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Evaluating the Impact of a Multimodal Therapeutic Exercise Program on Aerobic Capacity and Quality of Life in Patients with Chemotherapy-Induced Peripheral Neuropathy from Paclitaxel and Carboplatin drugs.

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Abstract

Chemotherapy-induced Peripheral Neuropathy (CIPN) is a common and debilitating side effect of chemotherapy, affecting up to 60% of patients and significantly impairing their quality of life. This randomized controlled trail aimed to assess the effectiveness of a multimodal therapeutic exercise program in managing CIPN in patients undergoing treatment with Paclitaxel and Carboplatin. The study included participants aged 25 to 55 years with Grade 2 to 3 CIPN as per the WHO classification. Participants were randomly assigned to either an intervention group (IG) that received a multimodal exercise regimen or a control group (CG) that underwent standard physiotherapy for 12 weeks. The primary outcomes were measured using the FACT-TAXANE version 4 and the Timed Up and Go (TUG) Test, assessed pre- and post- intervention Results showed that the multimodal exercise program was significantly more effective than conventional physiotherapy in reducing TUG scores and improving FACT-TAXANE scores across all domains, including physical, social, emotional and functional well-being ($p < 0.0001$). the IG demonstrated marked improvements in sensory-motor functions, aerobic conditioning, and overall quality of life with significant reduction in neuropathy symptoms. In conclusion, this study provides strong evidence supporting the incorporation of a multimodal therapeutic exercise program as a valuable strategy for improving functional performance and quality of life in cancer patients with CIPN, offering healthcare professionals an effective intervention to manage this condition.

Introduction

One major issue affecting public health is cancer. For 2022, the crude rate of incidence per 100,000 people is 100.4 on a national average; for males it is 95.6 and for females it is 105.4[1]. However, recent advances in medicine have led to an increase in survival rates by improvements in prevention, early detection, and various anti-cancer therapies [2]. For majority of cancer treatments, multitargeted or combination therapy is superior to single agent therapy. Hence, combination chemotherapy agents are used with distinct mechanisms of action and decrease toxicity. [3]

Chemotherapy is becoming more important for treatment of cancer, particularly when it is used as adjuvant with local therapy. Chemotherapy is administration of cyto-toxic chemicals, or chemicals

that kill cells, in an effort of completely eradicate the tumour or significantly reduce the tumour. This can lessen the symptoms associated with the tumour and possibly extend the patient's life. [4] However, neurotoxic side effects from chemotherapy are common and are often a reason to limit the dose of chemotherapy. Chemotherapy may cause peripheral neurotoxicity. [5] Peripheral neuropathy is a serious concern for individuals receiving chemotherapy as it affects up to 60% of patients. [6] Peripheral neuropathies are disorders of peripheral nerve cells and fibres that can arise as a secondary symptom of variety of other illnesses. The most common symptoms of peripheral neuropathy are paraesthesia and numbness; these may be accompanied by weakness, discomfort, and loss of deep tendon reflexes. While certain peripheral neuropathies develop more progressively, most peripheral neuropathies take months to years to develop. Since, it can impact motor, sensory and autonomic fibres, they can vary widely in severity and clinical symptoms. [7] Chemotherapeutic drugs have the potential to cause harm to the nervous system and can cause a variety of neuropathies, including cranial, autonomic, sensory and/or motor, large and small fibre, demyelinating and axonal and motor neuropathies. One of the most common neuropathies caused by antineoplastic agents is a condition known as chemotherapy-induced peripheral neuropathy (CINP). [8]

Chemotherapy-induced peripheral neuropathy (CINP) is a most frequent dose-limiting adverse effect that cancer patients experience after receiving chemotherapy [9]. According to a study conducted by Seretny, M et.al CIPN prevalence was 68.1% (57.7–78.4) when measured in the first month after chemotherapy, 60.0% (36.4–81.6) at 3 months and 30.0% (6.4–53.5) at 6 months or more. [10] The most frequent substances causing CIPN are vinca alkaloids, taxanes, platin derivates, and bortezomib and thalidomide.[11] In patients receiving paclitaxel, the incidence of taxane-induced peripheral neuropathy is significantly high, ranging from 57% to 83% overall, with severity in 2% to 33% of patients. [12]

