Original Article

The Effect of a Combined Exercise Program on the Fatigue Severity of Patients with Breast Cancer Undergoing Chemotherapy: A Randomized Clinical Trial Study

Abstract

Background: Breast Cancer (BC) is one of the most common cancers in the world, including in Iran. Chemotherapy as one of the basic treatments for BC leads to many side effects such as fatigue. This study aimed to examine the effect of a combined exercise program on the intensity of fatigue in patients with BC undergoing chemotherapy. **Materials and Methods:** This clinical trial study was conducted on 64 patients with BC undergoing chemotherapy referring to the Seyyed al-Shoada and the Al-Zahra clinics from January to April 2022. Eligible patients who met inclusion criteria were recruited by the convenience sampling and then assigned randomly to intervention and control groups. The combined exercise program in the intervention group was done for 8 weeks as three sessions a week (34 sessions) each for 35–40 min. Piper's Fatigue Scale was completed for both groups before and after the intervention. Data were analyzed using descriptive and inferential statistical methods. **Results:** The results showed that the mean score of fatigue intensity in both control and intervention groups had a statistically significant difference after the intervention (p = 0.004). The mean fatigue intensity score in the intervention group decreased significantly from mean (SD) 8.17 (1.88) to 5.56 (1.74). **Conclusions:** Based on the results, a combined exercise program can reduce fatigue in patients with BC. Therefore, nurses can utilize exercise programs and practices as a subset of complementary medicine alongside other treatment methods, which can effectively promote cancer patients' quality of life by reducing their fatigue.

Keywords: *Breast neoplasms, drug therapy, exercise, fatigue, nursing*

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Introduction

Breast Cancer (BC) is the most common cancer in women in the United States, except for skin cancers in 2023. It accounts for about 30% of all new female cancers each year.[1] In Iran, BC accounts for a major problem in women's health. Almost one out of ten Iranian women are prone to developing BC, which indicates the importance of the detection and control of this disease in Iran.[2] Unfortunately, the BC incidence rate is on the rise in Iranian women, and estimates show that BC is responsible for 30% of total cancers and 15% of cancer-induced deaths among women.[3] BC accounts for 23% of total cancers diagnosed in women in Iran, as reported by the Iran National Cancer Registry.[4] Although the treatment success has been a great endowment for prolonging patients' lifetime, increasing patients' survival alone is not sufficient because patients do not only want to survive but they also want to have a more untroubled life.[5]

Accordingly, increasing the lifetime of patients with cancer, including BC, has caused new challenges in healthcare systems. Inattention to such patients and leaving them behind to seek conventional and arduous treatments cause multiple problems such as anxiety, depression, chronic fatigue, sleep disorders, and, ultimately, a considerable decline in their quality of life.[6] For this reason, healthcare services provided to patients with cancer have been increasingly directed toward developing interventions to increase patients' lifetime, in addition to interventions to reduce complications and improve their quality of life.[5]

Currently, chemotherapy is widely used in patients with BC.[7] It is noteworthy

How to cite this article: Darvishi E, Musarezaie A, Bahrami M, Karimian J. The effect of a combined exercise program on the fatigue severity of patients with breast cancer undergoing chemotherapy: A randomized clinical trial study. Iran J Nurs Midwifery Res 2023;28:398-404.

Submitted: 26-Dec-2022. **Revised:** 17-May-2023. **Accepted:** 23-May-2023. **Published:** 24-Jul-2023.

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Access this article online

Website: https://journals.lww.com/jnmr

DOI: 10.4103/ijnmr.ijnmr_399_22

Quick Response Code:

