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ORIGINAL ARTICLE

Exercise-based rehabilitation for cancer survivors with chemotherapy-induced peripheral neuropathy

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Abstract

Purpose Chemotherapy-induced peripheral neuropathy (CIPN) affects up to 40% of cancer survivors and is associated with functional deficits and an increased falls incidence. There are presently no strongly recommended treatment strategies for CIPN. The aim of this study was to evaluate the impact of a multimodal exercise intervention on CIPN symptoms and related functional deficits, as well as neurophysiologic parameters.

Methods All outcomes were assessed before and after an 8-week exercise intervention (3-weekly sessions) and preceding 8-week control period at baseline, pre-exercise and post-exercise. Outcome measures were objective and patient-reported CIPN, standing and dynamic balance, mobility, quality of life, and sensory and motor nerve excitability and conduction studies.

Results Twenty-nine cancer survivors (8 male, 21 female; mean age 61.6 ± 11.8 years) with CIPN symptoms affecting function completed all assessments. Objective and patient-reported CIPN, dynamic balance, standing balance in eyes open conditions, mobility and quality of life were improved from pre- to post-exercise ($4.0 < F < 10.2$; $p < .05$), with no changes over the control period ($p > .21$). No changes were observed in sensory or motor neurophysiologic parameters ($p > .23$).

Conclusions This study provides encouraging evidence of the rehabilitative potential of multimodal exercise for persisting CIPN in a post-treatment cohort. Large randomised controlled trials are justified to confirm observed benefits and determine the mechanisms and clinical significance.

Keywords Survivorship · Balance training · Resistance training · Aerobic training · Neurophysiology

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and persistent complication in a growing population of cancer survivors, estimated to exceed 32 million people worldwide [1, 2]. CIPN occurs in 68% of patients treated with neurotoxic chemotherapies, with lasting symptoms estimated to affect up to 40% of cancer survivors [3, 4]. CIPN commonly presents as numbness and tingling in the hands and feet, leading to reduced quality of life [5], and balance and gait

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deficits [6]. These balance and gait deficits lead to a significantly increased fall incidence in patients with CIPN [6], underscoring the need for effective intervention strategies.

There is presently no strongly recommended prevention or treatment strategy for CIPN [7], although various exercise interventions have recently shown promise in both preventive [8–11] and rehabilitative [12–15] applications. The impact of a multimodal exercise intervention on rehabilitation of CIPN symptoms and functional deficits is still unclear, however, as it has yet to be investigated in an exclusively post-treatment cohort of patients with stable CIPN symptoms affecting daily functioning. Furthermore, previous studies of exercise in CIPN are limited by a lack of comprehensive assessments of CIPN symptoms using validated measures. Although no gold standard CIPN assessment presently exists [16], a combination of validated objective measures and patient-reported outcomes is advocated to provide the most comprehensive approach [17]. Accordingly, the aim of this study is to investigate the impact of exercise as rehabilitation for cancer survivors with persistent CIPN using comprehensive assessments of patient function and CIPN symptoms.

Methods

Study design

This investigation was a prospective pilot intervention study of exercise in patients with established CIPN who had completed chemotherapy treatment. A single-group pre-post design was used, with all outcomes assessed before and after an 8-week exercise intervention and a preceding 8-week control period for a total of three assessments: baseline, pre-exercise and post-exercise. The control period was included to assess changes in outcomes occurring without a formal exercise intervention, providing a point of comparison for any changes observed from pre- to post-exercise. All participants gave their written consent prior to participation. This study was approved by the South Eastern Sydney Local Health District human ethics committee (no. 15-318), performed in accordance with the Declaration of Helsinki, and prospectively registered with the Australian New Zealand Clinical Trials Registry (Trial ID: ACTRN12616000318482).

Recruitment

Patients were recruited between September 2016 and January 2018 from Prince of Wales Hospital, Royal Hospital for Women and Chris O'Brien Lifehouse in Sydney, Australia. Eligible patients were at least 3 months post-treatment with known neurotoxic chemotherapies (bortezomib, cisplatin, docetaxel, lenalidomide, nab-paclitaxel, paclitaxel, oxaliplatin, thalidomide, vincristine, vinblastine, vinorelbine) [2] and presenting grade ≥ 2 CIPN symptoms according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Eligible patients were required to be cleared to participate in a physical activity program by a physician. Patients with musculoskeletal impairments that prevented participation in exercise were excluded.

