Original Article

Cluster Symptoms Reduction via Telephone-Based Intervention in Thai Breast Cancer Patients Undergoing 4-Cycle Adjuvant Chemotherapy: A Randomized-Controlled Trial

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Background: Cluster symptoms are a common occurrence in breast cancer patients undergoing chemotherapy. The telephone is a well-recognized, convenient device for reaching out to patients for monitoring and managing their symptoms in an efficient, prompt, and appropriate manner.

Objective: To investigate the efficacy of telephone-based intervention to achieve energy conservation among breast cancer patients with the aim of alleviating fatigue, pain, sleep disturbance, and depression.

Materials and Methods: The present study was a two-armed, randomized control trial conducted in the university hospital between March and September 2019. Seventy-four breast cancer patients, receiving four courses of adjuvant chemotherapy, were randomly recruited and assigned into the experimental group and the control group. One face-to-face intervention interview for energy conservation was conducted, followed by 20-minutes telephone brief counselling and assessment sessions, scheduled on day 1, 2, 7, and 14.

Results: The scores for symptoms of median fatigue and pain in the experimental group were shown to be significantly reduced at the end of the study as compared to those scores within the control group ($p<0.05$). Similarly, scores for median sleep time and depression were greater at the end of cycle 1 and highest in cycle 2 ($p<0.05$, 0.001, respectively). Physical activity levels were also higher in the experimental group than in the control group in every cycle, with a statistical significance ($p<0.001$).

Conclusion: The present study intervention demonstrated an effectiveness for the reduction of cluster symptoms. Further studies would be needed in a larger population scale in the customary, randomized controlled trial manner.

Keywords: Cancer; Energy conservation; Fatigue; Pain; Sleep; Telephone

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Breast cancer is the third leading cause of death in Thailand. In 2018, it was the first ranked female cancer, accounting for 41% of female cancer patients in Thailand[1]. The mortality rate increased by approximately 29% between 2014 and 2018[2]. The most common chemotherapy regimen in early-stage breast cancer patient consists of four courses of adjuvant chemotherapy (AC) where doxorubicin and cyclophosphamide are administered every 21 days for four sessions. Routinely, breast cancer patients in Thailand, who are undergoing adjuvant therapy, are assigned for treatments and short advisory sessions at the outpatient department with follow-ups for a second course after an interval of 21 days. During the treatment period, these chemotherapy medications typically cause neurotoxicity and emesis in the patients. The cluster of symptoms usually include fatigue, pain, sleep disturbance, and depressive symptoms, being the primary concerns among this group. Furthermore, patients tend to experience these symptoms mostly on days 2 through 5 following chemotherapy while at home[3-6]. In addition, the previous studies indicated that breast cancer patients, who undergo chemotherapy treatment, routinely report the occurrence of more severe fatigue symptoms as the frequency of the chemotherapy treatments increase[7].

Energy conservation is an effective intervention

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strategy adopted in the symptom management procedure for cancer patients. The focus is on the balance between the two key elements of their rest time and daily activity[8]. Previous studies have suggested that a resting period with self-care management throughout the day, the prioritizing of daily activities, the promoting of leisure activities, exercise, and attaining quality of sleep, and the setting short and long-term goals are hallmark activities for energy conservation[8-10]. Most past studies have been carried out via face-to-face educational or consultation program with some online intervention approaches to engage patients' behavioral change as well as the utilization of the telephone as an economical device for consultation when deemed appropriate[11,12].

Even though many interventions are promising, they require professional effort from health care providers to monitor and support the patients' needs during the peak onset of symptoms. The vital nursing target of cancer care is to alleviate these cluster symptoms and to improve patients' ability for sustained daily self-care. Intervention that can engage patients at the time they are experiencing symptoms should be encouraged and actualized. Telephone interventions have been recognized as an effective strategy for nurses to remotely engage patients in monitoring their own symptoms, providing information and emotional support, and saving patients' transportation expense as well as travel time to the hospitals[13-15]. However, limited studies related to telephone-based energy conservation intervention to reduce cluster symptoms in 4-cycle AC course in Thai patients were published.

Materials and Methods

Research design

The present study was a two-armed randomized controlled trial, measures during four cycles of AC.