Paclitaxel-induced peripheral neuropathy (PIPN) is primarily a length-dependent axonal sensory neuropathy that correlates with paclitaxel dosage, infusion time, and other factors. It damages peripheral axons symmetrically due to its microtubule-stabilizing effects, disrupting axonal transport of essential components causing an axonal dying back pattern, particularly in Aβ-fibres. This leads to symptoms like numbness and tingling in the extremities. Mitochondrial dysfunction ATP depletion contribute to increased pain sensation, while inflammatory makers such as IL-1β, IL-8, TNF-α, and others exacerbate the condition. The immune response involves activation of microglial and astrocytes in the spinal cord and satellite glial cells (SGC) in the PNS, which release TNF-α and neurotransmitters that promote neuronal death. Macrophages infiltrate the dorsal root ganglia (DRG), driven by MMP-3 and MCP-1, further contributing to neuronal degeneration. Cannabinoid receptor agonists can potentially reduce neuropathic pain by modulating the immune response. [13] Platin-based chemotherapeutic agents, include oxaliplatin, cisplatin, and carboplatin. According to a study conducted by Yoon WK et.al the incidence of sensory, motor and severe neurotoxicity by carboplatin are 56%, 42% and 28% respectively [14]

Platinum drugs bind to nuclear DNA, forming adducts that inhibit DNA replication and RNA transcription, leading to apoptosis. These agents also cause mitochondrial dysfunction and oxidative stress, increasing ROS production and impairing mitochondrial function, which activates apoptotic pathways. Disruption of intercellular signaling through altered calcium signaling and activation of protein kinase and caspases further promotes neurodegeneration. Platinum drugs also dysregulate ion channels, such as Na+, K+, and TRP channels, altering neuronal excitability and contributing to neuropathic symptoms. Glial cell activation, particularly by oxaliplatin, involves astrocytes activation and altered adenosine signaling, exacerbating neuropathic pain. Additionally, chemotherapy triggers the release of pro-inflammatory cytokines from glial cells, leading to neuroinflammation and

sensitization of nociceptors, which further contribute to pain and neuropathy [15]
Most neuropathies caused by chemotherapy are sensory in nature. An early symptom is frequently tingling or numbness in the finger and feet. Sensory symptoms reported by patients include paraesthesia, dysesthesia, tingling, itching and burning, tight, stabbing, sharp, or aching pain. Gait deviation and sensory ataxia can result from sensory loss in legs and feet. Hand dexterity loss is frequently interpreted as "clumsiness". Less common symptoms include pruritus, Raynaud's phenomenon and muscle soreness. [11]

A meta- analysis shows that exercise is effective in reducing symptoms of CINP in cancer patients and survivors. Exercise can help decrease the severity of symptoms like tingling, numbness and pain and improve the ability to feel peripheral deep sensation. [16] In order to help individuals with CIPN to maintain stable symptoms, a multimodal exercise program that include endurance, resistance and balance training can be implemented. [17] Regular exercise has improved quality of life, improve functioning, reduce fatigue, reduce symptoms and improve mental health of patients suffering from CIPN [18] Research in this area will help provide the healthcare professionals to provide best care for their patients and learn how to suggest and prescribe specific exercise programs for their patients. This will ensure that patients receive the most effective care to manage symptoms of CIPN [19]

Aim and Objectives

Aim- To evaluate the Impact of a Multimodal Therapeutic Exercise Program on Aerobic Capacity and Quality of Life in Patients with Chemotherapy-Induced Peripheral Neuropathy from Paclitaxel and Carboplatin drugs.

Objective-

a. To study the effectiveness of multimodal therapeutic exercise program on aerobic conditioning in the subjects with Paclitaxel and Carboplatin chemotherapy induced peripheral neuropathy.

b. To study the effectiveness of multimodal therapeutic exercise program on quality of life in the subjects with Paclitaxel and Carboplatin chemotherapy induced peripheral neuropathy.

