Sensory-Enhanced Balance Training versus Conventional Balance Training for Improving Balance and Quality of Life in Patients with Chemotherapy-Induced Peripheral Neuropathy: A Randomized Controlled Trial.

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KEYWORDS

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ABSTRACT

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent side effect of cancer treatment, significantly affecting patient balance, mobility, and quality of life. Despite the potential of exercise-based interventions is known to affect the symptoms of CIPN, the comparative efficacy of adding sensory-enhanced balance training remains unexplored.
Objective: The objective of present study evaluates the comparative efficacy of Sensory-Enhanced Balance Training versus conventional balance training in improving balance and quality of life in patients undergoing treatment with paclitaxel and carboplatin.
Methods: A single-blind, parallel-group randomized controlled trial with 72 participants with grade 2-3 CIPN were randomized to receive either sensory-enhanced balance training (intervention group) or conventional balance training (control group). Both interventions were given be conducted 4 times weekly over 8 weeks. Primary outcomes include balance performance (Modified clinical test of sensory interaction on balance (mCTSIB), Timed Up and Go test) and quality of life (EORTC QLQ-CIPN20). Statistical analysis was conducted using paired and unpaired t-tests.
Results: The intervention group exhibited significantly greater improvements in balance (p- 0.0001) and quality of life ($p<0.0001$) as compared to the control group.
Conclusion: Sensory-enhanced balance training is superior to balance training alone in improving balance and a valuable intervention to improve the quality of life in cancer patients.
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Introduction:

The estimated number of new cancer cases in India for the year 2022 was reported to be 14,61,427, with a crude rate of 100.4 per 100,000 individuals. In India, one in nine individuals is likely to develop cancer at some point in their life [1]. With more effective targeted cancer treatments, long-term cancer survival is rising in high-income countries [2]. Most current cancer treatment strategies primarily involve the surgical removal of tumors, combined with physical

treatments like radiotherapy and chemical treatments like chemotherapy. The key issue with these approaches is the suppression of normal cell growth and the significant side effects related to systemic toxicity [3]. Chemotherapy is a widely used cancer treatment that employs chemical compounds to target specific cancer cells. Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent and challenging complication associated with several commonly administered antineoplastic agents [4]. The development of CIPN can lead to extended infusion times, dose reductions, or early discontinuation of chemotherapy, which may adversely affect both treatment efficacy and patient survival [5,6].

Affected patients suffer from symptoms like pain and paraesthesia, loss of sensation and proprioception in the lower extremities resulting in muscle weakness, balance problems, and gait instability may lead to a higher risk of falling [7].These functional limitations also contribute to decreased quality of life (QOL) and participati on restrictions.

Chemotherapy-induced peripheral neuropathy (CIPN) arises from neurotoxicity caused by six major drug classes: platinum-based compounds (notably oxaliplatin and cisplatin), Vinca alkaloids (such as vincristine and vinblastine), epothilones (like ixabepilone), taxanes (including paclitaxel and docetaxel), proteasome inhibitors (such as bortezomib), and immunomodulatory agents (like thalidomide) [8]. CIPN primarily impacts sensory nerves, with a particular effect on the large-diameter fibers responsible for proprioception and vibratory sensation [9]. The patho-mechanism underlying CIPN is complex and multifaceted, it involves several key processes, including disruption of microtubules, oxidative stress and mitochondrial dysfunction, dysregulation of ion channel activity, damage to myelin sheath, DNA injury, immune system activation, and neuroinflammation [10]. Chemotherapy agents, especially platinum-based drugs and taxanes, include axon degeneration through oxidative stress and mitochondrial dysfunction [11]. This leads to distal axonal loss and “dying-back” neuropathy, where nerve damage starts in the distal extremities and progresses proximally [12]. These agents directly and indirectly impact sensory nerves, leading to reduction in action potential amplitude and decrease in conduction velocity causing impaired sensory transmission [13]. Additionally, Chemotherapy alters sodium and potassium channels, reducing signal transmission and sensory sensitivity [9].

