

To Compare the Effect of Instrument Assisted Proprioceptive Training versus Conventional Proprioceptive Training on Peripheral Neuropathy and Balance in Colorectal Cancer Subjects Following Oxaliplatin Chemotherapy - A Comparative Study

Pruthvika Holmukhe¹, Trupti Yadav²

¹MPT Student, Krishna College of Physiotherapy, Krishna Vishwa Vidyapeeth "Deemed to Be University", Karad, India.
Corresponding Author Email: [holmukhepruthvika\[at\]gmail.com](mailto:holmukhepruthvika[at]gmail.com)

²Associate professor, Head of the department, Department of Oncology Physiotherapy, Krishna College of Physiotherapy, Krishna Vishwa Vidyapeeth "Deemed to Be University", Karad, India

Running Title: *The Effect of Instrument Assisted Proprioceptive Training versus Conventional Proprioceptive Training on Peripheral Neuropathy and Balance in Colorectal Cancer Subjects Following Oxaliplatin Chemotherapy.*

Abstract: **Background:** Peripheral neuropathy and loss of balance following oxaliplatin chemotherapy are major challenges facing colorectal cancer subjects as a side effect of the chemotherapeutic agent. It damages various cells in different ways, leading to neuropathy through a complex interaction among sensor cells, neurons, glial cells, and effector cells. These alterations in nerve function led to impaired reception, transmission, and response to stimuli, which consequently affect one's tactile sensory perception, inappropriate proprioceptive feedback, and hence impaired postural control and loss of balance in this subject. **Aim:** To study and compare the effects of instrument-assisted proprioceptive training using a modified trampoline with conventional proprioceptive training on peripheral neuropathy and balance in colorectal cancer subjects following oxaliplatin chemotherapy. **Subjects and Methods:** A total of 90 colorectal cancer subjects aged between 41 and 60 who have completed 12 cycles of oxaliplatin chemotherapy were selected by the convenience sampling method. In this comparative study, subjects were divided into Group A (n = 45) for instrument-assisted proprioceptive training and Group B (n = 45) for conventional proprioceptive training for 4 weeks. The pre- and post-assessment of peripheral neuropathy and balance was done using the FACT-GOG-NTX scale and the Brief BEST test, respectively. **Results:** There was an extremely significant difference in peripheral neuropathy and balance between groups post-treatment ($p < 0.0001$). Comparison between groups post-treatment revealed a significant decrease in peripheral neuropathy and thus an increase in the ability to maintain static as well as dynamic balance with instrument-assisted training (Group A) than to conventional proprioceptive training (Group B) ($p < 0.05$). **Conclusion:** The result suggested that instrument-assisted training was more effective than just conventional proprioceptive training to reduce peripheral neuropathy and improve balance in colorectal cancer subjects following oxaliplatin chemotherapy.

Keywords: oxaliplatin, peripheral neuropathy, balance, proprioception, modified trampoline

1. Introduction

Peripheral neuropathy is a well-recognised and unfortunate consequence often encountered by subjects undergoing antineoplastic chemotherapy for cancer treatment.¹ Cancer is commonly characterised by the rapid creation of abnormal cells that grow beyond their usual boundaries.² According to the National Cancer Registry Programme of the Indian Council of Medical Research (ICMR), India's growing cancer burden, i.e., cancer cases and deaths from the same, has increased in India between 2020-2022.³ Among these, colorectal cancer is the second leading cause of cancer-related deaths & is the third most common cancer in men & women.³

There are various treatments available to treat cancer; these treatments can lead to nerve involvement, nerve damage, and nerve pain.⁴ One specific treatment, known as antineoplastic chemotherapy, involves interventions aimed at eradicating

tumours by acting on cell division and the cell cycle.⁵ However, this can result in the interruption and proliferation of cells, causing toxicity² to the peripheral nerves and leading to a condition called peripheral neuropathy following chemotherapy.⁶ The effect of chemotherapy on the nervous system varies among different classes of medications⁷, such as platinum-based drugs like oxaliplatin and cisplatin, as well as other agents like docetaxel, ixabepilone, and thalidomide.⁷ Among these chemotherapeutic agents, oxaliplatin is a commonly used choice of anti-neoplastic chemotherapy treatment in colorectal cancer subjects.^{8,9}

