The sham therapy consisted of the same procedures as the laser intervention (visit schedule, eye mask, equipment, and application points) but with the laser aperture occluded by an opaque aluminium cover, with the intention of maintaining the same sensory experience as the intervention arm. Each treatment was recorded on a case report form.

Outcomes and assessments

Participants completed assessments for CIPN and quality of life at baseline, at the completion of the intervention period (6 weeks) and at 12 weeks follow-up. Due to the COVID-19 pandemic, participants were allowed to defer their follow-up visit if they were required to stay home due to a public health order.

Assessments comprised the following validated measures:

(1) Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity scale (FACT/GOG-Ntx 13), a patient-reported neurotoxicity symp-

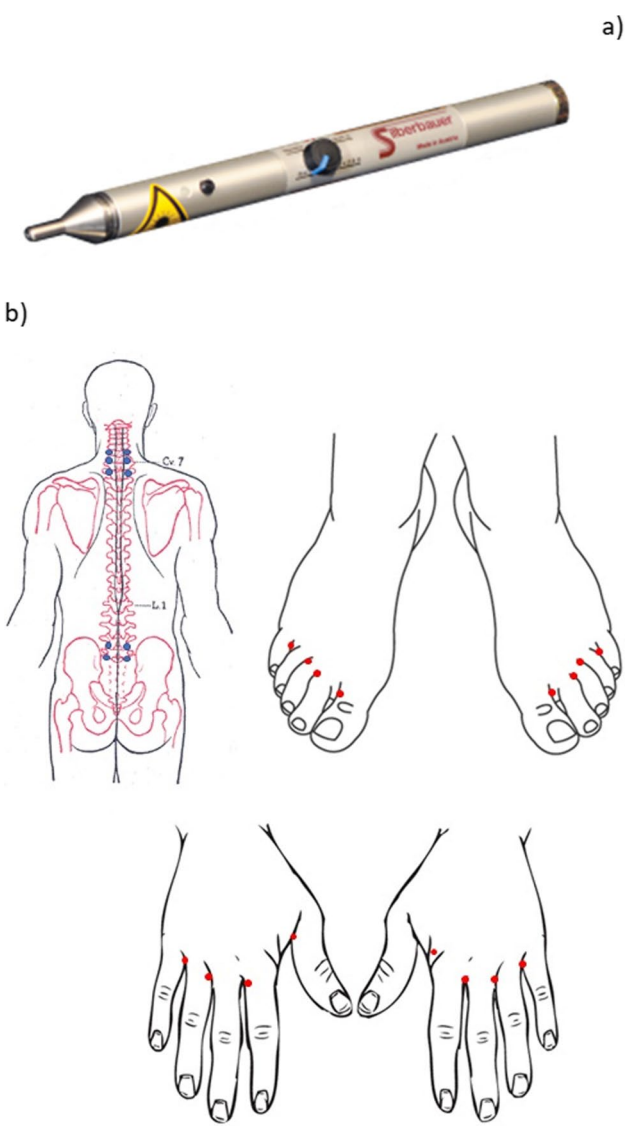

Fig. 1 **a** Acupak CL Mini Laser apparatus; **b** intervention and sham treatment points denoted by red and blue spots

tom questionnaire (range 0–52, higher scores indicate greater symptoms) [32];

(2) European Organisation for Research and Treatment of Cancer chemotherapy-induced peripheral neuropathy questionnaire (EORTC QLQ-CIPN 20), a patient-reported neurotoxicity symptom questionnaire (linearly transformed to 0–100 scale, higher scores indicate greater symptoms) [33];

(3) the Functional Assessment of Cancer Therapy (FACT-G), a quality of life questionnaire comprising four subscales, physical (range 0–28), social/family (range 0–28), emotional (range 0–24), functional (range 0–28) with total score a sum of the subscales. Higher score indicates better quality of life [34];

(4) Karnofsky performance status, a patient reported functional assessment (range 0–100, higher score indicates better function) [35];

(5) the total neuropathy score (TNSc), a composite neuropathy measure combining clinical findings and patient symptoms (range 0–28, higher score indicates greater neuropathy) [36]; and

(6) clinician graded peripheral sensory neuropathy via common terminology criteria of adverse events version 5 (CTCAE) range 0–5, higher grade indicates greater neuropathy [37].