that chemotherapy, as an essential and primary treatment of BC, results in many side effects, including fatigue, nausea, vomiting, sleep disorders, and many other complications.[8] In addition, chemotherapy causes fatigue in patients more than other cancer treatment methods.[9] Therefore, fatigue falls into the most common problem of patients with BC (caused by the disease or treatment procedures, particularly chemotherapy). A noteworthy issue is the very high prevalence of fatigue in patients undergoing chemotherapy as 90% to about 100% of cancer patients undergoing chemotherapy suffer from fatigue.[10-12] For many cancer patients, cancer-related fatigue is so severe that it disrupts and limits their daily activities. Fatigue is a combination of weakness, lack of energy, impatience, lack of concentration, boredom, and exhaustion, which can sometimes lead to insufficient coping with the disease and discontinuation of treatment.[13] The adverse effects of fatigue on patients' quality of life expand in a wide range of physical activity reduction to extension in other aspects, such as anxiety, depression, sleep disorders, reduced concentration and memory, reduced survival, and increased mortality.[14,15] The costs caused by patients' reduced activity, loss of occupation, or fatigue-induced absenteeism make the treatment process more difficult.[16,17] Thus, fatigue in cancer patients is so severe that it necessitates treatment considerations.[18] In addition, the existing therapeutic and medicinal strategies are costly and sometimes associated with many unwanted complications; these strategies are not easily available to all patients. Therefore, it is necessary to find a non-medicinal, non-invasive, easy, and cost-effective strategy for these problems. Consequently, the tendency to use complementary and alternative therapies as supportive treatments with community-based nature has increased in many healthcare centers in recent years.[19,20]

Exercise falls under a subset of complementary medicine. In nursing science, exercise and its applications in various populations have been considered effective in professional nursing care evolution. Despite exercise advantages in disease prevention and treatment, it is important for nurses to identify opportunities to promote Exercise-Based Interventions (EBIs) as nursing interventions.[21] EBIs have also been considered in nursing theories, such as Levine's conservation theory (the first and second principles of quadruple principles). Studies conducted based on Levine's conservation model of nursing indicate that nurses can directly and indirectly help patients with EBIs to reduce their fatigue after cancer diagnosis.[22,23]

Despite the presence of positive findings on the effectiveness of exercise programs and practices, the ineffectiveness of exercise programs in fatigue levels and other measured indices has been reported in a significant number of studies. For example, Jiang *et al*. (2020)[24] and Husebø *et al*. (2014)[25] presented evidence that exercise programs were ineffective in the fatigue reduction of BC patients undergoing chemotherapy. In a study on cancer patients, Coleman *et al*. (2012)[26] found that exercise intervention could not statistically reduce their fatigue severity. Other results of clinical trials in England (Tsianakas *et al*. 2017)[27] and Germany (Kuehr *et al*. 2014)[28] also suggested the ineffectiveness of exercise practices in cancer-induced patients' fatigue.

Studies conducted in other countries or on other patient groups have reported statistically significant effects of combined exercise programs on selected dependent variables. However, no similar research is available among domestic studies on BC patients (scarce evidence of domestic research). In addition, contradictory findings and high ambiguities concerning the effects of exercise practices on BC patients' fatigue severity are observed in studies conducted in other countries. The interventions should also have exclusive features, namely easy implementation, low dependence on specific equipment or setting, and inexpensiveness. Therefore, this study aimed to evaluate the effect of combined stretching and aerobic exercise practices on the fatigue severity of BC patients undergoing chemotherapy referring to selected centers of Esfahan city in 2020.

Materials and Methods

This randomized clinical trial (IRCT20141127020108N1) study with no blinding was conducted on 64 female BC patients (32 patients in the control group and 32 in the intervention group) undergoing chemotherapy from January to April 2022 for four months referring to the Seyyed al-Shoada (as) clinic and the Al-Zahra super-specialty benevolent health center. The sample size was 64 BC patients taking into account a confidence interval of 95% and a power factor of the test of 80%. Eligible patients who met inclusion criteria were recruited by the convenience sampling and assigned randomly to intervention and control groups. The researcher randomly determined at first that the patients who were assigned odd and even numbers were in the test control groups, respectively. Then, individual patients closed their eyes and put their fingers on one of the digits of the random number table. The direction of movement was predetermined at the same time. The researcher selected the required even and odd numbers by moving in the table of random numbers. The numbers were placed in separate envelopes all in one box. Card number one was opened for the included samples who met the inclusion criteria by the convenience method. They were then assigned to one of the test or control groups depending on an even or odd number on this card. The main inclusion criteria were patients' knowledge of their illness, lack of mental retardation, blindness, deafness, physical and mobility impairment problems, inclusion in the adult age group (18–65 years), at least 1 month after diagnosis, experiencing at least two chemotherapy sessions, no history of all cancer types other than BC, no participation

in similar exercise sessions during last 2 months, and access to WhatsApp software. Exclusion criteria included absence in over three of all exercise sessions and regular participation in similar aerobic exercise programs (three or more sessions a week) during the intervention.