Neuropathy onset may vary depending on the cumulative doses of the chemotherapeutic agent used.⁷ A total dose of 540–850 mg/m² of the oxaliplatin chemotherapeutic agent is typically administered, which is equivalent to 9–10 cycles at a dose of 85 mg/m², or 6 cycles at a dose of 130 mg/m² which causes peripheral neuropathy in these cancer subjects

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following oxaliplatin chemotherapy.¹⁰The specific agent used and the quantity of chemotherapy sessions received affect the incidence and prevalence of peripheral neuropathy.^{7,11}This demonstrates that peripheral neuropathy is more common (68.1%) following the first month of chemotherapy treatments.⁷

When comparing changes in small and large nerve fiber function tests, it is suggested that oxaliplatin primarily affects large myelinated nerve fibers.¹² Specifically, large myelinated fibers types IA and II sensory neurons are responsible for proprioceptive sensitivities.¹³The effects of oxaliplatin have been observed to increase the amplitude and duration of compound action potentials as well as a prolong of the refractory period of peripheral nerves.¹² These alterations in nerve function led to impaired reception, transmission, and response to stimuli, which consequently affect one's tactile sensory perception.¹² Additionally, sensory and motor nerve damage occurs, ultimately resulting in the loss of proprioception and balance in subjects following oxaliplatin chemotherapy.¹²For each symptom reported by subjects, they are assessed on an Oxaliplatin Sanofi-specific scale.¹²

Proprioception, or awareness of one's own body's position and motion, is essential for maintaining equilibrium and coordinating movements.¹³ Impaired proprioception can cause balance issues, an elevated risk of falling, and a lower quality of life.⁶ In order to enhance balance and proprioception in different populations, therapies focusing on proprioceptive training have been investigated.¹⁴This study compares the effects of traditional proprioceptive training with instrument-assisted proprioceptive training on peripheral neuropathy and balance in oxaliplatin-treated colorectal cancer subjects.

Conventional proprioceptive training focuses on exercises that improve body awareness and control, such as single-leg stance and heel-to-toe walking, as well as standing with a narrow base of support on an even surface like the floor or a mat.^{15,16}On the other hand, instrument-assisted proprioceptive training involves the use of specialised devices such as balance boards, wobble boards, foam pads, and trampolines.¹⁷Modified Trampoline is a recent method of rehabilitation used for proprioceptive training.¹⁸It consisted of not only static balance training, such as standing and weight shifting, but also dynamic balance training, including walking and performing tasks.¹⁸Therefore, it not only improves the subjects static balance but also enhances their ability to maintain their dynamic balance, which distinguishes it from conventional proprioceptive training.¹⁸

2. Literature Survey

- 1) Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, Colvin LA, Fallon M. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain@*. 2014 - This study provides a qualitative summary of factors reported to alter the risk of CIPN. It states that Different chemotherapy drugs were associated with differences in CIPN prevalence.CIPN prevalence was 68.1% when measured in the first month after chemotherapy, 60.0% at 3 months and 30.0% at 6 months or more.
- 2) Joohee hahn, pt, msc, seonhae shin, jd, wanhee lee, PT, PhD 2015 - In this study it shows the effect of modified trampoline training on balance, gait and fall efficacy of stroke patients. Subjects were randomly allocated to one of two groups by using BBS and TUG test results found that improvement was significantly greater in trampoline group than in the control group and is effective at improving balance, dynamic gait and fall efficacy after stroke.
- 3) Fernandes J, Kumar S. Effect of lower limb closed kinematic chain exercises on balance in patients with chemotherapy-induced peripheral neuropathy: a pilot study. *International Journal of Rehabilitation Research*. 2016 Dec.- The present study concludes that CKC exercises are helpful in treating the symptoms associated with CIPN.Patients were assessed at baseline using the mTNS and Berg Balance Scale and reassessed after 15 sessions. mTNS score decreased and Berg Balance Scale increased but the limitations of this study were that a long-term follow-up and fatigue level did not assess.
- 4) Marshall TF, Zipp GP, Battaglia F, Moss R, Bryan S. Chemotherapy-induced-peripheral neuropathy, gait and fall risk in older adults following cancer treatment. *Journal of Cancer Research and Practice*. 2017-This study suggested that gait speed and step length are key indicators for fall risk.cancer patients with CIPN may display slower gait velocities, shorter step length, and are at an increased fall risk as indicated by TUG scores. The presence of CIPN appears to increase fall risk, which may easily be assessed in a clinical setting using the TUG test.
- 5) Andhare N, Yeole UL, Malusare as. Effect of proprioceptive training on balance in cancer patients with chemotherapy induced peripheral neuropathy. *Int J Physiother Res*. 2019 - In this study, it shows effect of proprioceptive training on balance in cancer patients with CIPN. Pre and Post Intervention Berg Balance Scale and mTNS score were noted. The study concluded that there is significant effect of Proprioceptive training on balance in CIPN.
- 6) KAUR J, SINGH A, GREWAL S. 2020 - In this study it shows effect of balance training with improvement in dynamic posture control and dynamic balance among collegiate female athletes when it is performed on unstable surface as compared to when it is performed on stable surface.

