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Game-like interactive exercise versus visual feedback in patients with chemotherapy induced peripheral neuropathy post mastectomy: A randomized comparative study

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***Abstract*---**Background Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most frequent side effects of antineoplastic agents, with a prevalence of 19 to 85%. In terms of clinical manifestations, CIPN is primarily a sensory neuropathy with motor and autonomic alterations of varying intensity and duration. CIPN consider as major problem for both cancer patients and survivors, as well as for their healthcare providers, possibly increasing the risk of falling. Objective: To evaluate the efficacy of game-like interactive exercise versus visual feedback training on the risk of falling and sensory integration in patients with chemotherapy-induced peripheral neuropathy after mastectomy. Methods: In this randomized comparative study, 30 female patients diagnosed with chemotherapy-induced peripheral neuropathy after mastectomy were randomly allocated into two equal groups; group (A) underwent game-like interactive exercise using the Biodex Balance System (BBS), while group (B) underwent a visual

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feedback training program using BBS. The treatment was applied for three sessions per week for four consecutive weeks. All subjects in both groups were assessed using the fall risk index and sensory integration test (sway index) in four sensory conditions at baseline and at the end of the study for both groups. Results: There were significant reductions in the risk of fall index in both groups post-treatment in favor of study group A (p-value ≤ 0.001), while there was no significant difference between both groups in mean values of the sway index of sensory integration (p-value = 0.174). Conclusion: According to our results, it was concluded that game-like interactive exercise was more effective in decreasing the risk of falling in patients with CIPN.

Keywords----Game-like interactive, visual feedback, sway index, neuropathy.

Introduction

Cancer is the largest cause of death in the world today. However, advances in medicine and the adoption of more effective therapies have resulted in an increase in the number of cancer survivors [1]. Although these survivors have overcome cancer, many of them have poor outcomes as a result of a variety of syndromes that diminish their quality of life as a result of cancer therapy, such as pain, which they often feel for a long time after treatment is completed [2]. The degeneration of sensory neurons causes sensory integration dysfunction that includes impairment in processing data from the different senses (vision, auditory, touch, olfaction, and taste), the vestibular system (movement), and proprioception [3].

Breast cancer is the most commonly diagnosed malignancy in women and the primary cause of cancer death; even when appropriate breast and axillary surgery is performed, regional and distant recurrences occur, thus compromising survival [4].

Chemotherapy-induced peripheral neuropathy (CIPN) is a common, potentially life-threatening, and dose-limiting complication of cancer treatment [5]. Type of chemotherapy, treatment schedule, combinations of different neurotoxic agents and patients' characteristics (age, preexisting causes of peripheral neuropathy such as diabetes mellitus, renal or hepatic dysfunction, and vitamin B12 deficiency) are all factors that influence the development of CIPN [6].

According to the WHO rating scale, a grade 0 corresponds to no symptoms of neuropathy, a grade 1 corresponds to paresthesia (a tingling, tickling, or prickling sensation) and/or decreased tendon reflexes, a grade 2 corresponds to severe paresthesia and/or mild weakness, grade 3 corresponds to intolerable paresthesia and/or marked motor loss, and a grade 4 corresponds to paralysis [7].

Sensory symptoms such as tingling, burning, pain, and numbness, as well as motor symptoms such as muscle cramps, weakening, and wasting, are all part of the CIPN clinical picture. In about 30% of patients, CIPN symptoms may persist for six months or longer after completion of neurotoxic chemotherapy [8]. The underlying causes of CIPN are various pathophysiological changes in the somatosensory (afferent) and motor (efferent) peripheral nerve fibers, with marked affection of lower limb proprioception, which often develop into balance problems that can significantly increase fall risk and posture sway, concomitant with gait instability, associated with further medical complications, and considerably deteriorated quality of life [9]. Other problems such as a deficit in tactile sensitivity, vibration sense, lower limb proprioception, kinesthesia, and greater postural instability occur. Postural instability is usually attributed to the lack of accurate proprioceptive feedback from the lower limbs [10].