Balance is a complex motor skill requiring the integration of multiple sensory inputs to generate the motor commands [14]. CIPN often disrupt somatosensory feedback, particularly proprioceptive input from the lower limb, leading to postural instability [15]. The somatosensory deficits in CIPN often results in impaired postural control strategies, decreased stability, reduced gait speed, increased postural sway, and heightened fall risk [16]. As a result, People who are receiving chemotherapy for cancer are more likely to fall compared to people who are not receiving cancer treatment [17]. Conventional balance training (CBT) has been cornerstone in managing balance deficit, focusing primarily on motor control and functional stability by improving muscle strength, endurance, flexibility, and postural control and reduce fall risk [18]. However, emerging evidence suggests that sensory integration plays a vital role in optimizing balance recovery, particularly in neuropathic conditions [19]. Sensory- enhanced balance training (SEBT) is an emerging rehabilitation approach that integrates sensory stimulation techniques to augment proprioceptive input and improve postural stability [20]. Sensory-enhanced Balance Training incorporates the use of various sensory modalities such as tactile stimulation, proprioceptive training, visual and auditory feedback to enhance motor learning and neuromuscular coordination [21]. Sensory-enhanced balance training is an innovative approach that targets the sensory deficits associated with CIPN [22]. By incorporating somatosensory, auditory, and vestibular stimuli,

SEBT aims to improve the brain's ability to integrate multisensory information, thereby enhancing postural control and functional balance [23]. Techniques such as unstable surface training, sensory reweighting, and augmented feedback are central to SEBT, promoting neuroplasticity and compensatory strategies in individuals with sensory deficits [24].

Despite the growing recognition of chemotherapy-induced peripheral neuropathy (CIPN) as a multifaceted problem requiring holistic management, its effective rehabilitation remains underexplored [25]. While conventional balance training (CBT) focuses primarily on addressing motor deficits, a sensory-oriented approach like the SEBT offers potential for superior outcomes by leveraging neuroplasticity and sensory integration [26].

This randomized controlled trial (RCT) aims to fill this gap by comparing the effectiveness of SEBT and CBT in improving balance and quality of life in patients with CIPN. The study emphasizes the need for sensory-based interventions, recognizing that conventional physiotherapy may fall short in addressing the complex sensory deficits associated with CIPN.

By introducing a sensory-driven paradigm, SEBT could not only restore physical function but also enhance psychological well-being and social participation, providing a more comprehensive rehabilitation approach. This research seeks to provide evidence for implementing sensory-based protocols in CIPN management, potentially revolutionizing rehabilitation strategies and improving the long-term functional outcomes and quality of life for cancer survivors.

Materials and Methods

Study Design and Participants

Ethical approval was obtained from the Institutional Ethical Committee under Protocol No. 496/2022-23. A single-blind, parallel-group randomized controlled trial with 72 participants with grade 2-3 CIPN, according to the World Health Organization's classification. They were randomized to receive either sensory-enhanced balance training & multimodal therapeutic exercises (intervention group) or conventional balance training and routine physiotherapy exercises (control group). Participants were excluded if they had central nervous system dysfunctions (e.g., hemiparesis, cerebellar ataxia), a history of peripheral neuropathies unrelated to chemotherapy, cardiovascular diseases, or visual/auditory impairments.

Assessment tools:

Primary outcomes included balance performance (Modified clinical test of sensory interaction on balance (mCTSIB), Timed Up and Go test (TUG)) and quality of life (EORTC QLQ-CIPN20). Data were collected pre- and post-intervention.

Intervention:

The interventions received by the interventional group were sensory-enhanced balance training & multimodal therapeutic exercises which included static and dynamic balance exercises with patient wearing the pressure insole with a biofeedback device. All the exercises were performed on different textures like soft, hard, rough etc. while the control group received only static and dynamic balance exercises. Control group received routine balance training and exercise regime. Both interventions were conducted 4 times weekly over 8 weeks.

Statistical Analysis:

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26. Paired t-tests were used to assess within-group differences, while unpaired t-tests were employed to compare differences between groups. A p-value of <0.05 was considered statistically significant.