Exercise intervention

The exercise intervention consisted of an individualised prescription of resistance training, balance training and cardiovascular exercises delivered over an 8-week period. One-hour exercise sessions were conducted three times per week; half of the sessions were completed in clinic under the supervision of a qualified exercise physiologist at two clinics in the Sydney area, with the other half prescribed and completed at the patient's home. During intervention weeks 1–4, patients attended two weekly sessions in clinic and completed one session at home. For the second half of the intervention (weeks 5–8), patients attended one weekly session in clinic and completed two sessions at home.

The intervention began (week 1, session 1) with a comprehensive clinical assessment of patient fitness and function consisting of a medical history, range of motion assessment, upper and lower body strength assessment, progressive balance assessment, and familiarisation protocol on the patient's preferred aerobic exercise modality (treadmill or stationary bike). This initial assessment provided a basis for an individualised exercise prescription, with all exercises designed to be conducted at a rating of perceived exertion (RPE) of 13–15 ('somewhat hard' to 'hard' exercise) [18] and according to American College of Sports Medicine guidelines for cancer survivors [19]. Rating of perceived exertion (RPE) was the selected intensity metric because of its strong correlation to varied objective measures of exercise intensity in all three exercise modalities [20, 21]. RPE thus facilitated simple and streamlined prescription, monitoring and progression of intensity without need for equipment both in clinic and at home.

Both clinic sessions and home exercise prescriptions were divided into roughly equal proportions of resistance training, balance training and cardiovascular exercise, with exercises prescribed based on the set-up of Table 1. Adherence to exercise prescriptions was monitored based on attendance at clinic sessions and completion of prescribed exercises at each home session as noted in patient adherence diaries.

Outcome measures

CIPN assessment tools

An objective assessment of CIPN severity was provided by the Total Neuropathy Score–clinical version (TNSc), which

Table 1 Exercise prescription framework, with sample exercises noted in parentheses

	Resistance training (two sets of each exercise; 20 min)	Balance training (two sets of each exercise; 20 min)	Cardiovascular exercise (20 min)
Session A	Upper body horizontal press (dumbbell/Theraband chest press)	Two leg exercise (tandem standing for 30 s, eyes open)	Walking, incline walking, or stationary cycling at RPE = 13–15
	Upper body horizontal pull (dumbbell/Theraband row)	Two leg exercise (tandem walk)	
	Lower body single leg press (1-leg sit-to-stand)	Single-leg exercise (single leg stance for 15 s)	
	Lower body double leg pull (Romanian deadlift)	Single-leg exercise (single leg stance with arm extension; eight reps each leg)	
Session B	Upper body vertical press (dumbbell/Theraband shoulder press)	Two leg exercise (tandem standing for 15 s, eyes closed)	Walking, incline walking, or stationary cycling at RPE = 13–15
	Upper body vertical pull (machine/Theraband lat pulldown)	Two leg exercise (tandem walk with torso rotation)	
	Lower body double leg press (squat)	Single-leg exercise (single leg stance with torso rotation	
	Lower body single leg pull (1-leg Romanian deadlift)	Single leg exercise (single leg stance, eyes closed—hands progressively moved off wall)	

RPE rating of perceived exertion

combines a clinical assessment of muscle weakness and numbness and tingling with pinprick sensibility, vibration sensibility, tendon reflex, and strength assessments [22]. Greater CIPN severity is reflected in a higher score on the TNSc (range 0–24).

The EORTC CIPN-20 questionnaire [23], a validated 20 item questionnaire regarding sensory, motor, and autonomic neuropathy symptoms, was used to assess patient-reported CIPN. Each item is scored from 1 (not at all) to 4 (very much), with the total converted to a sumscore on a scale from 0 to 100; a greater score denotes greater CIPN symptom burden.

Functional assessment tools

Mobility was evaluated using the 6-min walk test, an easy to administer assessment which has been previously demonstrated to be responsive to exercise-induced mobility improvements in a neuropathy population [24]. Patients were instructed to walk between two markers set 15 m apart as many times as possible over 6 min. Scripted verbal encouragement was given at 1-min intervals. A greater distance (metres) covered over 6 min indicated greater mobility.