The research was registered in the Iranian Registry of Clinical Trials center, which was conducted for 4 months from June to September 2021. After obtaining the code of ethics, researchers collected data in the study location through the completion of questionnaires by the subjects by observing ethical considerations. Informed consent was also obtained from the patients. The first and second parts of the questionnaire were about demographic information and Piper's Fatigue Scale (PFS) containing 27 items evaluating four behavioral, emotional, sensory, and cognitive/mood dimensions. The total score of PFS is calculated from the total score obtained from 22 items divided by 22. Thus, the total score of this questionnaire is calculated by dividing 220 (the maximum possible score) by 22, that is, the obtained score will range between 0 and 10. Five additional items (1 and 24–27) are not used in calculating the scores of subscales and the total score of the fatigue scale. Hence, these five additional items are not needed in calculating this scale and are only used in evaluating descriptive data and enriching the scale. The PFS is widely used in the cancer patient community in which acceptable reliability of this scale was obtained by Cronbach's alpha (r = 0.64; r = 0.8).[29,30] This questionnaire was also validated and used in Iran and was recognized as a tool with acceptable validity and reliability.[31]

The combined exercise program was planned for 8 weeks (2 months) during which the intervention was presented as an in-person session for teaching, followed by a home-based exercise program guided by the researchers. Based on a review of different articles and the policy of the American College of Sports Medicine Certification (ACSM), the home-based structured exercise protocol was designed by a specialist in physical education. According to the designed exercise program, the exercise intervention in the intervention group was implemented for 8 weeks as three sessions a week (24 sessions) each for 35–40 min, lasting for about 4 months. The protocol included three sections, warm-up, aerobic exercise, and cool-down. Stretching exercises were incorporated in the warm-up and cool-down sections. A physioball, Pilate's elastic band, and exercise rope were among the instruments used in this study. The designed exercise program includes a variety of exercises including gentle running, fast walking, exercises to strengthen the abdominal muscles, standing balance exercises, open leg squats, leg, arm, and neck stretching exercises, trunk rotation, training with the stretch loop to strengthen the muscles of arms and legs, various movements with dumbbells, swimming movements, dynamic movement exercises, etc. In this research, the intensity of exercise movements was evaluated based on the Maximum Heart Rate (MHR) and increased gradually. The exercise intervention was performed with low-moderate intensity (55% of the MHR), 55%, and 75% of the MHR in the first, second, and the last 4 weeks, respectively.[32-34] In the first session, the patients were taught to calculate MHR using the formula "MHR = 220 – age". All stages of research implementation and sports exercises were carried out under the supervision of a sports expert.

In our home-based structured exercise protocol, the first session was held face-to-face, but all other sessions were held virtually at the participants' homes. The participants performed the exercise programs offline through the contents provided on DVDs. Nonetheless, online video communication through WhatsApp or two-way interaction through WhatsApp was made possible for the participants before, during, and after each session. The researchers supervised the correct implementation of the intervention through the formation of a WhatsApp group and continuous telephone follow-up with the patients. Before the start of each session, all the texts and videos related to the session were uploaded to the WhatsApp group to remind the BC patients how to perform the exercise for that day and session. About half an hour before the session time, the researcher made a phone call (as a reminder) to each member of the group and asked them to examine the content uploaded to the WhatsApp group. If there were any problems in doing sports, the participants would ask questions in the WhatsApp group, and the researcher and sports expert would answer the questions interactively. The questionnaire was completed face-to-face in medical centers before the intervention. However, due to difficult access to the patients after the intervention (the remoteness of some patients and the COVID-19 pandemic conditions), the fatigue questionnaire was sent to both groups for completion and was completed virtually in Google form format. The control group received routine care. To fulfill ethical considerations, the same exercise intervention was also done for patients in the control group upon their request and attended the first session face-to-face after the end of the project. The normality of the data distribution was confirmed using the Kolmogorov–Smirnov test. Parametric tests were used due to the quantity of the data (mean score) to confirm the assumption of the normality of data distribution. There was no sample attrition in this study. Data were analyzed by SPSS 26 statistical software (SPSS Inc., Chicago, IL) using descriptive (frequency distribution, mean, and standard deviation) and inferential (Chi-square and paired/independent t-test) statistics.

Ethical considerations

This research was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (ethics code: IR.MUI.RESEARCH.REC.1399.592). All participants signed the written informed consent form and their rights were respected under the Helsinki Declaration.