Participants and methods

With a sample size of 90 participants, convenience sampling was used to perform this comparison study.They were divided into two groups: Group A, Instrument Assisted Proprioceptive Training (n=45), and Group B, Conventional Proprioceptive Training (n=45). The participants underwent scrutiny based on inclusion and exclusion criteria, and consent was obtained from those who met the inclusion criteria.

Inclusion Criteria: Both male and female subjects willing to participate, aged between 41 and 60 years, diagnosed with colorectal cancer, and having completed six cycles of

oxaliplatin chemotherapy as part of their antineoplastic treatment. Additionally, subjects who scored Grade 3 on the Oxaliplatin Sanofi Specific Scale were included.¹²

Exclusion Criteria: Subjects over the age of 60 were excluded. Subjects with balance issues caused by other neurological problems (such as brain tumour or metastasis or multiple myeloma) were also excluded. Additionally, subjects with a MMT (Manual Muscle Testing) strength grade of less than 3 for bilateral lower limb muscle and those with other systemic problems (such as vision or auditory disorders, severe dyspnoea, chest pain, peripheral vascular disease, osteoporosis and recent unhealed lower limb fracture or deformity) were excluded. Subjects with a past or present history of diabetes mellitus were also excluded.

Outcomes: Functional Assessment of Cancer Treatment Gynecologic Oncology Group Neurotoxicity (FACT-GOG-NTX) subscale in a longitudinal study of cancer patients treated with chemotherapy.¹⁹ Health, Neuropathy, and quality of life outcomes and the Brief Balance Evaluation Systems (Brief BEST) test for the assessment of balance. The Brief BEST test is a clinical balance assessment tool and an abbreviated version of the Balance Evaluation Systems

Test (BESTest).²⁰ It is designed to assess both static and dynamic balance.²⁰

3. Statistical Analysis

IBM SPSS statistical software (version 25; IBM, ARMONK, NY, USA) was used to analyse the data in this study. Descriptive statistics like the mean and standard deviation were computed to provide a summary of the data. To analyse the significance of the difference between the pre- and post-values of the FACT-GOG-NTX score and the Brief BEST Test among the groups using the paired student t test and "p" values. Z tests were also carried out to look into the link between the post values of the Brief BEST Test and the FACT-GOG-NTX score for the comparison of the two groups. These statistical techniques aided in evaluating the relationships and variations between the variables of interest and gave useful insights into the data.

4. Results

A total of 90 samples were taken. Out of 45 participants in instrument-assisted proprioceptive training showed an extremely significant effect on the Brief Best Test and the FACT-GOG-Ntx scale.