Participants

The inclusion criteria of participants were adults aged 20 years or older diagnosed with breast cancer stage I to III and planned to receive the AC regimen chemotherapy using doxorubicin and cyclophosphamide, for at least four cycles in 21 days intervals. Patients who developed an advanced stage of the disease during the study, necessitating a change of the treatment regimen, were excluded from further participation in the study.

Sample size was calculated by using Glass formulation (1976)[16]. The calculated values allowed for an error of 0.05, power (1–β) of 0.8, and effect size of 0.7 from the study conducted by Jacobsen et al (1999)[17] in investigating fatigue among women receiving AC for breast cancer. The result was 32 participants in each group. Allowing an attrition rate of 20 percent, the sample size was 39 participants in each group.

Seventy-eight participants were recruited between March 2019 and September 2019 from the outpatient department in the university hospital in Bangkok, Thailand. Patients were randomized by the researchers to the experimental or control group with the allocation sequence generated by random number table. Before signing consent forms, the patients were informed about the purpose of the study as well as their vital roles in participating in the present study.

Intervention

After receiving the hospital standard nursing care, the experimental group received intervention consisting of the set of prescribed activities to alleviate cluster symptoms in breast cancer patients. Twelve sessions were delivered over the course of the four cycles of AC regimen chemotherapy, with each cycle, one face-to-face intervention was provided on day one, and another two sessions were delivered via telephone on day 2 and day 7. The energy conservation program in the study focused the arrangement of daily activities, day-time sleep patterns, and appropriate methods for self-relaxation.

On day 1, prior to receiving chemotherapy, a baseline assessment of cluster symptoms and an assessment of self-care potential were performed. Following these assessments, the therapeutic activity provided 30 minutes of face-to-face health education in symptoms management including priority settings for the patients to practice methods to reduce fatigue, to develop breathing techniques for pain management, and to keep a record of all-day sleep patterns to rearrange sleeping times, and to become aware of symptoms of depression. Essential skills and discussion were carried out, including being able to adapt to the context within the home or workplace. Patients also received a manual of self-care guidelines for AC treatment and symptoms management as well as a logbook for energy conservation practices. All documents were developed by the researchers.

On day 2 and day 7 of the chemotherapy treatment, a 20-mins scripted telephone call drafted by the researchers was made to each participant. Each call initially began with the researcher's assessment of the participant's self-care activity and the monitoring of clinical symptoms to judge and to encourage each

patient's awareness of their individual symptoms. Then, the priority arrangement for future activities and a reminder to set goals for success were discussed. Brief education for the management of symptoms and counselling to achieve restful night-time sleep were also provided when appropriated. In particular, informative content, including overcoming barriers in self-care, the balancing of daily activities during daytime fatigue and pain, and recognizing the need to take a nap, was provided. At the end of the discussion, patients were required to lay out their plans for their upcoming activities ahead of the next assessment.

Participants in the control group received the standard nursing care protocol for chemotherapy patients, including chemotherapy education, the management of side-effects, and with the inclusion of an information booklet. They were asked to maintain their daily activities such as physical activity and dietary consumption during the study period. In addition, they were asked to record activities on the daily activities in the logbook provided to them.

Outcome assessment

Data generally were collected in the experimental and control groups on day 1, 2, 7, and 14 for each of the four chemotherapy cycles, and the score for depression was collected only on day 1 and 14 of each cycle. All participants were asked to complete self-administration questionnaires on day 1, and thereafter, the data on day 2, 7, and 14 were collected via telephone in both groups. Data for socio-demographic and clinical characteristics, including age, gender, education level, income level, underlying disease, marital status, medical history including diagnosis, treatment, and medication such as anti-nausea and vomiting drug and hypnotic drug, and average physical activity duration, were also collected.

Cluster symptoms were assessed with a brief questionnaire concerning fatigue, pain, and sleep disturbance. The measurements for levels of fatigue were measured on a numeric rating scale ranging 0 to 10. The questionnaire asked participants to quantify fatigue with the following question: "On how many of the past day(s) did you feel a lack of energy or experience physical or mental tiredness and/or any remaining discomforts?" The higher the score the more fatigue symptoms were indicated among the participants.