Results

In terms of demographic information, most of the participants in the control and intervention groups were female (100%) and mostly married (90.60%). The demographic information of the subjects is partly presented in Table 1. The Chi-square test results indicated that the frequency distribution of demographic variables was not significantly different before the intervention ($p > 0.05$), suggesting the homogenous distribution of these variables in both groups. According to the independent *t*-test results, the means of the variables (age, time after the diagnosis, and chemotherapy sessions) were not significantly different in the intervention and control groups before the intervention ($p > 0.05$), indicating the homogenous distribution of these variables in both groups.

The independent *t*-test results revealed a significant difference in the average scores of fatigue severity in the intervention and control groups after the intervention ($t_{62} = -4.30$, $p = 0.004$(. After the intervention, the average score of fatigue severity declined significantly from 8.17 (1.88) to 5.56 (1.74) in the intervention group ($t_{31} = -5.92$, $p = 0.001$).

The paired *t*-test results showed no significant difference in the average scores of fatigue severity in the control group before and after the intervention ($p > 0.05$). Based on the independent *t*-test results, the control and intervention groups were not statistically different in the average scores of fatigue severity before the intervention ($p > 0.05$) [Table 2].

Discussion

The results of this study demonstrated that the average scores of fatigue severity were significantly different in the intervention group before and after the intervention, indicating that the designed exercise intervention could reduce the average score of fatigue severity in the test group. Schmidt *et al.* (2015)[35] investigated the effects of resistance (two sessions for 12 weeks) on fatigue and quality of life in BC patients undergoing chemotherapy. They observed that exercise practices significantly reduced the fatigue level ($p = 0.04$), which is in line with our results. In a study on the effects of a supervised home-based exercise intervention on cancer-related fatigue during chemotherapy for 6 weeks, Andersen *et al*. (2013)[36] reported that the fatigue score decreased significantly in the intervention group ($p = 0.002$). Our findings are also in agreement with the mentioned studies. These results can be attributed to the fact that participation in exercise classes increases physical and cardiovascular readiness and reduces patients' sense of fatigue. Because muscle atrophy is a problem in most cancer patients, stretching and aerobic exercises can effectively prevent this condition.

Contrary to our results, Husebø *et al.* (2014)[25] studied the effect of a home-based exercise program on the fatigue, activity, and physical readiness of 67 BC women undergoing chemotherapy in Norway. The test group performed resistance exercises, including strength exercises with elastic bands, walking, and aerobic exercises, 3 days a week. The results revealed that the average fatigue severity scores of BC patients were not significant in the test group before and after the intervention ($p < 0.05$). The

Table 1: The frequency distribution of qualitative demographic variables in the intervention and control groups

Frequently distribution Variable	Classification	Control Group Number (%)	Intervention Group Number (%)	df	*p*
Gender	Male	-	-	-	-
	Female	32 (100)	32 (100)		
Marital status	Widow	3 (9.40)	1 (3.10)	2	0.223
	Married	29 (90.60)	29 (90.60)		
	Divorced	0	2 (6.30)		
Level of education	High school	25 (78.10)	16 (50.0)	2	0.087
	Diploma	4 (12.50)	9 (29.0)		
	University	3 (9.40)	6 (19.40)		
Employment status	Employed	7 (21.870)	7 (21.870)	1	0.312
	Housewife	25 (78.12)	24 (75.00)		
	Retired	0	1 (3.13)		
Income status	Low	16 (50.0)	16 (50.0)	1	0.435
	Medium	10 (31.25)	11 (34.37)		
	Good	6 (18.75)	5 (15.62)		
Type of chemotherapy	Ac*	7 (21.90)	9 (28.10)	3	0.087
	Caf**	3 (9.40)	0		
	Cef***	5 (15.60)	1 (3.10)		
	Other	17 (53.10)	22 (68.80)		

*Adriamycin - Cyclophosphamide. **Cyclophosphamide- Adriamycin- Fluorouracil. ***Cyclophosphamide- Epirubicin- Fluorouracil

Table 2: Within- and between-group comparisons in terms of the total mean score of the fatigue severity