Unique feature of the Biodex Balance System is an attached LCD monitor that provides augmented visual feedback. As the subject tries to keep the cursor in the center of the screen's grid, the monitor delivers information on the subject's ability to balance on the platform via a screen trace [11]. Visual feedback training incorporates a gaming element into balance training to improve motivation, increase patient participation, improve joint perception, improve posture stability, and maximize the effects of exercise by causing patients to become fully immersed in the games and enhancing major influential factors on the risk of falling [12].

Reducing the risk of falls and preventing their occurrence is essential for patients with CIPN to remain functionally independent. Balance-based exercise training using interactive video game programs is more enjoyable and attractive, thereby increasing both the frequency of practice and the level of attention during training. Patients are more willing to practice on a regular, long-term basis and are more compliant. It also had positive effects on functional balance and enhances postural stability in patients with CIPN [13].

The significant of this study to reduce risk of falling by using game-like interactive exercise as a new method in physical therapy field so the purpose of the study was to assess the influence of game-like interactive exercise versus visual feedback training on the risk of falling and sensory integration in patients with chemotherapy-induced peripheral neuropathy after mastectomy.

1- Material and methods

Study Design

A single-blinded randomized comparative study design

Setting and timescales

It was conducted in the biomechanics lab at the Faculty of Physical Therapy, MTI University, Egypt, for four consecutive weeks (three sessions per week) from September 2021 to February 2022.

Participants

40 female patients with chemotherapy-induced peripheral neuropathy (Grade I) after mastectomy were selected from the outpatient clinic, Faculty of Physical Therapy, MTI University, Egypt. They were eligible to participate in this study, but seven patients were excluded due to uncontrolled blood glucose levels, recent lower limb injuries, and toe deformities, while three patients refused to start assessment and treatment. The total number of patients is 30.

Inclusion and exclusion criteria

Inclusion criteria: Patients' ages ranged from 40 to 55 years; body mass index (BMI) ranged from 25–29.9 kg/m2, the average duration of the last session of chemotherapy treatment was one month; and the degree of neuropathy was grade I according to the WHO neuropathy scale.

A neurophysiologist referred all patients with sensorimotor peripheral neuropathy. selected patients experienced pain, numbness, and/or burning feelings, as well as distal motor weakness and the ability to walk without assistance.

Exclusion criteria: Patients with a recent history of foot ulcers, or lower limb fractures, toe amputation, visual disturbance, severe osteoporosis and arthritis, history of severe peripheral vascular diseases, patients with balance disturbance rather than diabetic peripheral neuropathy (e.g., labyrinthitis, other neurological disorders), patients with a history of any other neuropathy, such as diabetic neuropathy, patients who are starting new therapy or dose modification during the study period [16].

A modified total neuropathy score (mTNS) was used to assess the severity of CIPN pre-and post-treatment for both groups. Two constructs should be considered when assessing neuropathy: Neuropathy signs (altered vibratory and pinprick sensation, diminished reflexes, and muscle weakness) and symptoms (numbness, tingling, and neuropathic pain). To measure these structures, the (mTNS) is the most often used tool. It contains six items, each rated from 0 to 4 according to the severity of the patient's symptoms, for a total grade of 0 to 24. The higher the grade, the worse the neuropathy. It is graded as mild (1:9), moderate (10:19) and (20:24) severe [14].

Randomization and informed consent

Before the start of the study, all participants read and signed a consent form; anonymity and confidentiality were assured, and all procedures followed applicable laws and institutional norms. All patients were randomly assigned to one of two groups using the closed envelope: study group (A), n =15 who received game-like interactive exercise, and study group (B), n =15 who received visual feedback training (Figure 1).