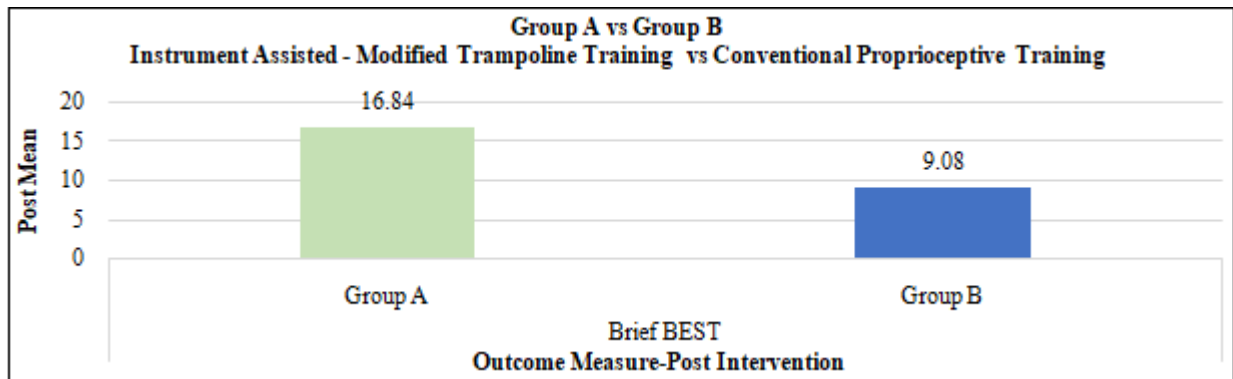
Table 1: Baseline Characteristics:

Characteristics		Mean±SD (Group A)	Mean±SD (Group B)
Age		51.17 ±4.493	51.11±4.553
Pre-Brief-BEST		8.66±1.079	8.64±1.246
Post-Brief-BEST		16.84±1.224	9.08±1.427
Pre FACT-GOG-NTX	Physical Well- Being	14.57±1.454	14.22±1.38
	Social Well – Being	14.93±3.407	12.86±2.446
	Emotional Well -Being	12.64±2.091	12.11±2.036
	Functional Well -Being	11.24±1.956	11.42±1.751
	Neuropathy	30.82±5.844	28.04±4.348
Post FACT-GOG-NTX	Physical Well- Being	26.15±1.595	14.89±1.945
	Social Well - Being	23.31±3.456	13.2±2.702
	Emotional Well -Being	21.28±1.89	12.51±2.139
	Functional Well -Being	23.68±2.429	11.77±1.941
	Neuropathy	8.93±1.558	27.71±4.341
Post Brief-BEST		16.84±1.224	9.08±1.427
Post FACT-GOG-NTX	Physical Well- Being	26.15±1.595	14.89±1.945
	Social Well – Being	23.31±3.456	13.2±2.702
	Emotional Well -Being	21.28±1.89	12.51±2.139
	Functional Well -Being	23.68±2.429	11.77±1.941
	Neuropathy	8.93±1.558	27.71±4.341

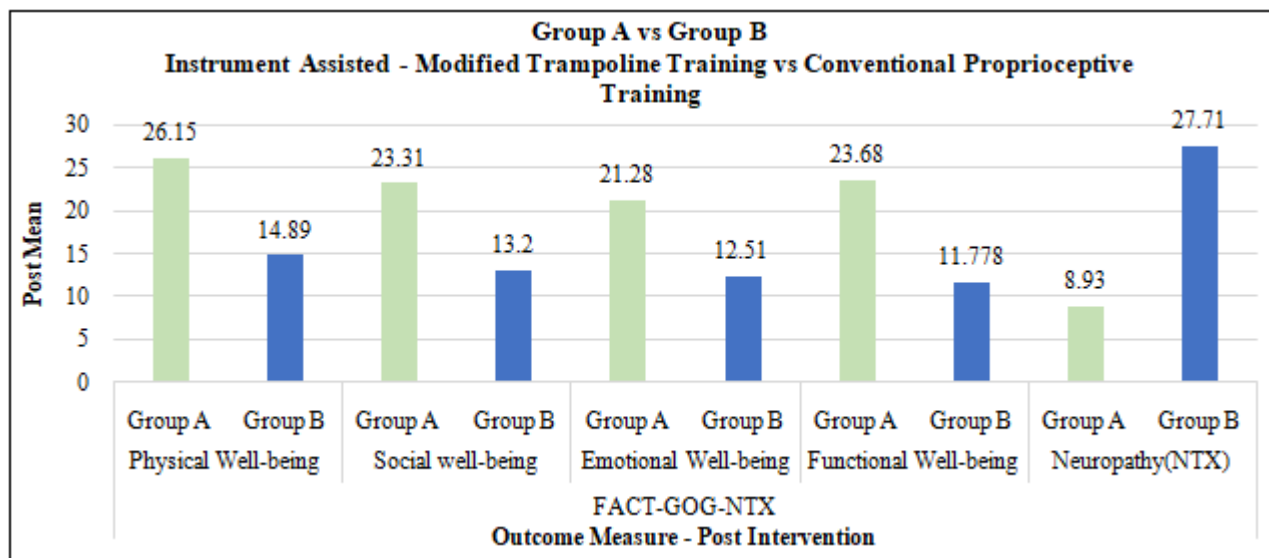
Table 2: Comparison of Post values of Brief BEST Test and FACT-GOG-NTX Score between Instrument Assisted Training (Group A) and Conventional Proprioceptive Training (Group B).