Paper questionnaires were completed at the study visits. TNSc was performed by an unblinded physician investigator. Adverse events were documented at study visits as described by the patient, then retrospectively assigned CTCAE grading by an oncologist investigator.

Sample size

The sample size of approximately 45 participants was calculated allowing for 10% attrition, based on Simon's two-stage design [38]. Participants were recruited in a 2:1 (active:control) ratio until the target of 27 active participants was achieved. An interim analysis was performed after 13 patients were accrued to the active arm, with the plan to stop the study if no responses were identified. The null hypothesis that the true response rate is 5% was to be tested against a one-sided alternative hypothesis. This sample size yields a type I error rate of 5% and power of 80% when the true response rate on treatment is 20%.

Randomisation

The NHMRC Clinical Trials Centre employed the minimisation technique for randomisation. This adaptive technique uses current imbalances between treatment arms across the stratification factors, along with the new participant's stratification levels, to determine treatment allocation. As an adaptive technique, there is no allocation sequence generated prior to start of recruitment. Prespecified stratification factors were (1) type of prior chemotherapy (platinum, taxane, or both); (2) age ($< / \geq 65$ years); (3) baseline grade of neuropathy (CTCAE); (4) months since completing neurotoxic chemotherapy (< 6, 6–12, > 12).

Statistical methods

The primary outcome was CIPN response at the completion of the PBM intervention, defined as the proportion of patients in each arm who experience either (1) resolution of symptoms from any score to zero on FACT/GOG-Ntx-13 subscale or (2) reduction in FACT/GOG-Ntx-13 subscale by

4 points, which was a conservative estimate of the minimally clinically important difference (1.38–3.68) [39]. The study null hypothesis was that the true response rate is 5% versus a one-sided alternative.

Secondary endpoints were the serial FACT/GOG-Ntx-13, EORTC QLQ-CIPN20, TNSc scores, quality of life, and functional status over the study timeline. Number and severity of adverse events were recorded.

For continuous and 3-category outcomes, linear regression was used to estimate mean differences and risk differences between intervention and control groups. For dichotomous outcomes, Poisson regression with robust variance estimators was used to estimate intervention effects as relative risks. Participants with missing outcome values were assigned no CIPN response for the primary outcome and baseline observations carried forward (BOCF) for all other outcomes.

Reporting was done according to CONSORT statement and extended guidance for nonpharmacologic treatments [40].

Results

Of 99 patients screened, 44 consented to participate and were randomised between July 2020 and December 2021. Four participants required the assistance of a carer to complete questionnaires, for English language support. Two participants in the intervention group withdrew following the baseline visit, one due to travel issues amid COVID-19 lockdown, and one due to infection (these patients were included in analyses of outcome and were assigned no CIPN response for the primary outcome; BOCF was applied for all other outcomes). The CONSORT diagram of participant recruitment is shown in Fig. 2. Reasons for exclusion were patients having chemotherapy ($n=6$), language barrier ($n=4$), CIPN resolved ($n=4$), patient using complementary therapy ($n=2$), and non-solid organ malignancy ($n=1$). Reasons patients declined participation were unable to meet time commitment ($n=15$), patient felt their CIPN was too mild or improving ($n=9$), transport issues ($n=5$), not interested in intervention ($n=5$), patient having other