I. Methodology

This randomized controlled trial was conducted in oncology department of Krishna College of Physiotherapy, Karad. Participants eligible for this study included both male and female subjects between the ages 25 to 45 years who were receiving chemotherapy with neurotoxic agents such as paclitaxel and carboplatin. Additionally, participants were required to have chemotherapy-induced peripheral neuropathy (CINP) of grade 2 to 3, as per World Health Organization classification. Subjects were excluded if they have Central Nervous System (CNS) dysfunction like hemiparesis, myelopathy, or cerebellar ataxia; a history of Peripheral Nervous System (PNS) pathology; cardiovascular diseases (e.g., angina or myocardial infarction); or systemic problems, such as vision or auditory disorders, severe dyspnea, chest pain, peripheral vascular disease, osteoporosis, recent unhealed lower limb fractures or deformities. Additionally, individuals with a past or present history of diabetes mellitus or those who are unwilling to participate in the study were also be excluded. The outcomes were measured by, FACT Taxene version 4 and Timed Up and Go (TUG) Test.

The methodology for this study aimed to assess the effectiveness of a multimodal therapeutic exercise program on improving aerobic capacity and quality of life in patients suffering from chemotherapy-induced peripheral neuropathy (CIPN) due to treatment with Paclitaxel and Carboplatin. The study was structured as a randomized controlled trial (RCT) conducted in the oncology department of Krishna College of Physiotherapy, Karad. It involved specific inclusion and exclusion criteria,

randomized assignment of participants, an intervention design, and a detailed exercise program protocol.

A. Participant Selection

Participants were selected based on predefined inclusion criteria. Eligible individuals were patients between the ages of 25 and 45 who had been diagnosed with CIPN of grades 2 to 3, according to the World Health Organization's classification. These patients were undergoing chemotherapy treatment with neurotoxic agents, specifically Paclitaxel and Carboplatin. Individuals with specific conditions such as CNS dysfunction (e.g., hemiparesis, myelopathy, cerebellar ataxia), a history of peripheral nervous system (PNS) pathology, or cardiovascular diseases (e.g., angina, myocardial infarction) were excluded from the study. Other exclusion criteria included vision or auditory impairments, severe dyspnea, chest pain, peripheral vascular disease, osteoporosis, recent unhealed lower limb fractures, or deformities. Patients with diabetes mellitus or those unwilling to participate were also excluded.

B. Study Design

The study included two groups: an intervention group (IG) and a control group (CG). Randomization was employed to assign participants to either group to minimize bias and ensure comparability. The intervention group (IG) participated in a multimodal therapeutic exercise program tailored specifically to mitigate symptoms of CIPN, while the control group (CG) received conventional physiotherapy treatments. Both groups underwent a 12-week program with pre- and post-intervention assessments.

C. Exercise Program

Participants in the IG attended four exercise sessions per week, including one supervised session and three home-based sessions. Each session began with a warm-up consisting of breathing exercises to prepare the body and included a cool-down phase to conclude the workout. The main exercise program combined endurance, resistance, and balance training. These components were chosen to target multiple physical functions impacted by CIPN, such as sensory-motor function and overall aerobic conditioning. The exercises were gradually intensified over the weeks to adapt to the participants' progress and tolerance.

The CG, meanwhile, underwent a standard physiotherapy program focusing on general physical rehabilitation and did not include the multimodal approach.

D. Outcome Measures

Two primary outcomes were measured pre- and post-intervention to gauge the effectiveness of the multimodal program. First, the Timed Up and Go (TUG) Test assessed mobility and functional ability, a critical metric for patients with CIPN. Lower TUG scores indicate better functional performance and mobility. Second, the Functional Assessment of Cancer Therapy (FACT)-Taxane version 4 questionnaire measured the quality of life across physical, social, emotional, and functional

domains. Improvement in these scores would reflect enhanced quality of life and reduced symptoms of neuropathy.

E. Data Collection and Analysis

After screening and randomization, baseline measurements for both the TUG and FACT-Taxane scores were collected. Following the 12-week program, post-intervention scores were gathered and statistically analyzed. Statistical significance was set at $p < 0.05$, with specific focus on improvement trends in both groups. The study aimed to determine whether a multimodal therapeutic exercise regimen could significantly improve the TUG and FACT-Taxane scores in comparison to conventional physiotherapy, thus providing an evidence-based recommendation for managing CIPN symptoms in cancer patients.