Pain severity was also measured by one item on the numeric rating scale ranging 0 to 10. Participants were asked the question "On how much of the past day(s) did you feel pain?" to indicate the degree of pain experienced by her. The higher the score, the greater the pain experienced by the patient.

Sleep disturbance referred to the difficulty to sleep; it was measured by the average duration in minutes of nighttime sleep. All the foregoing information was recorded daily in the manual logbook.

The symptom of depression was assessed and validated using the Thai version of the Patient Health Questionnaire (PHQ-9)[18]. This self-rating questionnaire contained nine items related to characteristics of depression, ranging in severity from 0 (not at all) to 3 (nearly every day). Scores can range from 0 to 27, with a score higher than 9 indicating the condition of clinically relevant depression. The Cronbach alpha of the questionnaire was 0.72.

Statistical analysis

Data were analyzed by Stata, version 14 (StataCorp LP, College Station, TX, USA). Descriptive statistics were used to analyze participants' characteristics. Frequency, percentage, average, and standard deviation when applicable were calculated by chi-squares and Independent t-test. The normality test of the data was conducted by Shapiro-Wilk Test and resulted in non-normal distribution; therefore, the Mann-Whitney U test and Wilcoxon signed-rank test were used to compare median values between and within groups, respectively, and results were presented in medians and interquartile ranges (IQR). All differences were considered significant at p-value less than 0.05.

Ethical approval

The study was approved by the Human Ethical Committee (si 008/2019) in accordance with the 1964 Declaration of Helsinki.

Results

Seventy-eight out of 134 eligible participants were recruited, and 39 participants (each) were allocated in the experimental and the control group. However, only 74 participants ultimately completed the study. In the experimental group, two patients withdrew from the study due to residential transfers of the hospital. In the control group, a patient withdrew due to admission to the hospital with fever, and another participant refused to receive chemotherapy in the next cycle (Figure 1).

Baseline socio-demographic and clinical characteristics are reported in Table 1. No differences between groups in age, gender, education, employment,