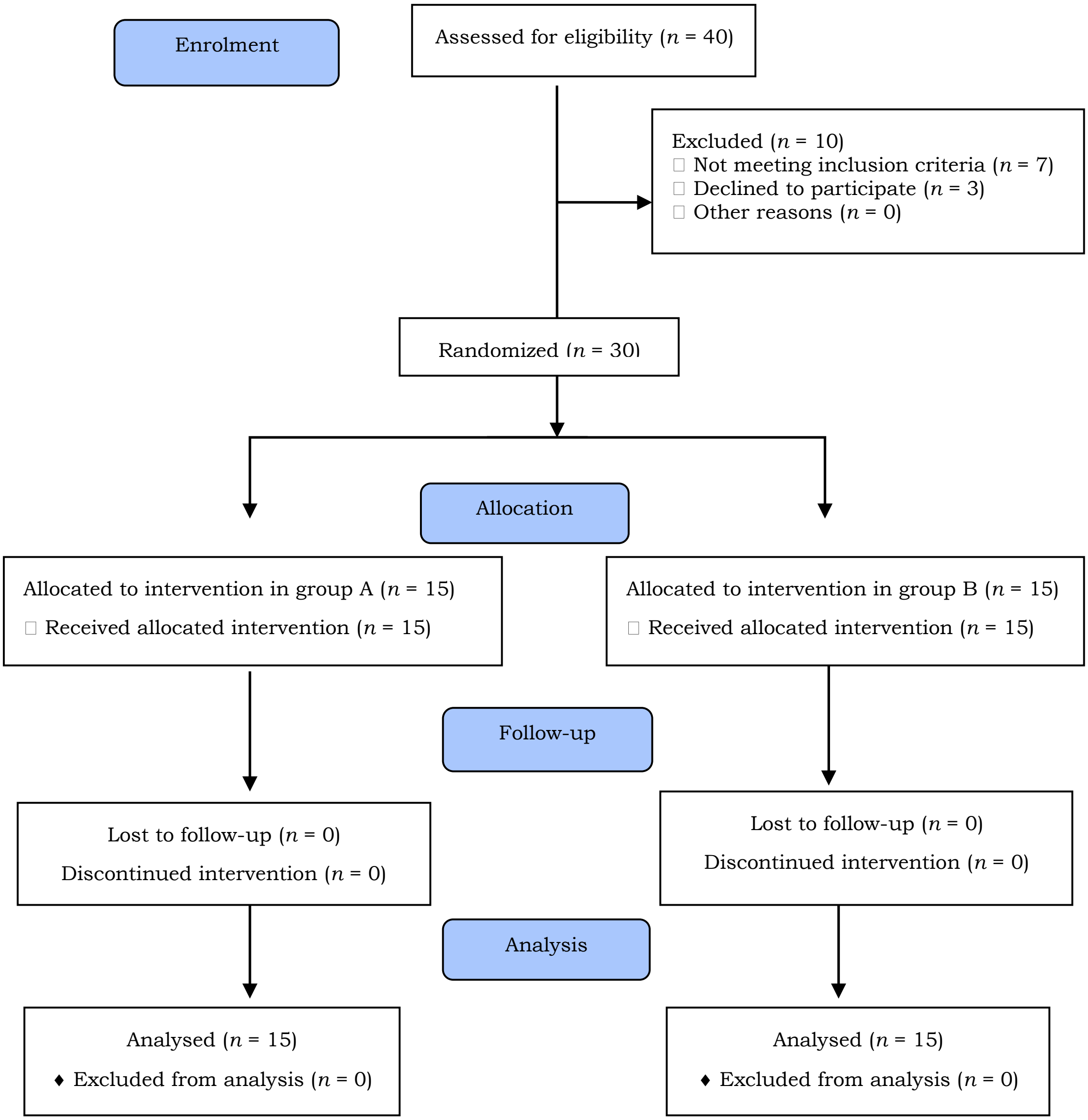

Fig. (1): The study flow chart

Ethical approval for the study:

The study was ethically authorized by the Institutional Ethical Committee of the Faculty of Physical Therapy, Cairo University, Egypt (**No: P.T.REC/012/003387**).

The Sample size power analysis

The sample size calculation is critical and fundamental for designing a study protocol. The sample size calculation was performed by using the G*Power analysis software version 3.1, Heinrich Heine-University, Düsseldorf, Germany for a one-tailed test, discovered that the suitable sample size was n =30.

Instrumentation:

- Risk of falling and sensory integration Assessment: patients underwent pre-treatment and post-treatment assessment using the biodex balance system (Biodex-medical system. Inc., brook baren R&D plaza, 20 Ramsey Road, box 702, Shirley, Newyork 11967-0702), this machine consists of a multiaxial standing platform which adjusted to provide varying degrees of platform tilt (level 1 to level 12) [15].