II. Procedure

After obtaining approval from the protocol and the ethical committee, the subjects were selected based on the inclusion and exclusion criteria, and those willing to participate were divided into interventional group (IG) and a control group (CG). The IG received the multimodal exercise training for 12 weeks, while the CG received regular Physiotherapy treatment with outcome measures assessed pre- and post- intervention. Participants engaged in four exercise sessions per week, consisting of one supervised session and three home-based sessions. Each session included a warm-up with breathing exercises before starting the main exercise program and a cool-down session at the end.

A. Recruitment and Ethical Approval

The study began with obtaining ethical approval from the institutional ethics committee to ensure adherence to ethical guidelines for research involving human participants. The recruitment process was conducted in the oncology department of Krishna College of Physiotherapy, Karad. Participants were informed about the study's purpose, risks, and potential benefits, and informed consent was obtained from each patient who met the inclusion criteria. Eligible participants were males and females between the ages of 25 and 45, diagnosed with grade 2 or 3 CIPN as per WHO classification, and currently receiving neurotoxic chemotherapy agents like Paclitaxel and Carboplatin.

B. Randomization and Group Allocation

Participants were randomly assigned to either the intervention group (IG) or the control group (CG). This randomization helped reduce bias and ensured comparability between the groups. The intervention group (IG) received the specialized multimodal therapeutic exercise program, while the control group (CG) received conventional physiotherapy treatments without the multimodal components.

C. Baseline Assessment

Upon enrollment and group allocation, baseline data was collected for each participant. This included demographic details and initial measurements for the Timed Up and Go (TUG) Test and the FACT-Taxane version 4 questionnaire. The TUG Test assessed functional mobility and physical

performance, with lower scores indicating better performance. The FACT-Taxane questionnaire, on the other hand, measured quality of life across physical, social, emotional, and functional domains, as well as neuropathy symptoms. Baseline assessments were crucial for comparing changes pre- and post-intervention.

D. Intervention Protocol

The multimodal therapeutic exercise program administered to the IG was a 12-week program combining endurance, resistance, and balance training. Each week included four exercise sessions, with one session supervised at the oncology department and the remaining three home-based. Sessions began with a warm-up phase involving breathing exercises to prepare the body for the workout, followed by the main exercise routines, and concluded with a cool-down phase.

1. **Endurance Training**: Endurance exercises were designed to improve aerobic capacity, focusing on moderate-intensity activities such as brisk walking or stationary cycling. These exercises were gradually increased in duration and intensity as the participants adapted over time.
2. **Resistance Training**: Resistance exercises targeted muscle strength to help with physical stability and reduce CIPN symptoms. Bodyweight exercises and resistance bands were used initially, with intensity progressively increased to build strength.
3. **Balance Training**: Balance exercises aimed at enhancing postural control, essential for patients with CIPN who may experience gait instability. Simple exercises like standing on one leg or using a balance board were implemented to help improve proprioception and body awareness.

The control group (CG) followed a standard physiotherapy program, which primarily included general physical conditioning exercises without targeted endurance, resistance, or balance training.

E. Monitoring and Adherence

Participant adherence to the exercise regimen was monitored during weekly supervised sessions, and participants were encouraged to maintain a log of their home-based sessions. Any issues or side effects experienced during the program were documented and addressed. Compliance was further reinforced through weekly check-ins, ensuring that patients followed the prescribed exercises at home.

F. Post-Intervention Assessment

After completing the 12-week program, participants in both groups underwent post-intervention assessments identical to the baseline. The TUG Test and FACT-Taxane questionnaire were administered again to measure any changes in functional mobility, quality of life, and neuropathy symptoms. These outcomes were compared between the pre- and post-intervention stages within each group and between the IG and CG to determine the effectiveness of the multimodal therapeutic program over conventional physiotherapy.

G. Data Analysis and Reporting

The collected data from baseline and post-intervention assessments were statistically analyzed to evaluate the impact of the multimodal exercise program. Statistical tests determined if the differences between the pre- and post-intervention scores in the IG were significant compared to those in the CG. Findings were summarized and reported to provide evidence-based recommendations for managing CIPN in patients undergoing chemotherapy.