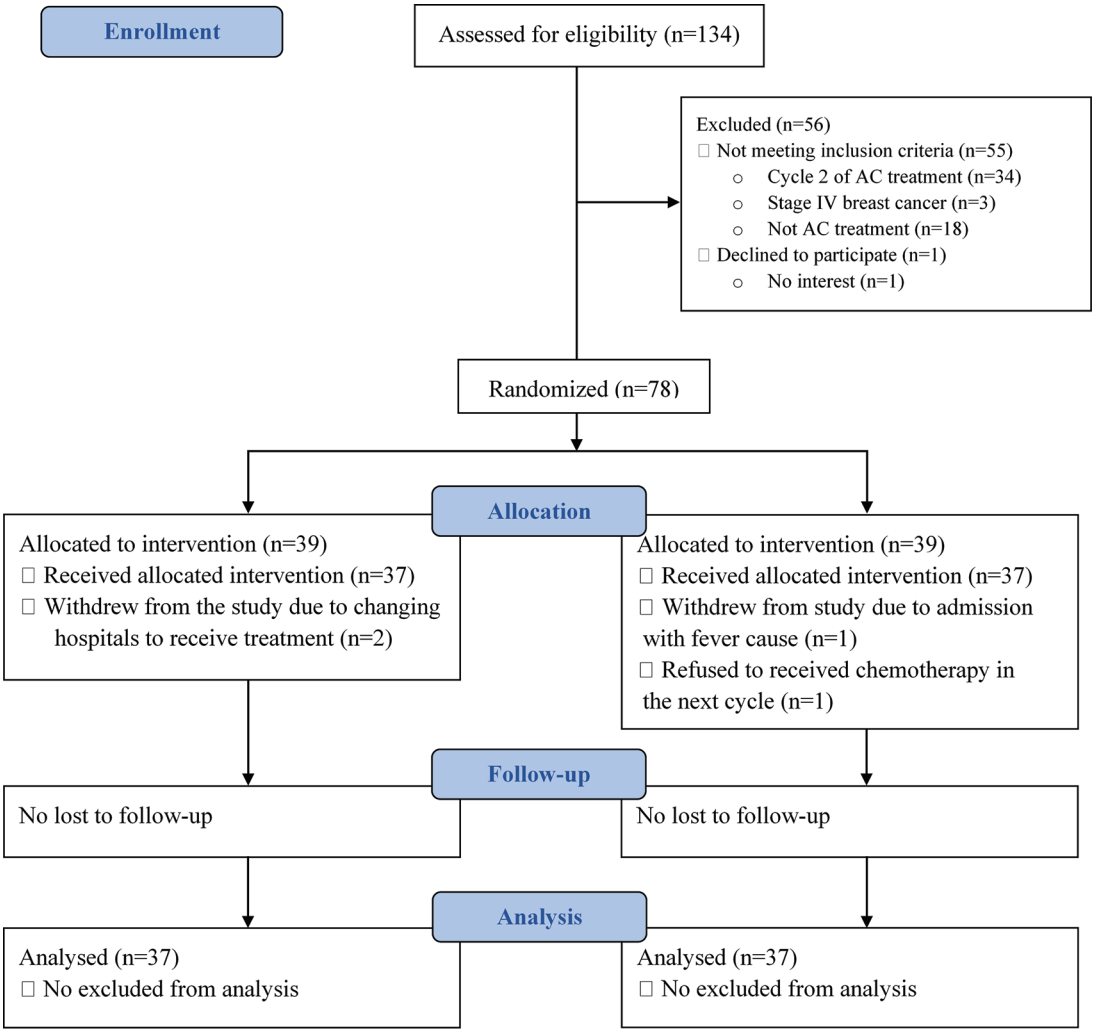

Figure 1. The study flow diagram.

income, body mass index, treatment history, duration, and stage of disease ($p>0.05$), and baseline cluster symptoms including fatigue, pain, night-time sleep, and depressive symptoms were found to exist between the two groups ($p=0.61$, 0.71, 0.83, and 0.17, respectively). Participants in the experimental group were more likely to increase duration of physical activity over time as compared to the control group.

Fatigue, pain, sleep time, and depressive symptoms in the experimental group improved significantly at the post-intervention period, compared to the control group. The median fatigue score in the experimental group was lower than in the control group since the first cycle on day 14, with statistical significance ($p<0.01$). In cycle 2, fatigue scores on day 7 and 14 in the experimental group was significantly lower than in the control group ($p=0.02$ and 0.01, respectively). In cycle 3, only fatigue scores on day 7 in the experimental group were significantly lower than those in the control group ($p=0.04$), and in cycle 4, fatigue scores on day 1, 2, 7, and 14 in the experimental group were significantly lower than in the control group ($p<0.001$, 0.04, 0.01, and 0.01, respectively).

Median pain scores of the experimental group were significantly lower in the control group on day 1 of the third cycle, and day 7 of the fourth cycle ($p=0.02$ and 0.01, respectively). The duration of night-time sleep significantly increased in the experimental group in cycle 1 on day 14 ($p=0.01$), and cycle 2 on day 2, 7, and 14 compared to the control group ($p=0.04$, 0.04, and 0.02, respectively). Moreover, the duration of physical activities in the experimental group was greater than in the control group in every

Table 1. Socio-demographic and clinical characteristics (n=74)

	Experimental group (n=37); n (%)	Control group (n=37); n (%)	p-value*
Age (years)			0.23[a]
Mean±SD	50.11±8.57	52.76±10.13	
Min to max	35 to 68	32 to 67	
Marital status: married	25 (67.6)	20 (54.1)	0.23[b]
Education: higher than secondary school	25 (64.6)	22 (59.5)	0.47[b]
Employed	26 (70.3)	28 (75.7)	0.60[b]
BMI (kg/m^2)			0.23[a]
Mean±SD	25.15±5.79	23.68±4.44	
Min to max	19.00 to 42.80	14.10 to 34.00	
History treatment: surgery	24 (64.9)	31 (83.8)	0.06[b]
Duration of the disease (month); mean±SD	1.85±0.84	2.66±3.81	0.21[a]
Stage of the disease			0.80[b]
I	12 (32.4)	14 (37.8)	
II	17 (46.0)	17 (46.0)	
III	8 (21.6)	6 (16.2)	
Laboratory; mean±SD			
Hct (%)	38.51±3.13	38.85 (2.95)	0.64[a]
Platelet (/uL)	303,783.8±72,458.85	305,189.2 (54,667.09)	0.93[a]
WBC (/uL)	7,500.27 (1,575.24)	7,058.92 (1,737.88)	0.25
ANC (/uL)	4,634.95 (1,356.96)	4,372.41 (1,195.63)	0.38[a]
Fatigue; median (IQR)	0 (0 to 2)	0 (0 to 2)	0.61[c]
Pain; median (IQR)	0 (0 to 2)	0 (0 to 1.5)	0.71[c]
Night-time sleep (minute); median (IQR)	450 (390 to 502.5)	450 (360 to 495)	0.83[c]
Depressive symptoms; median (IQR)	1 (0 to 3)	1 (1 to 5)	0.17[c]