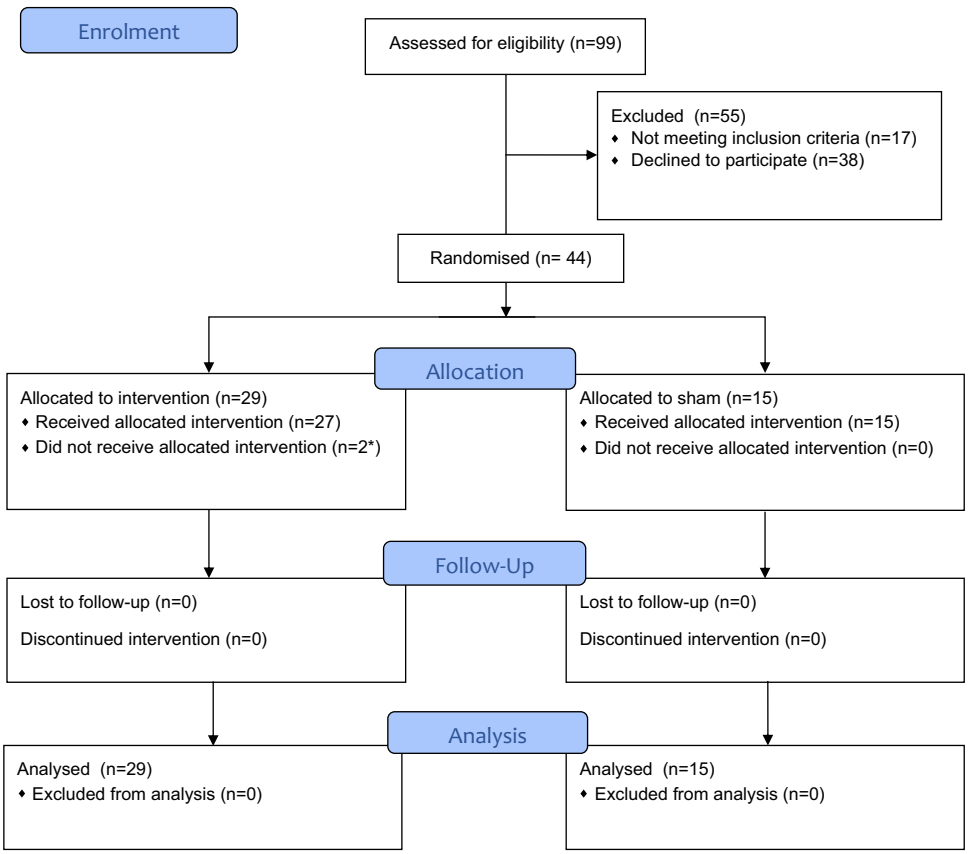

Fig. 2 CONSORT diagram demonstrating recruitment and retention of participants

* One patient withdrew due to travel issues amid COVID-19 lockdown, and one due to hospitalization for pre-existing infection. Participants with missing outcome values were assigned no CIPN response for the primary outcome and baseline observations carried forward for all other outcomes.

interventions ($n=3$), and unwilling to participate with randomised design ($n=1$).

Baseline characteristics of the participants are summarised in Table 1. Participants were predominantly female (61%), with breast or colorectal cancer. Demographic, disease, and treatment related data were similar between the two groups. Interim analysis did not meet the prespecified criteria for early termination of the study.

Primary and secondary endpoints

Table 2 summarises primary and secondary outcomes in the intervention and control groups. In the PBM group, the primary endpoint (CIPN response via FACT/GOG-Ntx13) was observed in 48% of participants at 6 weeks, and 45% at 12 weeks. In the sham group, CIPN response was 53% at 6 weeks and 33% at 12 weeks. The null hypothesis that the true response rate is 5% in the intervention arm was rejected at both 6 and 12 weeks ($p<0.001$ for both). There were no complete responders as measured by primary endpoint.

For other outcome measures, both true laser and sham groups performed similarly with improvement of CIPN in clinician and patient-reported symptom scores at the 6-week timepoint. Improvements in the sensory symptom scores in the laser intervention arm were sustained at the week 12 timepoint, whereas the control group had their symptoms return to near baseline levels. Patient-reported function was unchanged over the course of the study.

