Using Pranayama and Deep Breathing Exercises to Reduce Cancer-Related Fatigue and Insomnia During Radiotherapy: A Randomized Controlled Study

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Research Article

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Abstract

**Background:** Patients receiving radiotherapy often experience cancer-related fatigue and insomnia. These experiences negatively affect patients’ physiological and psychological well-being. The study aims to evaluate the effectiveness of pranayama and deep breathing exercise in reducing fatigue and insomnia in patients receiving radiotherapy due to breast cancer.

**Materials and methods:** This randomized controlled interventional study was carried out with 60 patients divided into the pranayama (20), deep breathing exercise (20) and control group (20). Data were collected with the Piper Fatigue Scale (PFS), the Pittsburgh Sleep Quality Index (PSQI) and the Visual Analog Scale (VAS).

**Results:** While patient fatigue in the control group significantly increased during the treatment process (p<0.05), the deep breathing exercise group (p<0.05) did not experience the same increase in fatigue. The post-treatment insomnia VAS score of the pranayama and deep breathing exercise groups decreased compared to the pre-treatment scores (p<0.05). In the group comparison of PSQI scale scores, the subdimensions *subjective sleep quality* and *daytime dysfunction* were negatively affected at the end of the treatment in the control group (p<0.05) and the subdimension *subjective sleep quality* was positively affected in the deep breathing exercise group (p<0.05).

**Conclusion:** Pranayama and deep breathing exercises are effective in reducing fatigue and insomnia in patients receiving radiotherapy due to breast cancer.

Introduction

Cancer-related fatigue is defined as “a disturbing, persistent, subjective physical, emotional and/or cognitive exhaustion or burnout feeling associated with cancer and its treatment unrelated to recent daily activities”. Unlike the fatigue experienced by healthy individuals, cancer-related fatigue is not known to resolve by rest and gives the individual more trouble than a normal feeling of fatigue [1]. The prevalence of fatigue related to cancer or cancer treatment varies between 41% to 88% [2-7]. In addition, studies have shown that together with fatigue; depression, anxiety disorders and a decrease in life and sleep quality occur in cancer patients [3, 8-12].

Not only pharmacological but also complementary/nonpharmacological methods are used to prevent, reduce and treat cancer-related fatigue. Some of these methods include exercise, acupuncture, massage, acupressure, cognitive behavior therapy, nutritional counseling, awareness-based stress reduction and yoga [1,13-18]. Yoga is a mind-body focus and consists of eight limbs (yama, niyama, asana, pranayama, pratyahara dharana, dhyana, samadhi-trans) developing harmony with all aspects of consciousness [13,19,20]. Studies have shown that yoga is effective in decreasing fatigue, sleep disorders, depression and anxiety and in increasing quality of life in breast cancer patients [13, 19, 21-24].
Pranayama however, one of the eight aspects of yoga, consists of breathing techniques that aim to regulate one or more respiratory functions directly and consciously [25-30]. The calm, soothing breathing techniques of pranayama (nadi shodana, bhramari pranayama etc.) reduce sympathetic stimulus and increase parasympathetic activity [24-31]. These breathing exercise methods carried out with slow breaths, ensure relaxation and is effective in relieving stress and related fatigue. Besides pranayama there are also other slow breathing exercises (diaphragmatic breathing, pursed lip breathing, etc.). These breathing exercises constitute an effective integrative body-mind technique to deal with stress and psychosomatic conditions, which decreases fatigue by increasing parasympathetic activity [32-35].

Chakrabarty et al. (2015), Dhruva et al. (2012), and Mustian et al. (2013) reported in their studies that pranayama reduces cancer-related fatigue, increases sleep quality and reduces the use of sleeping medication [14, 25, 36]. Pranayama also lowers cortisol, which is a factor in the development of fatigue, increases functional capacity and quality of life in breast cancer patients and reduces sleep disorders [22, 38, 39]. Therefore, both pranayama (yogic breathing exercises) and slow breathing exercises can be easily used with oncology patients such as breast cancer patients to reduce fatigue. These exercises are easy-to-learn, can be done individually or as a group anytime and anywhere and do not cause harm to the person [25, 40, 41].

The oncology nurse plays an important role in the evaluation, prevention, reduction and follow-up of cancer-related fatigue, developing a care plan related to fatigue management. Including nonpharmacological methods such as yoga, an effective exercise, together with pharmacological methods in the management of fatigue increases the quality of care. The nurse is in a significant position to manage fatigue using evidence-based practice in observing the patient, teaching the patient non-pharmacological practices that ensures the control of fatigue and by encouraging the patient to use these techniques. Well-designed clinical trials are needed to evaluate the contribution of breathing exercises to the recovery process of cancer patients. Therefore, this research was conducted to evaluate the effect of pranayama and deep breathing exercise on fatigue and sleep quality in women receiving radiotherapy due to breast cancer.