III. Results

Table 1 – Baseline Characteristics:

Characteristics		Mean±SD (Group A)	Mean±SD (Group B)
Age		49.8±5.594	48.3±6.701
Pre-TUG Test		26.8±4.341	27.8±5.438
Post-TUG Test		11.9±1.912	20±3.751
Pre FACT-TAXANE Version 4	Physical Well-Being	13.8±1.619	13.5±1.434
	Social Well – Being	15.4±3.134	13.4±3.307
	Emotional Well - Being	12.6±2.336	12.2±1.874
	Functional Well - Being	10.9±2.079	11.5±1.650
	Neuropathy	27.2±5.827	26.1±4.149
Post FACT-TAXANE Version 4	Physical Well-Being	25.4±1.838	15.2±1.317
	Social Well - Being	22.9±3.213	13.8±3.521
	Emotional Well - Being	20.8±2.44	13±1.886
	Functional Well - Being	23.7±2.058	11.7±1.767
	Neuropathy	09.1±1.595	25.6±4.222
Post TUG Test		11.9±1.912	20±3.751

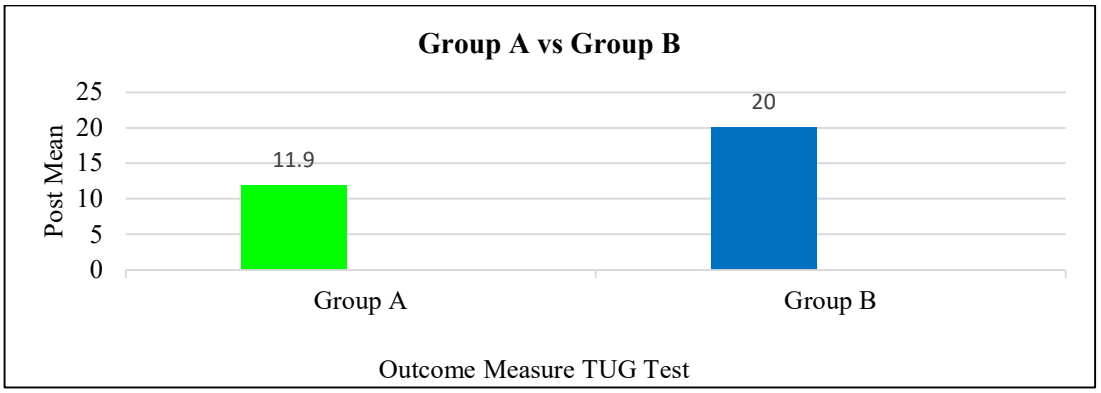
Post FACT-TAXANE Version 4	Physical Well-Being	25.4±1.838	15.2±1.317
	Social Well – Being	22.9±3.213	13.8±3.521
	Emotional Well - Being	20.8±2.44	13±1.886
	Functional Well - Being	23.7±2.058	11.7±1.767
	Neuropathy	09.1±1.595	25.6±4.222

Table 2: Comparison of Post values of TUG Test and FACT-TAXANE version 4 between Multimodal Therapeutic Exercise Program (Group A) and Conventional Exercise Program (Group B).