Table 3 summarises the quality of life outcomes measured during the study. Overall, both groups performed similarly with improvements in FACT-G scores at 6 and 12 weeks.

Table 1 Participant baseline characteristics

	Sham control ($n=15$)	Laser intervention ($n=29$)	Total ($n=44$)	*P* value
Age (years), mean (SD)	61.7 (11)	61.8 (9)	61.8 (9)	0.96
Sex *n* (%) female	9 (60)	18 (62)	27 (61)	0.89
Cancer primary, *n* (%)				
Breast	5 (33)	10 (34)	15 (34)	0.98
Colorectal	7 (47)	14 (48)	21 (48)	
Other	3 (20)	5 (17)	8 (18)	
Months since chemotherapy, mean (SD)	15.0 (15)	15.8 (17)	15.5 (16)	0.88
Prior chemotherapy				
Oxaliplatin	7 (47)	14 (48)	21 (48)	0.96
Docetaxel	1 (7)	2 (7)	3 (7)	
Paclitaxel	2 (13)	6 (21)	8 (18)	
Platinum and Taxane	4 (27)	7 (24)	11 (25)	
Other*	1 (7)	0 (0)	1 (2)	
Neuropathy grade (%)^				
1	9 (60)	19 (66)	28 (64)	0.87
2	6 (40)	10 (34)	16 (36)	

SD standard deviation

*Other, nab-paclitaxel

^Clinician rated peripheral sensory neuropathy as per Common Terminology Criteria for Adverse events

Safety and adverse events

An adverse event was reported for 19 and 8 participants in the laser intervention and control groups respectively. The summary of adverse events is detailed in Table 4. Adverse events were mild (Grades 1 and 2) and typically not requiring intervention. Pain was reported by more participants treated with active laser than sham (28% vs 13%) though this did not require any intervention (e.g., simple analgesia). Participants in both arms reported sensations of tingling and temperature change (hot or cold) in both arms — while not specifically relating to a described CTCAE toxicity, this was recorded as an outcome of interest.

One participant sustained a mechanical fall at home unrelated to the study therapy which required oral analgesia and managed as an outpatient. A participant had worsening of pre-existing lymphoedema in the context of prior axillary dissection for breast cancer, which was managed by enforcing compliance with compression aids. Both these events were deemed unrelated to the study therapy.

Compliance/fidelity

All 42/44 patients who remained on study intervention completed the assessments at the 6- and 12-week timepoints. Interruptions to the 6-week treatment period occurred for 9 participants who missed a total of 14 appointments. The majority of these (10/14) were due to either illness or COVID-19 lockdown restrictions.

Discussion

Results from this randomised phase II study indicate that PBM may provide clinically meaningful symptom benefit in patients with established CIPN. While no statistical comparisons between treatment arms were performed, the laser treatment group performed better than expected according to the study null hypothesis. Reduction in the mean FACT/GOG Ntx-13 score by 2.8 at 6 weeks exceeded the lower limit for the estimate for the minimal clinically important difference (MCID, 1.38–3.68) [39]. The reduction in mean score by 4.3 at 12 weeks exceeded the MCID. Similarly, improvements exceeding the MCID was observed on both the sensory and motor subscales of the EORTC