Standing balance, quantified as 'postural sway', was measured using a Swaymeter (Neuroscience Research Australia, Sydney), a valid, reliable and portable method of quantifying standing balance without a force plate [25]. The Swaymeter measured the total movement of the centre of mass (millimetres), while patients stood 'as still as possible without talking' for 30 s while barefoot in four conditions of increasing difficulty: on floor with eyes open and eyes closed (stable surface); on foam with eyes open and eyes closed (unstable surface).

Lower limb strength and dynamic balance were assessed using the five-times-sit-to-stand test, a valid and reliable functional assessment previously utilised in populations with balance deficits [26]. The five-times-sit-to-stand test was conducted twice at each time point, with the average time to completion across the two tests used for analysis. A shorter time to completion reflects better leg strength and dynamic balance.

Disability and quality of life

Changes in overall disability were assessed using the CIPN Rasch Built Overall Disability Score (CIPN-R-ODS), a domain-specific disability questionnaire designed to address functional limitations relevant to CIPN [27]. Quality of life was assessed using the widely validated SF-36 instrument [28]. Both questionnaires are scored from 0 to 100, with higher scores denoting greater functional ability and better quality of life, respectively.

Neurophysiology

Nerve conduction studies were undertaken in the left tibial and sural nerves according to standard procedures [29]. Tibial nerve was stimulated at the medial malleolus, with compound motor action potentials (CMAPs) recorded from the abductor hallicus muscle. Sural nerve was stimulated mid-calf, and compound sensory action potentials (CSAPs) were recorded from the lateral malleolus. Axonal excitability testing, a technique used to quantify axonal ion channel changes [30], was performed using previously detailed protocols [31] and QTRAC software (Institute of Neurology, London, UK). The median nerve was stimulated at the wrist of the dominant

hand, while CMAPs and CSAPs were recorded from abductor pollicis brevis and the second digit, respectively. Standard excitability parameters were recorded, including recovery cycle parameters, refractoriness at 2.5 ms (change in threshold at an interstimulus interval of 2.5 ms), superexcitability (minimum mean threshold change of 3 adjacent points in the recovery cycle) and threshold electrotonus (TE) parameter TE hyperpolarizing 90–100 ms (threshold change 90–100 ms after the onset of hyperpolarizing current) [30]. Neurophysiologic test data were only available for subsets of patients due to patients declining neurophysiologic testing or recording difficulties.

Sample size calculations

Sample size was calculated based on previous study demonstrating significant improvements in mobility assessed by the 6-min walk test following a 12-week exercise intervention in patients with diabetic neuropathy [24]. Using these data and 80% power, a total of 23 participants were required to detect a significant change ($\alpha = 0.05$) in patient mobility. Compensating for a 10% drop-out rate, the required sample size was 26 patients.

Statistical analysis

Repeated measures ANOVAs were conducted for all CIPN, functional and disability/quality of life outcomes. Significant main effects were further evaluated using a least significant difference (LSD) post hoc test. Nerve conduction and excitability parameters were assessed at pre- and post-exercise time points using a dependent samples t test. All analyses were conducted in SPSS Statistics 24.0 (IBM; Armonk, NY), with significance set at $\alpha = 0.05$. All values are reported as mean ± standard error.

Results

Thirty-five patients were enrolled and completed baseline testing, with data available for analysis for 29 patients who successfully completed the exercise intervention (see Fig. 1 for CONSORT diagram, including details of patient drop outs). Patients who were contacted but did not enrol ($N = 36$; mean age 61.5 years) were similarly aged to enrolled patients. The majority of patients received paclitaxel (37.9%) or oxaliplatin treatment (31.0%) and reported numbness and/or tingling in both the hands and feet (82.8%); all patients reported CIPN symptoms in the feet. Full patient demographics are reported in Table 2.

Overall intervention adherence was 83.1%; patients attended 97.5% of clinic sessions (11.7 of 12 sessions; range 10–12 sessions) and completed 66.7% of prescribed home exercises (range 0–100%; median 69.5%).

Effects of exercise on CIPN, disability and quality of life

Data for all outcomes are displayed in Table 3. The exercise intervention significantly improved symptoms of CIPN, both patient-reported (CIPN20, $p < .01$, Fig. 2a) and objectively assessed (TNSc, $p < .01$, Fig. 2b), with no significant change over the control period ($p > .34$). Similarly, patient-reported disability was significantly reduced from pre- to post-exercise (CIPN-R-ODS, $p < .03$), with no significant change over the control period ($p = .82$). Quality of life was also significantly improved from pre- to post-exercise (SF-36, $p < .01$), with, again, no significant change over the control period ($p = .88$).