Assessment Procedure

The Evaluation protocol to assess the risk of the falling score by the Biodex balance system:

In the risk of the falling test, the patient stood on the platform and tried to compensate for the platform tilting until the end of the test trial. The test consists of three trials. The time of each trial is 20 seconds. The test calculated the velocity of postural sway to predict the risk of falling. Velocity means the speed of an individual's sway when trying to maintain balance.

After completion of the test, the instrument recorded the fall index and compared it to the normal data matched to the same age. A higher sway velocity indicates postural control deficits. Assessment of sway index for sensory integration and risk of fall index for each patient in both groups was performed pre-and post-treatment [16].

Evaluation protocol to assess sensory integration by the Biodex balance system:

The patient was standing in a comfortable upright position. Level eight was selected (stable level), then the postural stability testing mode was selected, and then the data of the patient was inserted into the device. The patient was instructed to try to achieve a centered position on the platform once the platform was set to motion. This is performed by adjusting the patient's feet to a position where the cursor on the visual feedback screen may easily be kept in the middle of the screen. The platform was kept level beneath the patient's feet after the cursor was centered in the middle.

The sensory integration test measures the ability of the patient to integrate various senses to balance and the ability to compensate when one or more of those senses were compromised. The modified clinical test of sensory integration and balance (M-CTSIB) consisted of four conditions; Condition one: The patient stood on a firm surface with opened eyes and looked at a target on the display screen during platform tilt so incorporated visual, vestibular, and somatosensory inputs. Condition two: The patient stood on a firm surface with closed eyes and eliminated visual input to evaluate vestibular and somatosensory inputs during platform tilt. Condition three: The patient stood on a foam surface with opened eyes and looked at a target on the display screen during platform tilt to evaluate somatosensory interaction with visual input. Condition four: The patient stood on a foam surface with closed eyes during platform tilt to evaluate somatosensory interaction with vestibular input. The device records the actual postural sway and calculates the variance from the center, which is expressed as a balanced index. The sway index is the stability index's standard deviation. The higher the sway index, the more unsteady the person was during the test. The patient performed three trials; the trial duration was 20 seconds with a rest period of 25 seconds [17].

Treatment protocol:

30 patients were randomly divided into two equal groups; Patients in Group A received game-like interactive exercise, while patients in Group B received visual feedback training; the patients attended the rehabilitation center for one-on-one therapy (three times per week for four weeks), and session duration was about 30 minutes.

Game-like interactive exercise (Group A): Catch Game is an opportunity to work on balance skills in a game-like setting and provides standardized training protocols. A used game-like interactive exercise-based rehabilitation can be challenging, engaging, and fun. The use of a game exercise in the biodex balance system allows the patient to kick a ball to reach the target while she shifts her body weight on the platform of the biodex balance system.

Visual feedback (Group B): the patient was standing on both feet and grasping the handrails of the biodex balance system. The patient was told to try to get into a balanced position on the platform (once the platform was set to motion). This is achieved by shifting the patient's feet to a position where it was easy to keep the cursor on the visual feedback screen in the blinking center box, (16 boxes arranged around the center, the boxes at the top represent the anterior limits of stability (LOS); the boxes on the right and left of center represent medial and lateral LOS, and the boxes at the bottom represent the posterior LOS).

Statistical Analysis

All statistical calculations were done using the computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, USA) release 22 for Microsoft Windows [18]. A Test of normality (Shapiro-Wilk test) was used before applying statistical analysis, and it showed that data was not normally distributed, so we used a non-parametric test, Paired t-test was used for comparison within each group, an unpaired (Independent) t-test was used for comparison between groups, and P-values less than 0.05 were considered statistically significant, and less than 0.01 was considered highly significant [19].

Results

This study included 30 post-mastectomy patients with CIPN.

Subjects' demographic data

There was no significant difference between both groups regarding age, weight, height, and BMI (p-value > 0.05) **(table 1).**

Table (1): General demographic data

Variable	Group A (n=15) Mean ±SD	Group B (n=15) Mean ±SD	F	P-value
Age (Year)	45.42 ± 5.26	47.60 ± 4.92	0.179	0.837
Weight (kg)	82.20 ±6.23	79.23 ±6.27	1.444	0.247
Height (cm)	173.73 ±5.07	170.67 ±5.77	1.183	0.316
BMI (kg/m²)	27.23 ±1.64	26.80 ±1.84	1.663	0.202

SD, Standard deviation; p-value statistical significance; BMI, body mass index.