Table 2 Differences between intervention and control groups in study outcomes

Outcome	Baseline	Week 6	Δ from baseline at Week 6	Week 12	Δ from baseline at Week 12
CIPN response[1] (% with response)					
Laser intervention	n/a	48%	n/a	45%	n/a
Sham control	n/a	53%	n/a	33%	n/a
Relative risk	-	0.7, $p=0.6$	-	0.8, $p=0.8$	-
FACT/GOG-Ntx13 (mean scores)					
Laser intervention	17.9	15.1	−2.8	13.6	−4.3
Sham control	14.4	11.5	−2.9	12.3	−2.1
Mean difference	-	3.5, $p=0.2$	0.0, $p=0.9$	1.3, $p=0.6$	−2.2, $p=0.3$
EORTC QLQ-CIPN20 Sensory scale (mean scores)					
Laser intervention	37.8	32.4	−5.4	31.4	−6.4
Sham control	32.1	24.0	−8.1	28.4	−3.7
Mean difference	-	9.1, $p=0.1$	1.7, $p=0.7$	3.9, $p=0.5$	−3.5, $p=0.5$
EORTC QLQ-CIPN20 Motor scale (mean scores)					
Laser intervention	25.7	20.2	−5.4	17.7	−7.9
Sham control	16.2	11.5	−4.7	12.7	−3.5
Mean difference	-	8.8, $p=0.1$	0.7, $p=0.9$	5.1, $p=0.3$	−4.4, $p=0.2$
EORTC QLQ-CIPN20 Autonomic scale (mean scores)					
Laser intervention	14.9	13.4	−1.5	15.9	1.0
Sham control	15.9	13.7	−2.2	13.3	−2.6
Mean difference	-	−0.3, $p=0.1$	0.7, $p=0.9$	2.6, $p=0.6$	3.6, $p=0.4$
EORTC QLQ-CIPN20 Total (mean scores)					
Laser intervention	30.2	25.2	−5.0	23.9	−6.3
Sham control	23.7	17.8	−5.9	20.3	−3.4
Mean difference	-	7.4, $p=0.1$	0.9, $p=0.8$	3.6, $p=0.4$	−2.8, $p=0.4$
Total Neuropathy Score (clinical) (mean scores)					
Laser intervention	8.2	5.8	−2.4	6.5	−1.7
Sham control	8.7	6.2	−2.5	7.0	−1.7
Mean difference	-	−0.4, $p=0.7$	0.0, $p=0.9$	−0.5, $p=0.6$	−0.1, $p=0.9$
Grade of peripheral neuropathy (CTC-AE v5) (% with Grade 2)[2]					
Laser intervention	37.9%	17.2%	−20.7%	17.2%	−20.7%
Sham control	40.0%	26.7%	−13.3%	13.3%	−26.7%
Risk difference	-	−0.1, $p=0.5$	−7.4%, $p=0.7$	0.0, $p=0.8$	6.0%, $p=0.7$
Physical function measured by Karnofsky performance status (mean scores)					
Laser intervention	80.7	85.7	5.9	85.0	4.5
Sham control	80.7	86.7	5.0	84.7	2.9
Mean difference	-	−1.0, $p=0.8$	0.9, $p=0.8$	0.3, $p=0.9$	1.6, $p=0.6$

Calculation of differences between groups and *p*-values were conducted post hoc and were not expected to be statistically significant given the non-comparative trial design

FACT/GOG Ntx-13 Functional Assessment in Cancer Therapy/Gynecological Oncology Group Neurotoxicity Questionnaire-13 items score (higher score indicates more neuropathy), *EORTC QLQ-CIPN20* European Organisation for Research and Treatment of Cancer quality of life questionnaire–chemotherapy-induced peripheral neuropathy (higher score indicates more neuropathy), *TNSc* Total Neuropathy Score (higher score indicates worse impairment); clinician rated peripheral sensory neuropathy as per Common Terminology Criteria for Adverse events (higher score indicates worse impairment)

[1]CIPN response is defined as either (1) resolution of symptoms from any score to zero on FACT/GOG-Ntx-13 subscale or (2) reduction in FACT/GOG-Ntx-13 subscale by 4 points

[2]One intervention group participant had grade 0 neuropathy at week 12 and was combined with grade 1 neuropathy for analyses

Table 3 Differences between intervention and control groups in quality-of-life outcomes