SD=standard deviation; BMI=body mass index; Hct=hematocrit; WBC=white blood cell; ANC=absolute neutrophil count; IQR=interquartile range

* p<0.05; a Independent t-test; b Chi-square test; c Mann-Whitney U test

cycle with statistical significance (p<0.001). Median scores for depression (PHQ-9) in the experimental group tended to decrease over time and were lower than in the control group with statistical significance since day 14 of the first cycle (p<0.001).

As shown in Figure 2, the parallel line plots of the changes in cluster symptoms showed a similar pattern of central tendency and dispersion. Comparison of fatigue mean scores of fatigue and depression over time points demonstrated similar patterns in both groups, with significant reduction in the experimental group over time (p<0.001, <0.001 respectively). Similarly, the mean scores of nighttime sleeps were statistically improved over time in the experimental group, compared to those in the control group (p=0.02). However, there were no statistically significant differences between groups in mean score of pain at the end of cycle 1 to 4 (p=0.10, 0.25, 0.24, and 0.12 respectively), and throughout the study (p=0.09). All participants reported without the use of analgesic dose of fentanyl.

Discussion

A telephone-based intervention demonstrated the significant improvement of fatigue, pain, and sleep disturbance in patients that underwent AC. These findings are in accordance with Barsevick et al (2004)[8], in which energy conservation strategies, delivered and monitored by telephone, had a significant therapeutic impact on cluster symptoms reduction, particularly fatigue. In the present study, fatigue was the most intense symptom registered and was highest on day 2 of each cycle, gradually declining prior to the next cycle in both groups. The result was significantly lower in patients who received the intervention from the first cycle and throughout the study. This factor reflects the success of the energy conservation method by prioritizing