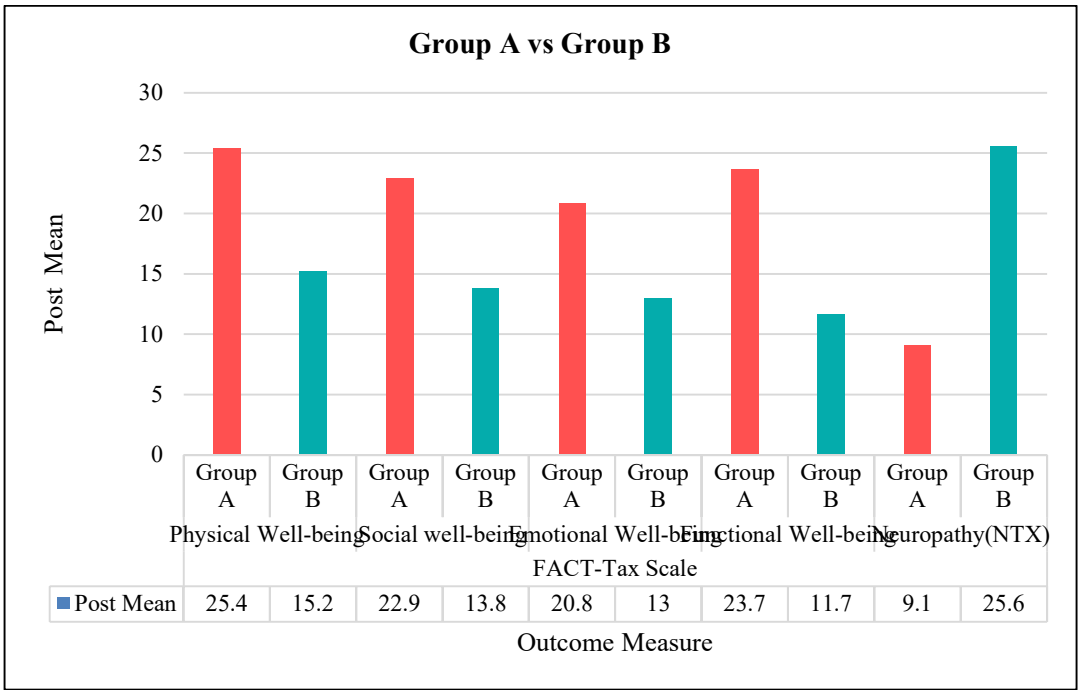
Parameters	Outcome Measure	Group A		Group B		p-value
		Post		Post		
		Mean	SD	Mean	SD	
TUG Test	TUG Test Score	11.9	1.912	25	3.972	<0.0001*
b. FACT-TAXANE -version 4	Physical Well- Being	25.4	1.838	15.2	1.317	<0.0001
	Social Well - Being	22.9	3.213	13.8	3.521	<0.0001
	Emotional Well -Being	20.8	2.44	13	1.886	<0.0001
	Functional Well -Being	23.7	2.058	11.7	1.767	<0.0001
	Neuropathy	9.1	1.595	25.6	4.222	<0.0001

These results highlight the substantial impact of Multimodal Therapeutic Exercise Program (Group A) over Conventional Exercise Program (Group B) on Paclitaxel and Carboplatin chemotherapy induced peripheral neuropathy.

Graph 1a - Comparison of Post values of TUG Test between Multimodal Therapeutic Exercise Program (Group A) and Conventional Exercise Program (Group B).



Graph 1b - Comparison of Post values of FACT-TAXANE Version 4 between Multimodal Therapeutic Exercise Program (Group A) and Conventional Exercise Program (Group B).



The results of the study demonstrate a significant difference between Group A and Group B across various outcome measures.

- The Timed Up and Go (TUG) Test scores indicate a substantial improvement in Group A (Mean = 11.9, SD = 1.912) compared to Group B (Mean = 25, SD = 3.972), with a p-value of <0.0001. **This suggests that the intervention or treatment administered to Group A has a notable positive impact on mobility and functional abilities, as assessed by the TUG Test.**
- Furthermore, the FACT-TAXANE version 4 questionnaire results show statistically significant improvements in Physical Well-Being, Social Well-Being, Emotional Well-Being, Functional Well-Being, and Neuropathy for Group A compared to Group B, all with p-values <0.0001. **These findings suggest that the intervention not only has a positive effect on physical mobility but also contributes to enhanced overall well-being, including social, emotional, and functional aspects, as well as a reduction in neuropathy symptoms.**

In conclusion, the study results strongly support the effectiveness of the intervention in improving both physical and psychosocial outcomes in Group A compared to Group B. The findings highlight the potential benefits of the intervention in enhancing the quality of life and functional abilities of individuals undergoing the treatment with paclitaxel and carboplatin chemotherapy agent.

IV. Discussion:

The data demonstrate the significant effectiveness of the Multimodal Therapeutic Exercise Program (Group A) compared to the Conventional Exercise Program (Group B) in managing chemotherapy-induced peripheral neuropathy, particularly from Paclitaxel and Carboplatin.

The baseline characteristics data compare two groups (Group A and Group B) on various parameters, including Timed Up and Go (TUG) Test scores, and FACT-TAXANE (Version 4) subdomains assessing quality of life aspects in patients with chemotherapy-induced peripheral neuropathy (CINP).