Outcome	Baseline	Week 6	Δ from baseline at Week 6	Week 12	Δ from baseline at Week 12
Physical well-being FACT-G (means scores)					
Laser intervention	21.2	22.1	0.9	23.5	2.3
Sham control	21.2	22.4	1.2	23.7	2.5
Mean difference	-	−0.3, $p=0.8$	−0.3, $p=0.8$	−0.2, $p=0.8$	−0.2, $p=0.9$
Social family well-being FACT-G (means scores)					
Laser intervention	22.1	22.1	0.0	22.4	0.3
Sham control	22.1	22.0	0.0	21.9	-0.2
Mean difference	-	0.0, $p=0.9$	0.0, $p=0.9$	0.6, $p=0.8$	0.5, $p=0.6$
Emotional well-being FACT-G (means scores)					
Laser intervention	17.3	18.2	0.9	19.5	2.2
Sham control	19.1	19.9	0.8	19.1	0.1
Mean difference	-	−1.7, $p=0.2$	0.0, $p=0.9$	0.4, $p=0.8$	2.1, $p=0.04$
Functional well-being FACT-G (means scores)					
Laser intervention	20.0	19.8	−0.3	21.3	1.3
Sham control	19.3	21.3	2.1	20.2	0.9
Mean difference	-	−1.6, $p=0.4$	−2.3, 0=0.03	1.1, $p=0.6$	0.4, $p=0.7$
Total score FACT-G (means scores)					
Laser intervention	80.6	82.1	1.5	86.8	6.1
Sham control	81.6	85.7	4.1	84.9	3.3
Mean difference	-	−3.5, $p=0.5$	−2.6, $p=0.4$	1.9, $p=0.7$	2.9, $p=0.3$

Calculation of differences between groups and *p*-values were conducted post hoc and were not expected to be statistically significant given the non-comparative trial design

FACT-G Functional Assessment of Cancer Therapy–General (a higher score indicates better quality of life)

Table 4 Adverse events recorded between intervention and control groups

Symptom *n* (%)	Sham control ($n=15$)		Laser intervention ($n=29$)	
	Grade 1	Grade 2	Grade 1	Grade 2
Pain	2 (13)	-	8 (28)	-
Fatigue	3 (20)	-	5 (17)	-
Tingling	3 (20)	-	5 (17)	-
Numbness	2 (13)	-	3 (10)	-
Temperature change*	1 (7)	-	3 (10)	-
Headache	2 (13)	-	2 (7)	1 (3)
Other**	1 (7)	-	4 (14)	2 (7)

*Feeling hot or cold in extremities

**Other: 1 patient each had dysuria, cramps, diarrhoea, fall, lymphoedema, nausea, and rash. No grade 3 events were reported

QLQ-CIPN20 (MICD 2.5–5.9 for sensory subscale, 2.6–5.0 for motor subscale) [41].

As well as being clinically meaningful, this study demonstrates improvements in CIPN can be sustained following the laser intervention, as measured by improvement in patient-reported CIPN symptoms at the 12-week follow0up via both questionnaires used. The durable benefit suggests a delayed onset of symptom benefit beyond the immediate intervention period, which is biologically plausible as CIPN symptoms can worsen after the cessation of neurotoxicity (as seen with oxaliplatin). While accelerated recovery has not been specifically evaluated in this or prior studies, a prior study showed that PBM recipients demonstrated improvements between 4 and 8 weeks even though PBM ceased at 6 weeks. The sham group did not experience any change [42]. The NEUROLASER trial of CIPN during adjuvant taxane therapy suggested expedited recovery of breast cancer [43].

Overall quality of life was similar after treatment, and mild pain was reported more frequently in the laser group, suggesting biological activity of the intervention. While there were more reported adverse effects in the true intervention group, the majority were grade 1 and did not require treatment. Prior studies evaluating PBM for CIPN either did not report side effects, or reported only those observed at the time of the therapy. [23, 42, 43]

While symptom improvement was observed at 6 weeks in the control group, benefit was not sustained at 12 weeks, perhaps suggesting a placebo effect from the sham procedure used as a control. While the improvement may reflect the natural history of CIPN where some patients have resolution of symptoms without intervention, a systematic

review of data in a colorectal cancer population estimates the prevalence of CIPN declines by 28% per year after completion of chemotherapy [3].