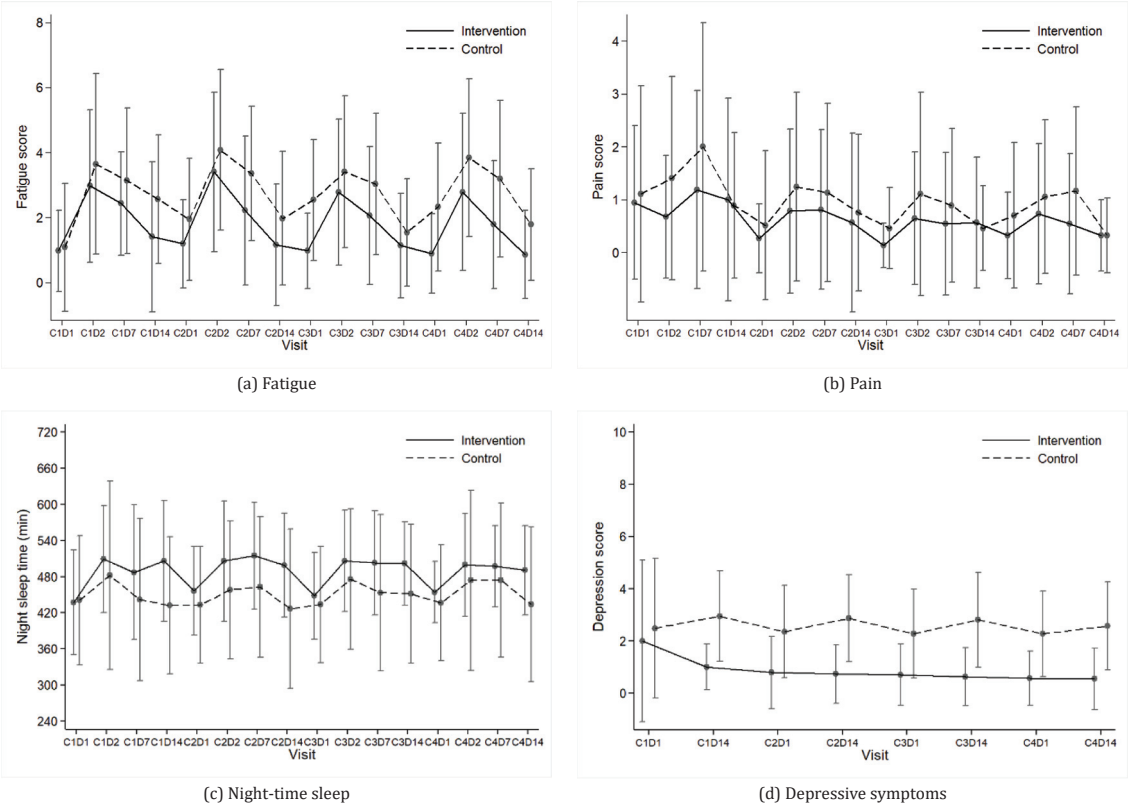

Figure 2. Changes over time in cluster symptoms.

C1D1=cycle1day1; C1D2=cycle1day2; C1D7=cycle1day7; C1D14=cycle1day14; C2D1=cycle2day1; C2D2=cycle2day2; C2D7=cycle2day7; C2D14=cycle2day14; C3D1=cycle3day1; C3D2=cycle3day2; C3D7=cycle3day7; C3D14=cycle3day14; C4D1=cycle4day1; C4D2=cycle4day2; C4D7=cycle4day7; C4D14=cycle4day14

activities and reallocating time to promote physical activity depending on their symptoms at home via short-script telephone.

As predicted, the pattern of scores demonstrated a relationship among the symptoms of fatigue, pain, sleep disturbance, and depression. Patterns of fatigue corresponded to depression levels on day 1 and day 14 of each cycle. Findings also demonstrated that as night-time sleep improved so were patients' fatigue levels reduced. These patterns are consistent with other studies, all of which have revealed that fatigue is a predictor of depression in patients with breast cancer. With fatigue symptoms patients were more likely to take a nap during the day resulting in insomnia at night[19,20].

Noticeably, patients who received intervention reported gradual pain reduction throughout the study, which was similar to the fatigue pattern, but it was not statistically significant changing over time. The present study has demonstrated that pain can be managed by breathing relaxation techniques without using analgesic dose of fentanyl, but it required time to become more effective and was evident in the later cycles. This finding calls for a further study in more effective breathing technique pain management among this group.

The strength of the present study lies in the study design, which decisively investigated the patients' experience of cluster symptoms over the course of the treatment protocol. When compared with the previous studies, the intervention was easily implemented by single in-person education session combined with telephone-based system for symptom management and periodic monitoring in each treatment cycle. This design proved to be both convenient and cost-effective in serving the needs of the patients. Despite the encouraging findings, some limitations should be addressed for generalization. First, the benefits of a similar intervention program might differ among patients with low literacy with difficulty in understanding the concise information. In the case of the present study, most of the participants were graduate of secondary school levels and above. Lastly, the sample size was small, limiting the statistical

power of the study and its conclusions.

Conclusion

Among breast cancer patients undergoing the 4-cycle AC, the intervention for energy conservation delivered by telephone as compared to the typical care paradigm resulted in the improvement of cluster symptoms, including fatigue, pain, sleep disturbance, and depression in a home environment. Further study should be considered within the context of a large-scale randomized controlled trial to validate the general efficacy of these findings.

What is already known on this topic?

Energy conservation reduces fatigue, pain, sleep disturbance, and depressive symptom for breast cancer patient who received chemotherapy. However, most program focused on face-to-face intervention, which limited proactive symptomatic monitoring.

What this study adds?

This study intended to evaluate the energy conservation strategy of utilizing telephone counselling for breast cancer patients at home, delivered via 20-minutes scripted segments. This approach revealed a potent form of agency for nurses within a user-friendly framework.

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Conflicts of interest

The authors declare no conflicts of interest.

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