Group A showed substantial improvement across all domains of the FACT-TAXANE scores post-intervention (e.g., Physical Well-Being: 15.2±1.317), with all p-values <0.0001. Notably, neuropathy scores improved significantly in Group A (9.1±1.595) while remaining high in Group B (25.6±4.222). this suggests that the multimodal program applied in Group A was more effective in improving functional abilities and quality of life for patients experiencing CIPN

The above observations in the outcomes may be because of following reasons that integrative multimodal therapeutic technique helps lessen side effects [20]. Exercises reduces CIPN by affecting blood circulation, inflammation, pain-relieving neurotransmitters, endogenous opioids, and mechanisms related to coping and symptom interaction [22]. Exercise enhances neuronal metabolism and stimulates the release of nerve growth factors, such as neurotrophins. This process supports the regeneration of damaged nerve fibres and enhance the plasticity of the peripheral nervous system, contributing to symptom relief during balance training [21]. Thus, the reduction in the neuropathy score may be because of above mechanism as the multimodal exercise program which focused on the aerobic, resistance and balance exercises. The improvement in the neuropathy score could be a reason that the physical wellbeing of the patients also improved. Improvement in physical wellbeing thus might have improved the social wellbeing of patients, socialisation of patients in community in turn could have led to an emotional improvement.

Group A shows a significant improvement in both pre- and post- intervention outcomes. 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 ($p<0.0001$).

Exercise based interventions trigger adaptive processes in neurons, muscles, and metabolic systems, leading to improved postural control, greater stability of the vestibular system, and enhanced overall body balance [21]. Exercises promotes neurogenesis and synaptogenesis in the brain [26]. Regularly, performed high-intensity exercises aid in the development of new brain connections and enhance motor skills [27]. The protein BDNF which promotes the survival, development, and differentiation of neurons and facilitates learning and memory, is found to be in higher concentrations when people exercise [28]. Exercise can modify neurotransmitter release and absorption, affecting mood regulation, motor control, and other physiological processes involving neurotransmitters including dopamine, serotonin, and norepinephrine [29]. Thus, a multimodal approach of exercises may have resulted a change in adaptive process of neurons, muscles, promotion of neurogenesis and synaptogenesis, release of neurotransmitters all these factors may have caused an improvement in the ability of patient to respond well to timed up and go test.

The current study correlates with the findings of Zimmer P et. al who also incorporated a multimodal

exercise program combining endurance, resistance, and balance training which helped maintain stable CIPN symptoms in patients (n=1 study; n=24 patients with metastasized colorectal cancer; intervention duration: 60 minutes, twice a week) [23].

A program incorporating progressive walking and resistance training positively impacted CIPN symptoms in patients (n= 1 study; n= 355 cancer-affected individuals; intervention duration: six weeks). Compared to the control group, the intervention group experienced a significant reduction in symptoms like hot/cold sensations in the hand and feet, numbness, and tingling. This improvement may be attributed to the ability of exercise top reduce chronic inflammation, which is believed to play a role in the development and management of CIPN.[24]

Another study confirmed the beneficial effects of exercise through a multimodal intervention that included resistance training, balance training and cardiovascular exercises (n= 1 study; n= 29 cancer surviors; intervention duration: three times per week for eight weeks)

V. Conclusion

The randomized controlled trial concludes that a Multimodal Therapeutic exercise Program is significantly more effective than a Conventional Exercise Program in managing Chemotherapy-induced Peripheral Neuropathy (CINP) in patients undergoing treatment with Paclitaxel and Carboplatin. The study demonstrated marked improvement in sensory-motor function, aerobic conditioning, and overall quality of life in patients who participated in the multimodal exercise program. Group A, which received this intervention, showed significant reductions in Timed UP and Go (TUG) Test scores and enhanced FACT-TAXANE scores across all domains, including Physical, Social, Emotional, and Functional Well-Being, with neuropathy symptoms significantly reduced (all p-values <0.0001). these findings suggest that incorporating a multimodal therapeutic exercise regimen could be vital strategy for improving both functional performance and the quality of life in cancer patients experiencing CIPN, providing valuable insights for healthcare professionals to tailor effective exercise interventions for the patient population.

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