**Methods**

2.1 Study Design

Randomized controlled intervention study.

2.2 Study sample

The study population consisted of patients diagnosed with breast cancer, who received radiotherapy in the radiation oncology unit of a hospital in Ankara, between June 01, 2017 and January 31, 2019.

The sample size was calculated with the G*Power (G*Power, Ver. 3.0.10, University Kiel Germany software program [http://wwwpsychouni-duesseldorfdetaap/projects/gpower/) using preliminary study data
since there are no similar studies in the literature. A preliminary study was conducted for each of the three 
groups containing eight, eight and seven participants, respectively. In the variables, the lowest effect 
width was determined as 0.25 and the highest effect width was 0.62. As a result of the analysis on 
fatigue and insomnia, which was the main variable in the study, the number of groups were determined 
as three, the repetitions to be carried out as two, type I error rate as 0.05, the power of the study as 0.95. 
The minimum number of volunteers required to determine the difference between the three groups with 
an effect width of $f=0.25$ was determined as 54 individuals (18 in each group). At least three additional 
volunteers (16%) for each group were added, considering monitoring and data loss during the follow-up. 
Thus, the number of subjects was determined as 63 individuals (21 for each group).

Of the 63 patients, one wanted to interrupt the treatment and two did not want to continue in the study, 

hence the study was concluded with 20 patients in each group (60 patients) (Figure 1).

Literate patients over the age of 18 years, who underwent breast resection or modified radical 

mastectomy, were planned for radiotherapy for the chest wall/breast and lymphatic area, had Stage II-III 

breast cancer according to the TNM (Tumor diameter, Node, Metastasis) classification system, had a 

hemoglobin (HgB) level of 10 gm/dL and above, scored 0 or 1 on the ECOG (Eastern Cooperative 

Oncology Group) Performance Scale and who agreed to participate in the study were included in the 

sample. Exclusion criteria included; having any problems that would prevent communication, having 

stage IV breast cancer according to the TNM classification system, using opioids or sedating drugs, 

scoring above 1 on the ECOG Performance Scale, having psychiatric illnesses, taking 

yoga/pranayama/deep breathing exercise lessons before or having done these exercises prior to 
diagnosis, having recurrent breast cancer and being unable to perform the exercises due to physical 

inability/respiratory distress. Interruption of the treatment regimen due to any complications, participation 
in less than 20 of the 25 sessions and the desire to leave the study were determined as termination 
criteria.

Individuals, who met the inclusion criteria, were assigned to the groups using a simple randomization 

method with a closed envelope. Individuals were asked to complete the data collection forms themselves. Those, who were not able to do so received support from a nurse within the unit.

2.3. Instruments

Descriptive characteristics questionnaire: This form contained seven questions regarding the patients’ 

descriptive characteristics (age, educational status, type of surgery etc.) and was created by the 

researchers in line with the literature [14, 23, 32, 42].

Fatigue Visual Analog Scale (VAS) Score: This scale which evaluates the severity of fatigue, was scored 
as follows: no fatigue= 0 points, mild fatig= 1-3 points, moderate fatigue= 4-6 points, severe fatigue= 7- 
9 points and unbearable fatigue= 10 points.

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Piper Fatigue Scale (PFS): This scale consisted of 22 items and evaluated the patient’s subjective fatigue perception with four subdimensions. Each item was scored between 0 and 10. A high score obtained from the scale indicated a high level of perceived fatigue. The Turkish validity-reliability study of the scale was carried out by Can [43,44]. In this study, the Cronbach’s alpha internal consistency coefficient was found as 0.98.

Insomnia Visual Analog Scale (VAS) Score: The scoring system of this scale was as follows: no insomnia= 0 points, mild insomnia= 1-3 points, moderate insomnia= 4-6 points, severe insomnia= 7-9 points and unbearable insomnia= 10 points.

Pittsburgh Sleep Quality Index (PSQI): PSQI is a self-report-based screening and evaluation tool that provides detailed information on sleep quality and type and severity of sleep disorder in the past month. The scale consists of 24 questions and seven components to evaluate subjective sleep quality, time it takes to fall asleep, sleep time, habitual sleep efficiency, sleep disturbance, use of sleeping pills and daytime dysfunction. The total PSQI score could vary from 0 to 21. A PSQI score over 5 points indicated that the person suffered serious problems in at least two areas related to sleep or that they suffered mild to moderate problems in more than three areas [45]. The validity and reliability study of the index was carried out by Ağırgün et al.[46]. In this study, the Cronbach’s alpha internal consistency coefficient was found as 0.80.