Effect of exercise on functional and neurophysiological parameters

Six-minute walk distance was significantly increased following the exercise intervention ($p < .02$), with no significant change in the control period ($p = .22$), indicating intervention-induced mobility improvements. Similarly, dynamic balance, measured by the five-times-sit-to-stand test, was improved following exercise ($p < .03$; control period $p = .47$). Standing balance tasks performed with eyes open on both stable and unstable surfaces were significantly improved from pre- to post-exercise ($p < .02$, Fig. 3a), with no significant changes from baseline to pre-exercise ($p > .38$). However, standing balance tasks performed with eyes closed on both stable and unstable surfaces did not significantly improve pre- to post-exercise ($p > .12$, Fig. 3b), although there was some improvement over the control period on the unstable surface ($p < .02$).

Exercise did not produce any significant changes in sensory or motor nerve amplitudes in either the upper or lower limbs ($p \geq .24$). Sensory and motor excitability parameters did not demonstrate changes following the exercise intervention ($p \geq .46$) (Table 3). Patients with available neurophysiologic data were demographically similar to the overall cohort in age and time since completion of neurotoxic cancer treatment ($p > .71$).

Discussion

This study provides evidence that 8 weeks of multimodal exercise training can reduce CIPN symptoms and related functional and quality of life deficits in cancer survivors with persistent CIPN. Using comprehensive and validated CIPN and functional assessments in a well characterised patient

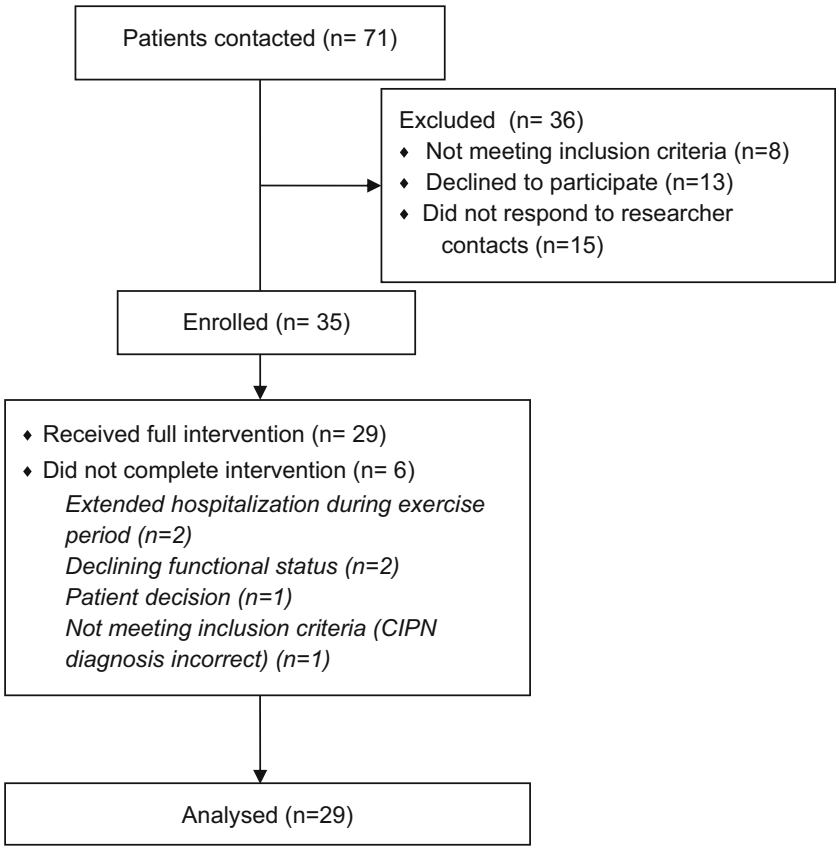

Fig. 1 CONSORT diagram

population, the study suggests that exercise training may be a useful rehabilitative strategy in established CIPN. Patient perceptions of the benefit of this exercise program to their CIPN symptom burden and quality of life are highly significant. However, further research is necessary to clarify the specific mechanisms and clinical and long-term impact of these exercise-induced improvements.