Parameters	Outcome Measure	Group A		Group B		Z score	p-value
		Post		Post			
		Mean	SD	Mean	SD		
a. Balance	Brief BEST Score	16.84	1.224	9.08	1.427	27.5813	0.0001*
b. FACT-GOG -NTX	Physical Well- Being	26.15	1.595	14.89	1.945	30.0287	0.0001
	Social Well – Being	23.31	3.456	13.2	2.702	15.0927	0.0001
	Emotional Well -Being	21.28	1.89	12.51	2.139	20.3868	0.0001
	Functional Well -Being	23.68	2.429	11.77	1.941	25.4051	0.0001
	Neuropathy	8.93	1.558	27.71	4.341	26.8999	0.0001*

These results highlight the substantial impact of instrument-assisted training on improving balance and peripheral neuropathy and its superiority over conventional proprioceptive training in this context.



Graph 1a: Comparison of Post values of Brief BEST Test between Instrument Assisted Training (Group A) and Conventional Proprioceptive Training (Group B).



Graph 1b: Comparison of Post values of FACT-GOG-NTX score between Instrument Assisted Training (Group A) and Conventional Proprioceptive Training (Group B).

The post-differences of the FACT-GOG-NTX score and the Brief BEST Test score in Groups A and B are shown in Graphs 1a and 1b, respectively. Notably, it can be seen that after receiving instrument -assisted Training in Group A, the mean values of the Brief BEST Test and FACT-GOG-NTX score show an improvement in balance and peripheral neuropathy in participants with colorectal cancer who have received Oxaliplatin chemotherapy. This improvement is evident as the post-mean of Group A is higher than the post-mean of Group B.

5. Discussion

The aim of the study was to study and compare the effect of instrument-assisted proprioceptive training using a modified trampoline with conventional proprioceptive training on peripheral neuropathy and balance in colorectal cancer subjects following oxaliplatin chemotherapy. Both acute and chronic types of peripheral neuropathy can be brought on by the chemotherapy drug oxaliplatin. It was discovered that patients with colorectal cancer were more likely to develop chronic neuropathy (80.7%)²¹ and its risk factors.²¹ The quality of life for cancer patients and survivors are

significantly impacted by this high incidence of chronic neurotoxicity.²² Subjects who had taken 6 cycles of chemotherapy with the anticancer drug oxaliplatin were included in this study.²³ As according to L Kang et al., chemotherapy which is equivalent to 9–10 cycles at a dose of 85 mg/m² or 6 cycles at a dose of 130 mg/m² causes peripheral neuropathy in cancer subjects when treated with oxaliplatin antineoplastic chemotherapy agent.²³

In the study, both males and females were included. In accordance with gender and the regional area from which the subjects for this study were selected, more than 60% of the population in the present study was male. This outcome is consistent with the conclusions reached in India by Smita Asthana et al., which state that, comparatively, men are more likely than women to develop colorectal cancer,²⁴ and the risk is highest in the Northeast region of India, followed by the South and Eastern regions of India.²⁴ Dietary factors like the consumption of beef, strong spices, and red meat may have contributed to the greater occurrence in these areas.²⁴

The study of Fatima A. Hagger et al. which concluded that Age-related familial and hereditary risk factors, as well as environmental lifestyle-related risk factors like physical

inactivity, obesity, smoking, and alcohol consumption, can all contribute to the likelihood of a colorectal cancer diagnosis after the age of 40, increasing gradually from that age onward, and sharply increasing after the age of 50.²⁵ Hence, the current study focused on the inclusion of the age group between 41 and 60 years (mean age 51.14).