Modified total neuropathy score (mTNS)

Within groups, Group A had shown a significant decrease in the mean values of mTNS post-treatment compared with that pre-treatment (p-value ≤ 0.001) and there was also a significant decrease in mTNS mean values in group B between pre-and post-treatment (p-value ≤ 0.001). Comparisons between groups had shown that there was no significant difference in mean values of the mTNS between groups pre-treatment (p-value = 0.903), while there was a highly significant difference in mean values of the mTNS between groups post-treatment (p-value ≤ 0.001). There was a significant decrease in the mTNS in favor of group A post-treatment, as shown in **(tables 2 and 3).**

Comparing sensory integration within and between groups

Within groups, Group A had shown a significant decrease in the mean values of sway index of sensory integration post-treatment compared with that in pre-treatment (p-value ≤ 0.001), and there was a significant decrease in sway index of sensory integration mean values in group B between pre-and post-treatment (p-value ≤ 0.001). Comparisons between groups had shown that there was no significant difference in mean values of the sway index of sensory integration between groups, neither in pre-treatment (p-value = 0. 0.332) nor in post-treatment (p-value = 0.174) **(tables 2 and 3).**

Comparing of risk of the falling index within and between groups

Within groups, Group A had shown a significant decrease in the mean values of risk of falling index post-treatment compared with that pre-treatment (p-value ≤ 0.001) and there was also a significant decrease in the risk of falling index mean values in group B between pre-and post-treatment (p-value ≤ 0.001). Comparisons between groups had shown that there was no significant difference in mean values of the risk of a falling index between groups pre-treatment (p-value = 0.471), while there was a highly significant difference in mean values of the risk of a falling index between groups post-treatment (p-value ≤ 0.001). There was a significant decrease in the risk of falling index in favor of group A post-treatment **(tables 2 and 3).**

Table (2): Comparison between mean values within each group (Pre-Post test)

Variable / Group		mTNS	SI	RFI
Group A (n=15) (Game-like interactive exercise)	Mean ± SD	5.07 ± 1.44	0.78 ± 0.35	0.75 ± 0.26
	T- value	13.65	8.76	11.16
	P-value	≤ 0.001*	≤ 0.001*	≤ 0.001*
Group B (n=15) (Visual feedback training)	Mean ± SD	7.20 ± 2.08	0.90 ± 0.67	1.66 ± 0.35
	T- Value	13.425	5.213	18.36
	P-value	≤ 0.001*	≤ 0.001*	≤ 0.001*

*P-value significant ≤ 0.05; mTNS, modified total neuropathy score; SI, Sensory integration; RFI, risk of falling index; SD, standard deviation.

Table (3): Comparison between mean values between both groups

Variable		**Group A (n=15)**	**Group B (n=15)**	**F**	**P- value**
		Mean ± SD			
mTNS	Pre-Test	10.47 ± 3.16	10.33 ± 2.795	0.330	0.903
	Post-Test	5.40 ± 2.03	3.13 ± 1.356	3.133	≤ 0.001*
SI	Pre-Test	2.73 ± 0.44	2.58 ± 0.37	0.268	0.332
	Post-Test	1.95 ± 0.51	1.68 ± 0.54	0.373	0.174
ROF	Pre-Test	3.25 ± 0.55	3.42 ± 0.59	0.358	0.417
	Post-Test	2.49 ± 0.52	1.76 ± 0.52	0.002	≤ 0.001*

*p-value significant ≤ 0.05; mTNS, modified total neuropathy score; SI, Sensory integration; RFI, risk of falling index; SD, standard deviation.

Discussion

This study was conducted to evaluate the efficacy of game-like interactive exercise versus visual feedback training on the risk of falling and sensory integration in patients with chemotherapy-induced peripheral neuropathy after mastectomy. In this randomized comparative study, 30 female patients were randomly allocated into two equal groups; group (A) underwent a game-like interactive exercise using the Biodex Balance System (BBS), while group (B) underwent a visual feedback training program using the BBS. The treatment was applied three sessions per week for four consecutive weeks. All subjects in both groups were assessed using the fall risk index and sensory integration test (sway index) in four sensory conditions, at baseline and at the end of the study for both groups.