Table 2 Patient characteristics

Mean age, years (range)	61.6 (32–79)	
Sex (female/male)	21:8	
Months since neurotoxic chemotherapy, mean (range)	18.7 (3–156)	
	N	%
Cancer type		
Breast	11	37.9
Colorectal	8	27.6
Ovarian	4	13.8
Endometrial	2	6.9
Appendix	1	3.4
Lymphoma	1	3.4
Myeloma	1	3.4
Urothelial	1	3.4
Neurotoxic chemotherapy type		
Paclitaxel	11	37.9
Oxaliplatin	9	31.0
Paclitaxel + carboplatin	6	20.7
Bortezomib	1	3.4
Cisplatin	1	3.4
Vincristine	1	3.4

The present study provides evidence of the ability of exercise to rehabilitate functional deficits in patients with CIPN, as well as reduce the severity of established and stable CIPN symptoms. Given the varying recovery timelines of the natural course of chronic CIPN related to interpatient variability and time since completion of chemotherapy [32], it was not expected that major changes would occur during the control period, in contrast to the clear benefits seen in the intervention. Previous research has demonstrated that exercise may be able to attenuate the progression of CIPN symptoms and functional deficits during chemotherapy treatment [8–11], as well as reduce CIPN symptoms and improve balance in combined cohorts of on- and off-treatment patients with established CIPN [12–14]. Study of a similar post-treatment cohort affected by CIPN symptoms demonstrated that balance training exercises alone reduced pain and improved tendon reflexes and vibration sensibility, but without improvements in patient-reported CIPN, standing balance or neurophysiology [15]. Accordingly, resistance and/or aerobic training components of the intervention in the present study appear to provide additional symptom and functional benefits. Improvements in

Table 3 Data for all outcomes at each time-point. All data presented as mean (standard error)

		N	Baseline	Pre-exercise	Post-exercise	*p*	*F*
Objective CIPN	TNSc	29	6.7 (0.6)	7.0 (0.7)	5.3 (0.5)*+	.001	8.5
Patient-reported CIPN	CIPN-20	29	26.6 (3.3)	25.4 (3.0)	18.5 (2.3)*+	< .001	10.2
Patient-reported disability	CIPN-R-ODS	29	80.2 (2.4)	79.9 (2.7)	83.2 (2.4)*	.04	3.4
Quality of life	SF-36	29	61.6 (3.9)	60.5 (3.7)	69.1 (3.6)*+	.003	6.6
Mobility	6-min walk test (m)	29	442.1 (18.2)	452.1 (17.4)	469.9 (20.5)*+	.02	4.7
Dynamic balance/leg strength	Five times sit-to-stand (s)	29	13.6 (1.1)	13.1 (0.8)	11.8 (0.6)*+	.03	4.0
Standing balance	Postural sway (mm)						
	Stable surface, eyes open	29	155.5 (28.0)	140.9 (23.6)	104.2 (13.6)*+	.006	5.8
	Stable surface, eyes closed	28	214.5 (22.7)	188.4 (24.3)	167.4 (17.2)+	.02	4.3
	Unstable surface, eyes open	28	246.5 (24.4)	230.1 (26.9)	165.8 (9.0)*+	.003	6.6
	Unstable surface, eyes closed	24	436.3 (36.5)	366.2 (24.2)+	345.0 (29.2)+	.01	5.6
Sensory neurophysiology	Peak sural amplitude (μV)	15		6.4 (1.5)	5.9 (1.3)	.45	
	Peak median amplitude (μV)	17		22.6 (3.1)	24.3 (2.7)	.66	
	Refractoriness (%)	17		14.9 (4.1)	13.3 (2.5)	.76	
	TEh90-100 ms (%)	17		− 138.0 (5.6)	− 135.6 (6.0)	.79	
	Superexcitability (%)	17		− 16.8 (1.0)	− 16.7 (1.2)	.91	
Motor neurophysiology	Peak tibial amplitude (mV)	17		7.5 (0.9)	7.0 (1.1)	.24	
	Peak median amplitude (mV)	24		8.3 (0.5)	8.7 (0.5)	.47	
	Refractoriness (%)	24		20.9 (4.6)	23.9 (4.5)	.61	
	TEh90-100 ms (%)	24		− 119.8 (3.5)	− 115.7 (3.5)	.46	
	Superexcitability (%)	24		− 22.9 (1.3)	− 22.9 (1.2)	.97	