Compared to cancer survivors without peripheral neuropathy, cancer survivors with peripheral neuropathy reported lower balancing function and worse quality of life (QOL) scores, particularly in the area of physical functionality.^{26,27,28} Peripheral neuropathy following chemotherapy is characterised by various neuromuscular symptoms resulting from nerve damage caused by the neurotoxic effects of chemotherapy drugs, which exert neurotoxic effects on different components of the afferent nerve, including the axon, mitochondria, voltage-gated channels, cell body, and dorsal root ganglion neurons, and result in numbness, tingling, burning sensation, discomfort, ataxia, loss of deep tendon reflexes, diminished sensation of touch, vibration, proprioception, muscle weakness, and balance issues.^{4,7,29,30} Peripheral neuropathy reduces somatosensory feedback,^{34,35} which is crucial for maintaining stable ambulation³⁶. Abnormalities in ambulation increase the risk of balance loss and falling, ultimately impacting the quality of life (QOL) among cancer survivors.^{31,32,33} Also, muscle weakness resulting from peripheral neuropathy can reduce the QOL of cancer patients.³⁷ According to the study done by Kober KM, cancer survivors with peripheral neuropathy exhibit lower balance function and worse QOL scores compared to those without peripheral neuropathy, which states that, in cancer survivors, physical function and QOL are highly correlated; poor physical function results in low QOL among them.^{38,39} Also, Shinichiro Morishita et al. stated that poorer quality of life among cancer survivors may be linked to reduced balancing function.⁴⁰

Shaoning Guo et al. study found that combined exercise can help cancer patients with chemotherapy-induced peripheral neuropathy to improve their quality of life (QOL), physical function (such as balance control and muscle strength), and their ability to tolerate neuropathic pain⁴¹. The advantages of exercise, particularly sensorimotor training, in assisting lymphoma patients receiving treatment were also stressed by F. Streckmann et al. According to their research, exercise therapies have the potential to improve QOL, reduce side effects such as peripheral neuropathy and boost balance, physical performance, and mobility.⁴² But there is no research devoted to reducing peripheral neuropathy and its associated impact on balance and quality of life (QOL) in patients with colorectal cancer receiving oxaliplatin-based anticancer therapy.

In the present study, subjects with colorectal cancer showed extremely significant improvements in balance, peripheral neuropathy, and hence their quality of life (QOL). Instrument-assisted proprioceptive training on a modified trampoline has contributed to these changes.⁴³ This might be due to advancements in proprioception, which is controlled by skin receptors on the soles of the feet and mechanoreceptors in muscles and joints. Mechanoreceptors in the muscles and joints provide more afferent input as a

result of postural sway on unstable surface and thus enhance proprioceptors activation.⁴⁴ Proprioceptive training on a modified trampoline consists of four phases of training: standing, transferring weight, walking, and doing tasks. Therefore, gravity also aids in enhancing proprioception and other sensory systems that are important for maintaining balance.⁴⁵

Changes in complex sensory motor stimulation with eyes closed may help participants perform better on balancing tests as they become accustomed to the unsteady trampoline surface which helps to retain their balance. Additionally, practicing balance on an unsteady surface activates receptors in tendons, ligaments, and joints.⁴⁶ Improved balance and mobility may result from the unstable surface's stimulation of the somatosensory system.⁴⁷ By boosting their functional status, balance training has been shown to enhance the QOL of cancer patients, claim Kneis S. et al.⁴⁸

The results of the current study demonstrated that, in contrast to conventional proprioceptive training, instrument-assisted modified trampoline training in colorectal cancer subjects following oxaliplatin chemotherapy significantly improved their balance assessed with the Brief BEST test (p value = 0.0001) and peripheral neuropathy and quality of life assessed with FACT-GOG-NTX score (p value = 0.0001)

6. Conclusion

The result suggested that instrument-assisted training was more effective than just conventional proprioceptive training to reduce peripheral neuropathy and improve balance in colorectal cancer subjects following oxaliplatin chemotherapy.

7. Limitation

This study had some limitations, and we suggest that more research be conducted to determine the effects of modified trampoline training in these subjects, with a focus on utilizing strength as an outcome.

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