Results

a) Participant Characteristics:

Variables		Frequency	
		Group A	Group B
Gender	Male	15	17
	Female	21	19
Total		35	36
Age (mean)		47.3±5.3	46.9 ±4.9

Table 1: Participant Characteristics

Of the 72 participants, 40 were female, and 32 were male, with a mean age of 46.9 years (±4.9) in the control group and 47.3 years (±5.3) in the intervention group. There were no significant demographic differences between the groups (p>0.05).

b) Pre & Post intervention values of outcomes in Group A and Group B:

Outcomes	**Mean ± SD (Group A)**	**Mean ± SD (Group B)**
mCTSIB		
Pre	56.44±5.43	55.89 ±4.88
Post	93.05±7.30	84.80 ±9.50
p value	<0.0001	<0.0001
TUG		
Pre	26.8±4.341	27.8±5.438
Post	11.9±1.912	20±3.751
p value	<0.0001	<0.0001
EORTC-QOL-CIPN 20		
Pre	35.36 ±1.95	34.06 ±1.02
Post	24.57±3.44	28.95± 3.23
p value	<0.0001	<0.0001

Table 2: Pre & Post intervention values of outcomes in Group A and Group

Both the groups were equally effective in improvement in balance and quality of life post treatment (p<0.0001)

c) Comparison of Post values of mCTSIB, TUG Test and EORTC -QOL - CIPN 20 between Group A and Group B:

Parameter	Group A	Group B	P value
mCTSIB	93.05+7.30	84.80 + 9.50	0.0001

TUG Test	11.9±1.912	20±3.751	<0.0001
EORTC -QOL - CIPN 20	24.57±3.44	28.95± 3.23	<0.0001

The post intervention analysis depicted that the Group A (interventional group) had a significant improvement in the balance (0.0001, <0.0001) and improvement in quality of life (<0.0001) as compared to the Group B (control group).

Discussion:

The current study focused on implementing sensory-enhanced balance training as prime intervention in treatment of balance related issues with patients suffering from chemotherapy induced peripheral neuropathy. This study demonstrates that balance training enhanced with sensory feedback significantly improves outcomes for cancer patients suffering from CIPN compared to balance training alone

A well balanced study design was observed in the present study in respect to the gender distribution. No significant differences in gender distribution or mean age between Group A and Group B ($p>0.05$) was observed. The equal distribution of male and female population along with no statistical difference in the mean age strengthens the internal validity of the present research. [27,28].

The present study marks an improvement in Modified clinical test of sensory interaction on balance for the intervention group. The mean mCTSIB scores significantly increased from 56.44±5.43 to 93.05±7.30 in Group A, compared to more modest improvements in the control group (55.89±4.88 to 84.80±9.50).

Similarly the subjects demonstrated a significant improvement in the post TUG Test scores for Group A decreased markedly (11.9±1.912) compared to Group B (20±3.751), indicating better mobility and functional performance in Group A ($p<0.0001$).

According to a study it is proved that patients with neuropathy rely more on the vestibular signals for balance as their sensory inputs are impaired. These patients may rely more on vestibular signals, which are known to carry a larger amount of noise [29] than on diminished proprioception to stabilize the posture. In study by S Kneis et al they observed no improvements in the eyes-closed conditions, so they concluded that patients did not change their posture strategy towards reducing vestibular in favor of proprioceptive cues [30]. According to this study they suggested focusing even more strongly on exercises without visual input during training. Thus the present study used a Sensory-Enhanced Balance Training as a measure to improve the balance.

The treatment protocol of present study incorporated Sensory-Enhanced Balance Training, in which static and dynamic balance training was given to the subject with an attachment of a pressure insole which had a biofeedback mechanism. The alternation in the pressure on the insole gave an indication of loss of balance and the subject emphasized on maintain the balance. Along with this the balance training was given on various sensory textures like soft, hard, rough which might have given a positive feedback on sensory input along with balance training. Therefore an integration of biofeedback along with sensory input might have helped in better outcome on balance.

The quality of life assessment revealed significant improvements in the intervention group. The mean EORTC-QOL-CIPN 20 scores decreased from 35.36±1.95 to 24.57±3.44 in Group A, indicating reduced negative impact of chemotherapy-induced peripheral neuropathy. In contrast,

Group B showed less significant improvements (34.06 ±1.02 to 28.95±3.23). The improvement in the neuropathy scores and balance must have a positive impact on the overall quality of life of the patients.