N values refer to the number of complete patient datasets available for analysis. *p* and *F* values for functional, symptom, quality of life and disability outcomes are reported with respect to ANOVA main effects

*Significantly different from pre-exercise ($p < .05$)

+ Significantly different from baseline ($p < .05$)

mobility, disability and quality of life in the present study mirror results of other investigations of exercise interventions in cancer survivors not specifically designed to target neuropathy [33]. The present findings also underscore the importance of selection of appropriate outcome measures in CIPN studies [34]; interpretation of results in the present study is strengthened by the inclusion of a comprehensive CIPN assessment strategy [17], objective neurophysiologic endpoints and a range of relevant and validated functional and quality of life measures.

Further research is still required to provide insights regarding the mechanisms of functional and symptom benefits observed in the present study given the absence of changes in motor and sensory axonal excitability and nerve conduction studies in the upper and lower limbs. Exercise-induced sensory neurophysiologic changes have been previously reported in studies of diabetic neuropathy [35] and peripheral nerve injury [36], albeit in parameters related to cutaneous fibre density and axonal outgrowth rather than maximum conduction amplitude and ion channel functioning. Accordingly, it remains possible that the mechanisms of recovery differ from the mechanisms of neurophysiologic changes underlying CIPN [30] and that exercise-induced neurophysiologic changes did occur but were not detectable by nerve conduction or axonal excitability studies. It is also possible that symptom improvements may be secondary to generalised recovery of quality of life deficits associated with CIPN [5]. Conversely, however, it is also possible that the observed functional improvements may simply be a result of training adaptations to established and unchanged neurophysiologic deficits; strength gains and spinal and cortical changes proposed in healthy and other clinical populations [37] provide potential explanations.

Selective improvements in standing balance with eyes open but not eyes closed were observed in the present study. The specificity of functional training adaptations [38] forms the most likely explanation for this selective improvement—while a small portion of balance training exercises were conducted with the eyes closed, the majority of the intervention was conducted with the eyes open. Significant improvements from baseline to pre-exercise in the most difficult balance condition (eyes closed, unstable surface) suggest that practice effects may be more significant in this most challenging test condition, as has been previously reported [39]. Prior study also indicates that sensory feedback is more strongly relied upon in standing balance tasks with eyes closed [40],

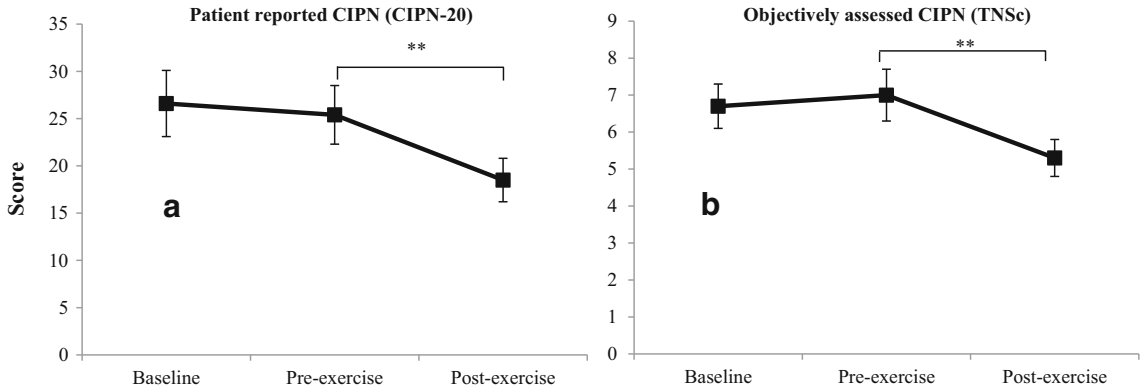

Fig. 2 **a** Patient reported CIPN. **b** Objectively assessed CIPN. Changes in CIPN symptoms with respect to the control and exercise intervention periods. **= $p < .01$

suggesting that exercise-induced improvement in sensation may not be of sufficient magnitude to eliminate deficits in standing balance with eyes closed.