Groups	Times		*p***	df**	*t***
	Before intervention	After intervention			
	Mean (SD)***	Mean (SD)			
Intervention (*n*=32)	8.17 (1.88)	5.56 (1.74)	0.001	31	-5.92
Control (*n*=32)	6.77 (1.67)	7.52 (1.89)	0.06	31	1.55
*p**	0.07	0.004			
df*	62	62			
*t**	1.19	4.30			

*The results of the independent sample *t*-test, **The results of the paired sample *t*-test. ***SD: Standard deviation

contradictory results may be attributed to different fatigue severity measurement tools (PFS versus Schwartz's Cancer Fatigue Scale in their study) and differences in the type and duration of the designed exercise program (stretching and aerobic exercises for 8 weeks, strength exercises with elastic bands, walking, and aerobic exercises in their study) in the two investigations.

According to the present results, statistically significant differences were observed between the average fatigue severity scores in the control and test groups. This finding corresponds to those of several studies evaluating the effects of exercise practices on cancer patients' fatigue severity, including An *et al.* (2019) in Canada,[37] Schmidt *et al.* (2015) in the United States,[35] and Andersen *et al*. (2013) in the United States.[36] These studies suggest the significant effects of physical and exercise practices on intervention groups compared to control groups.

Alongside the studies confirming our results, contradictory investigations are also observed in this context. For example, Tsianakas *et al.* (2017)[27] investigated the effect of walking on the quality of life in 42 patients with metastatic and recurrent cancers in two teaching treatment centers in London. The results indicated that physical activity did not significantly affect the fatigue severity of patients in the test group compared to the control group, and the cancer-related fatigue did not significantly decrease in these patients ($p < 0.05$). In another inconsistent investigation in the oncology ward of Carl Gustav Carus teaching hospital (Dresden, Germany), Schuler *et al.* (2017)[38] reported no significant effect of an exercise program on the fatigue severity of cancer patients undergoing chemotherapy in intervention groups compared to control groups ($p > 0.05$).

The discrepant studies in terms of different components may be considered possible reasons for these contradictions. These include differences in the type of participants' diseases (patients with metastatic breast, colorectal, digestive, prostate, and head/neck cancers in Tsianakas *et al*., or patients with digestive, lung, testis, breast, and brain cancers in Schuler *et al*. vs. non-metastatic BC patients in this study). Other reasons are differences in fatigue severity measurement tools (the Scottish physical activity questionnaire used in Tsianakas *et al*.,[27] or international physical activity and Berg's questionnaires used in Schuler *et al*.[38] vs. PFS used here). Differences in the type and duration of designed exercise programs (resistance exercises for 12 weeks in Schuler *et al*.,[38] or walking in 30 min for 12 weeks in Tsianakas *et al*.[27] vs. 24 sessions for 8 weeks in this research) are among other possible reasons for the discrepancies.

Since this research was conducted as a master's thesis with a time limitation, it is recommended to carry out a similar study with more sample size and in a longer time. The time limitation led to a short-term evaluation for the researcher, as a limitation in this study. Thus, evaluations should be implemented for longer times, for example, 1, 2, and 6 months.

Conclusion

Based on the results of this research, a combined aerobic and stretching exercise program can reduce fatigue severity in BC patients undergoing chemotherapy. Therefore, nurses can use exercise programs and practices as a subset of complementary medicine alongside other treatment methods, which can effectively promote cancer patients' quality of life by reducing their fatigue severity. In nursing science, exercise and its applications in various populations have been considered effective in professional nursing care evolution. As a nursing intervention, this study aims at developing and applying this science practically in the nursing field. Despite the exercise advantages in disease prevention and treatment, it is important for nurses to identify opportunities to promote exercise-based interventions as the nursing intervention. The success and effectiveness of exercise interventions in the nursing field result from the fact that nurses are in contact with these patients for longer times than other treatment personnel. As such, they possess a good opportunity to describe the goals and advantages of exercise practices and teach these simple movements to patients. Ease of use, safety, lack of side effects, low cost, and creating happiness and esprit (mood enhancement) are the other possible reasons for the success of the combined exercise program. A formulated investment can turn this program into a complementary strategy to control and reduce fatigue in cancer patients undergoing chemotherapy.

Acknowledgements

The authors would like to thank the women for their willingness to participate in this study. This manuscript was a part of the MSc dissertation (Project No: 399656).

Financial support and sponsorship

Isfahan University of Medical Sciences

Conflicts of interest

Nothing to declare.

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