This outcome is consistent with studies by Bennett et al. (2020), which emphasized the potential of comprehensive interventions in mitigating the psychosocial and functional challenges associated with CIPN [31].
The results underscore the importance of integrating sensory feedback into rehabilitation programs for CIPN, particularly for patients at high risk of falls due to balance impairments. Future studies should explore the long-term benefits of such interventions and investigate their applicability in other neuropathic conditions.

Conclusion:

Balance training with sensory feedback is a superior intervention for improving balance and enhancing the quality of life in cancer patients receiving chemotherapy. This method should be incorporated into standard physiotherapy practices for CIPN management.

References:

1. Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. Indian J Med Res. 2022 Oct-Nov;156(4&5):598-607.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA. 2018;68(6):394–424.
3. Yadav A, Singh S, Sohi H, Dang S. Advances in delivery of chemotherapeutic agents for cancer treatment. AAPS PharmSciTech. 2022 Jan;23:1-4.
4. Argyriou AA, Bruna J, Marmiroli P, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. Crit Rev Oncol Hematol. 2012;82(1):51–77.
5. Colvin LA. Chemotherapy-induced peripheral neuropathy: where are we now? Pain. 2019;160(Suppl 1):S1–10.
6. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Pain. 2014;155(12):2461–70.
7. Winters-Stone KM, Horak F, Jacobs PG, Trubowitz P, Dieckmann NF, Stoyles S, et al. Falls, functioning, and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. J Clin Oncol. 2017;35(23):2604–2612. doi: 10.1200/JCO.2016.71.3552. [DOI] [PMC free article] [PubMed] [Google Scholar]
8. Starobova, Hana, and Irina Vetter. "Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy." *Frontiers in molecular neuroscience* vol. 10 174. 31 May. 2017, doi:10.3389/fnmol.2017.00174
9. Zajączkowska, R., Kocot-Kępska, M., Leppert, W., Wrzosek, A., Mika, J., & Wordliczek, J. (2019). Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. *International journal of molecular sciences*, *20*(6), 1451. https://doi.org/10.3390/ijms20061451
10. Areti, Aparna et al. "Oxidative stress and nerve damage: role in chemotherapy induced peripheral neuropathy." *Redox biology* vol. 2 289-95. 18 Jan. 2014, doi:10.1016/j.redox.2014.01.006
11. Park, S. B., Cetinkaya-Fisgin, A., Argyriou, A. A., Höke, A., Cavaletti, G., & Alberti, P. (2023). Axonal degeneration in chemotherapy-induced peripheral neurotoxicity: clinical

and experimental evidence. *Journal of neurology, neurosurgery, and psychiatry*, *94*(11), 962–972. https://doi.org/10.1136/jnnp-2021-328323