Although the observed statistically significant improvements are promising, minimum clinically meaningful differences are yet to be established for any of our assessments in a CIPN population [34]. With respect to symptom improvements, prior studies using similar patient reported outcomes have classified 7–10% improvements in patient-reported CIPN as being clinically significant [41], suggesting clinically meaningful changes in patient-reported CIPN in the present study (CIPN-20 score − 27.2% from pre- to post-exercise); similar precedents are not available for TNSc scores. Improvements in postural sway in eyes open conditions moved our cohort from above to below mean values of elderly cohorts experiencing one or multiple [42] falls in the subsequent year, although, again, the clinical significance of this improvement in CIPN patients has yet to be determined. With respect to established values in other cohorts, improvements in quality of life [43] but not mobility and dynamic balance [44, 45] were clinically meaningful, albeit with similarly unclear relevance to CIPN.

Similarly, while the present study demonstrates exercise benefits using a comprehensive battery of validated outcomes, it remains ultimately limited by its small cohort, single-group design and lack of a follow-up assessment. The small cohort and single group design may reduce the prospective generalisability of results presented due to the potential influence of selection and recruitment biases. A randomised controlled trial with a large cohort would minimise these biases and is thus required to build the evidence base necessary to justify the integration of exercise training into standard care for survivors with CIPN as per recent recommendations [46]. Further, examination of the persistence of exercise intervention benefits over time in this population will require study designs including follow-up assessments. Additional investigations are also needed to elucidate the mechanisms and clinical relevance of exercise benefits, determine the impact of baseline fitness levels, inform the optimisation of the frequency, intensity, timing and types of exercises in the intervention, and determine the optimal delivery modality (i.e. clinic vs. home-based) for survivors with persistent CIPN.

In conclusion, this study provides promising evidence, using comprehensive assessments, of the rehabilitative potential of exercise for cancer survivors with persisting CIPN. Eight weeks of exercise training significantly reduced CIPN symptom burden and disability, and improved standing and dynamic balance,

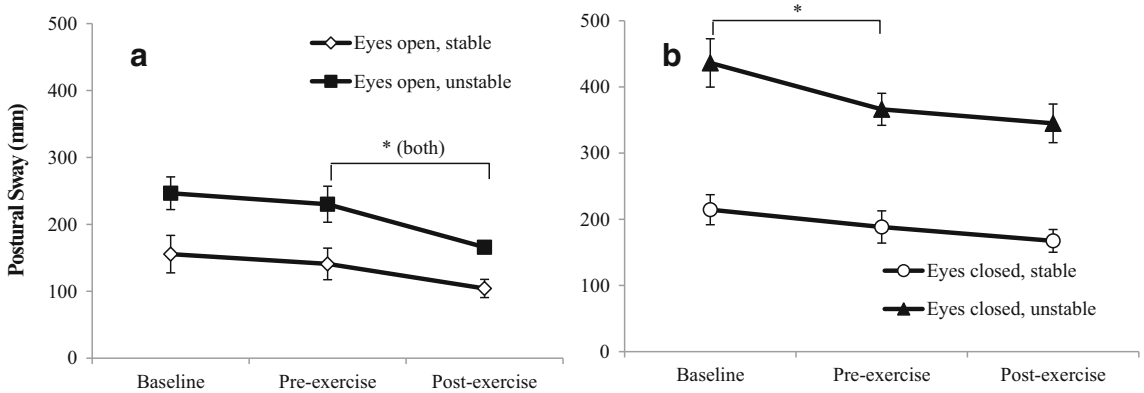

Fig. 3 **a** Eyes open conditions. **b** Eyes closed conditions. Changes in standing balance (postural sway) with respect to the control and exercise intervention periods. *= $p < .05$. For clarity, significant results only highlighted with respect to control (baseline to pre-exercise) and exercise intervention (pre- to post-exercise) periods

mobility and quality of life. As the identification of strategies to ameliorate CIPN are critical to ensure quality of life in cancer survivorship, large randomised controlled trials are justified to confirm observed benefits and determine the mechanisms and clinical significance of exercise effects in CIPN.

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Compliance with ethical standards

All participants gave their written consent prior to participation. This study was approved by the South Eastern Sydney Local Health District human ethics committee (no. 15-318), performed in accordance with the Declaration of Helsinki, and prospectively registered with the Australian New Zealand Clinical Trials Registry (Trial ID: ACTRN12616000318482).

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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