There were significant reductions in the risk of fall index in both groups post-treatment in favor of study group A (p-value ≤ 0.001), while there was no significant difference between both groups in mean values of the sway index of sensory integration (p-value = 0.174).

The Biodex balance system was used for the training of static and dynamic balance. This system focuses on the proprioceptive neuromuscular mechanisms that appear to affect both static and dynamic balance. The system acts as a valuable training device to enhance kinesthetic abilities that may provide some degree of compensation for impaired proprioceptive reflex mechanisms following injury [20].

The principal finding of the present study was that game-like interactive exercise was significantly more effective than visual feedback training in reducing the risk of falling, as measured by the Biodex balance system, in patients with CIPN. The incidence of CIPN in Egypt reached 46.8%, where most of them (70%) were grade I, and only 4.4% developed grade III. A data concluded in the meta-analysis of 31 studies of CIPN involving a total of 4,179 patients where the incidence of CIPN was 48% [21].

The findings of the current study are in line with other studies that analyzed the effects of visual feedback training for patients with PN. They reported that balance and postural stability can be improved, probably utilizing an increase in Proprioception, leading to a reduction of falls related to sensory deficits. The combination of the vestibular, visual, and sensory systems results in postural regulation, and any changes in one or more of these systems, such as sensory impairments on the feet, can lead to postural instability [22].

Proprioceptive training provides an unsteady surface that challenges the body to maintain balance. Sensory inputs were manipulated during the exercise intervention by changing the support surface. Participants were compelled to effectively reweigh the remaining inputs within the CNS as a result of these modifications. Evidence of similarly enhanced central integration, following sensory training, has been found in previous studies, demonstrating improved stability during the manipulation of the proprioceptive or vestibular environment. Moreover, proprioceptive training can also augment increased proprioceptive firing from the cutaneous receptors from the feet and also from mechanoreceptors of the muscles during co-contraction produced by the swaying movement. It's also possible that the new and expanded feedback will improve motor learning, which will have an impact on balance. Finally, proprioceptive training can be employed to improve functional balance in diabetic neuropathy patients straightforwardly and cost-effectively. This may help the patient to improve their quality of life by reducing the risk of falls when performing activities of daily living [23].

Reduced balance and postural control are major contributors to functional limitations and barriers to performing activities of daily living in patients with hemiparesis. This study reviewed existing evidence on gaming training on balance and postural control. Virtual reality training is safe and economical, and it may encourage user interest [24].

The results of this study were confirmed by [25] who demonstrated that the strongest evidence supports the fact that visual feedback balance training is an effective adjunct to routine physiotherapy to improve dynamic balance and static balance in patients with hemiparesis. The neurophysiological and behavioral benefits of movement observation, imagery, repetitive massed practice, and imitation therapies in facilitating voluntary movement production can be easily incorporated into gaming exercises to improve the training experience and allow the clinician to use sensory stimulation through gaming to facilitate targeted brain networks, such as the motor areas, which are critical for neural and functional recovery.

Also, [26] came in agreement with the result of this study, as their study mentioned that interventions using virtual reality may improve the balance and gait in patients with hemiparesis and develop their gross motor function, fine motor function, and coordination. Reported that virtual reality training is a safe and useful tool for enhancing the sensorimotor functions of patients with hemiparesis and for improving balance and gait during rehabilitation treatment. It's a good home-based alternative to physical treatment.

Finally, [27] conducted a study that concluded that the virtual reality Wii gaming system is feasible, promotes motor recovery after spinal injury, increases patient motivation, and enriches the treatment.

Conclusion

Within the scope of this study, game-like interactive exercise was more effective than visual feedback in decreasing the risk of falling in patients with CIPN while there was no significant difference between game-like interactive exercise and visual feedback in decreasing the sway index of sensory integration.

Recommendation

From the result of this study, we recommend using game-like interactive exercise in the rehabilitation program for chemotherapy-induced peripheral neuropathy patients with balance of falling disturbance. Also, further study is recommended to study the combined and long-term effect of game-like interactive exercise and visual feedback on the risk of falling and sensory integration in patients with chemotherapy-induced peripheral neuropathy after mastectomy

Conflict of authors

The authors state no conflict of interest.

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