12. Eldridge, S., Guo, L., & Hamre, J., 3rd (2020). A Comparative Review of Chemotherapy-Induced Peripheral Neuropathy in In Vivo and In Vitro Models. *Toxicologic pathology*, *48*(1), 190–201. https://doi.org/10.1177/0192623319861937
13. Jaggi AS, Singh N. Mechanisms in cancer-chemotherapeutic drugs-induced peripheral neuropathy. Toxicology. 2012 Jan 27;291(1-3):1-9.
14. Rasman, B. G., Forbes, P. A., Tisserand, R., & Blouin, J. S. (2018). Sensorimotor Manipulations of the Balance Control Loop-Beyond Imposed External Perturbations. *Frontiers in neurology*, *9*, 899. https://doi.org/10.3389/fneur.2018.00899
15. Reinmann, A., Bruyneel, A. V., Gligorov, J., Mesure, S., Combescure, C., Koessler, T., & Bodmer, A. (2022). Influence of chemotherapy on postural control and quality of life in women with gynaecological cancer: a protocol of a prospective observational study. *BMJ open*, *12*(9), e061664. https://doi.org/10.1136/bmjopen-2022-061664
16. Müller, J., Kreutz, C., Ringhof, S. *et al.* Chemotherapy-induced peripheral neuropathy: longitudinal analysis of predictors for postural control. *Sci Rep* 11, 2398 (2021). https://doi.org/10.1038/s41598-021-81902-4
17. Overcash, Janine. "Prediction of falls in older adults with cancer: a preliminary study." *Oncology nursing forum* vol. 34,2 (2007): 341-6. doi:10.1188/07.ONF.341-346
18. Khot A, Hande D. Effect of conventional balance exercises and electronic balance board on elderly individuals. International Journal of Multidisciplinary Research and Development. 2017;4(7):505-8.
19. Warutkar, V. B., & Krishna Kovela, R. (2022). Review of Sensory Integration Therapy for Children With Cerebral Palsy. *Cureus*, *14*(10), e30714. https://doi.org/10.7759/cureus.30714
20. Fil-Balkan, A., Salci, Y., Keklicek, H., Armutlu, K., Aksoy, S., Kayihan, H., & Elibol, B. (2018). Sensorimotor integration training in Parkinson`s disease. *Neurosciences (Riyadh, Saudi Arabia)*, *23*(4), 208–215. https://doi.org/10.17712/nsj.2018.3.20180021
21. Kneis, S et al. "It's never too late - balance and endurance training improves functional performance, quality of life, and alleviates neuropathic symptoms in cancer survivors suffering from chemotherapy-induced peripheral neuropathy: results of a randomized controlled trial." *BMC cancer* vol. 19,1 414. 2 May. 2019, doi:10.1186/s12885-019-5522-7
22. Schwenk, M., Grewal, G. S., Holloway, D., Muchna, A., Garland, L., & Najafi, B. (2016). Interactive Sensor-Based Balance Training in Older Cancer Patients with Chemotherapy-Induced Peripheral Neuropathy: A Randomized Controlled Trial. *Gerontology*, *62*(5), 553–563. https://doi.org/10.1159/000442253
23. Chaudhary, S., Saywell, N., & Taylor, D. (2022). The Differentiation of Self-Motion From External Motion Is a Prerequisite for Postural Control: A Narrative Review of Visual-Vestibular Interaction. *Frontiers in human neuroscience*, *16*, 697739. https://doi.org/10.3389/fnhum.2022.697739
24. Haran, F. J., & Keshner, E. A. (2008). Sensory reweighting as a method of balance training for labyrinthine loss. *Journal of neurologic physical therapy : JNPT*, *32*(4), 186–191. https://doi.org/10.1097/NPT.0b013e31818dee39

25. Stoller S, Capozza S, Alberti P, Lustberg M, Kleckner IR. Framework to leverage physical therapists for the assessment and treatment of chemotherapy-induced peripheral neurotoxicity (CIPN). Supportive Care in Cancer. 2023 May;31(5):293.
26. Deng J, Lei T, Du X. Effects of sensory integration training on balance function and executive function in children with autism spectrum disorder: evidence from Footscan and fNIRS. Frontiers in Psychology. 2023 Oct 25;14:1269462.
27. Altman, D. G. (1985). "Randomisation: A Comprehensive Guide to Reporting and Methods for Ensuring Blinding in Clinical Trials" Full Name: "Randomisation and Baseline Comparisons in Clinical Trials" Published in: British Medical Journal
28. Polit, D. F., & Beck, C. T. (2012). "Nursing Research: Generating and Assessing Evidence for Nursing Practice" Full Name: "Nursing Research: Principles and Methods" Published by: Lippincott Williams & Wilkins
29. van der Kooij H, Peterka RJ. Non-linear stimulus-response behavior of the human stance control system is predicted by optimization of a system with sensory and motor noise. J Comput Neurosci. 2011;30(3):759–778. doi: 10.1007/s10827-010-0291-y. [DOI] [PMC free article] [PubMed] [Google Scholar]
30. Kneis S, Wehrle A, Müller J, Maurer C, Ihorst G, Gollhofer A, Bertz H. It's never too late - balance and endurance training improves functional performance, quality of life, and alleviates neuropathic symptoms in cancer survivors suffering from chemotherapy-induced peripheral neuropathy: results of a randomized controlled trial. BMC Cancer. 2019 May 2;19(1):414. doi: 10.1186/s12885-019-5522-7. PMID: 31046719; PMCID: PMC6498676.
31. Bennett, M. I., et al. (2020). "Quality of Life in Patients with Chemotherapy-Induced Peripheral Neuropathy" Full Name: "Patient-Reported Outcomes and Quality of Life in Chemotherapy-Induced Peripheral Neuropathy: A Comprehensive Analysis" Published in: Journal of Pain and Symptom Management