There is limited published evidence evaluating laser (PBM) for CIPN; a comprehensive overview identified only two clinical studies [44]. A pilot study showed benefit in CIPN from laser acupuncture in patients with gastrointestinal cancers. Patients were treated with a 780-nm laser three times per week for 12 sessions [23]. Another study compared laser to either sham therapy or combination laser and physiotherapy in a gynaecology-oncology population and found significant reduction in CIPN with no additive benefit from physiotherapy. Patients were treated with a laser wavelength between 800–970 nm three times per week for 18 sessions [42].

The NEUROLAsER study compared PBM to inactive control for prevention of CIPN in 32 breast cancer patients receiving chemotherapy. In the study, patients received twice weekly laser for the duration of taxane treatment (12–18 weeks) with combined 905 and 808 nm wavelength. The authors reported no statistically significant difference between the control and intervention arms, with both groups appearing to benefit. There were improvements in the PBM group on selected secondary endpoints. No adverse event data were reported in that study. A further limitation is the high proportion of patients lost to follow-up ($n = 22$, 41%), and there are no data reported about dose reduction or cessation of taxane chemotherapy, which would be relevant to compare between arms in a prevention study [43].

There are challenges comparing studies using laser PBM because of heterogeneity in the delivery of intervention (treatment parameters and equipment used) and study populations (tumour type, prevention vs treatment of CIPN, concomitant interventions). This study differed from others as it included participants of heterogeneous cancer types and prior therapies. The twice-weekly treatment schedule was a compromise between maximizing potential benefit of the intervention and promoting adherence by minimizing the number of additional visits required per week in the context of the COVID pandemic. Notably, these participants were not otherwise having to regularly attend the hospital for review or treatment.

Methodological strengths of this study are the use of clinically meaningful, validated, patient-reported endpoints, and the randomised controlled study design with sham control. It is possible that the sham control had some physiological effects as it involved pressure on key points which are used in acupuncture. These include minor changes in circulation and alteration of neurophysiological responses. While this may not be an inert control, other laser trials have used a similar control strategy [27, 43]. Additional strengths of this study include a low attrition rate and high compliance with treatment and follow up visits.

Limitations of the study include the small sample size, short intervention period, unblinded clinical assessor and therapist, and unavoidable delays of study visits due to COVID-19 restrictions. Only one participant withdrew from the study due to the COVID-19 lockdown. Quantitative assessments of neuropathy such as neurophysiological studies were not performed due to resource constraints, but these may be a useful objective measure for a future trial. Whilst the non-comparative trial design did not allow for statistical comparisons between treatment and control arms in this study, the benefit of PBM warrants evaluation in an appropriately powered phase III trial.

Conclusion

This randomised trial suggests laser PBM may provide meaningful symptom benefit in patients with established CIPN, with 48% of participants having improved CIPN symptoms at the end of the treatment period, exceeding the minimal clinically important difference. Improvement in patient-reported symptom scores was sustained at 6 weeks following completion of the intervention. Further evaluation is reasonable, due to the proportion of responses in the sham arm, and to monitor long-term safety.

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Author contribution Study concept: CT; methodology: CT, JV; investigation and analysis: CT, SE; writing — original draft: CT; writing — review and editing: CT, SE, JV, PB; funding acquisition: CT, PB, JV; supervision: JV, PB.

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Data availability Any data sharing will be at the discretion of the corresponding author following a written request.

Declarations

Ethics approval and consent to participate The study protocol was approved by the Sydney Local Health District Human Research Ethics Committee–Concord Repatriation General Hospital. Informed consent was obtained from all individual participants included in the study.

Consent for publication No identifiable data included.

Competing interests The authors declare no competing interests.

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