Questionnaire on Patients’ Opinions of the Exercises: A form consisting of ten questions prepared by the researcher to determine the opinions of the patients on the feasibility and results of the exercises (difficulties in learning and doing the exercises, satisfaction with doing the exercises, etc.). The opinions of patients in the pranayama and deep breathing exercises groups were taken at the end of radiotherapy treatment.

Patients in the pranayama, deep breathing exercise and control group were evaluated six times in terms of fatigue and insomnia VAS scores. One time prior to the start of the 25-day session of radiotherapy treatment, four times during the radiotherapy treatment process (at the 1st through the 4th week) and one time at the end of the treatment. PFS and PSQI were evaluated once prior to and after the 25-day session of radiotherapy treatment.

2.4 Interventions

Protocols for pranayama and deep breathing exercises were prepared in line with the literature and the intervention was carried out (Figure 2). Prior to develop the protocol, certified training was received by the researcher for breathing exercises. Written opinions were received from seven experts regarding the content validity in order to evaluate the protocols in terms of expression, clarity, coverage and whether scientific errors are present. Following the opinions, the protocol content was edited and finalized.

**Pranayama and Deep Breathing Exercise Groups**: The patients were taught pranayama and deep breathing exercises by the researcher before the radiotherapy started. The patients were observed
performing these exercises for 10 minutes after each radiotherapy session (25 days) accompanied by the researcher in a quiet room within the radiotherapy unit containing two couches and a chair.

**Control Group:** The patients in this group did not receive any intervention.

2.5 **Statistical analysis**

Statistical analyses were made using IBM SPSS for Windows Version 21.0 software program. The compatibility of numerical variables to normal distribution was examined by using Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical variables that conform to normal distribution were reported using mean ± standard deviation and numerical variables that do not conform to normal distribution were reported using the median [minimum- maximum] values. In terms of numerical variables that conform to normal distribution, comparisons between groups were analyzed with one-way analysis of variance (ANOVA), taking into account the number of groups to be compared. Kruskal-Wallis test was used for comparison of numerical measurements that do not conform with normal distribution. Wilcoxon test was used for comparisons in dependent groups. The comparison of categorical variables between groups was examined with the Chi-Square test. Bonferroni-corrected Post-Hoc tests were used to identify the groups that made the difference in comparisons between groups with significant differences. The statistical significance level for all hypothesis tests was set at 0.05 and below.

2.6 **Ethical Considerations**

Ankara Yıldırım Beyazıt University Ethics Committee gave permission (study code: 486, approval date: 31.03.2017, number: 28) and the scientific committee of the hospital where the study was performed gave permission for the study. Patients gave written informed consents.

**Results**

**Table 1. Patients’ sociodemographic characteristics (n=60)**
| Characteristics                  | Control (n=20) | Pranayama (n=20) | Deep Breathing (n=20) | p   |
|---------------------------------|---------------|------------------|-----------------------|-----|
| Age (mean±SD)                   | 50.3±12.07    | 53±12.20         | 50.5±10.07            | 0.33|
| Marital Status                  |               |                  |                       |     |
| Married                         | 14 (70)       | 18 (90)          | 12 (60)               |     |
| Single                          | 6 (30)        | 2 (10)           | 8 (40)                | 0.09|
| Education                       |               |                  |                       |     |
| Primary School                  | 5 (25)        | 2 (10)           | 5 (25)                | 0.62|
| High School                     | 3 (15)        | 2 (10)           | 4 (20)                |     |
| Bachelor and above              | 12 (60)       | 16 (80)          | 11 (55)               |     |
| Employment status               |               |                  |                       |     |
| (During treatment)              |               |                  |                       |     |
| Employed                        | 2 (10)        | 3 (15)           | 4 (20)                | 0.67|
| Unemployed                      | 18 (90)       | 17 (85)          | 16 (80)               |     |
| Lives alone (During treatment)  |               |                  |                       |     |
| Yes                             | 1 (5)         | 2 (10)           | 3 (15)                | 0.57|
| No                              | 19 (95)       | 18 (90)          | 17 (85)               |     |
| Surgical Treatment              |               |                  |                       |     |
| Modified Radical Mastectomy(MRM)| 12 (60)       | 10 (50)          | 16 (80)               | 0.13|
| Breast Conserving Surgery (BCS) | 8 (40)        | 10 (50)          | 4 (20)                |     |
| Hormone treatment               |               |                  |                       |     |
| Yes                             | 8 (40)        | 5 (25)           | 9 (45)                | 0.39|
| No                              | 12 (60)       | 15 (75)          | 11 (55)               |     |

There was no statistically significant difference between the patients in the control, pranayama and deep breathing exercise groups in terms of sociodemographic characteristics, surgical treatment and hormone treatment. As specified in the table, all patients received 25 workdays of radiotherapy and prior to that all patients received chemotherapy (Table 1).

According to the results, the fatigue VAS score of the patients in the control group significantly increased after radiotherapy compared to before radiotherapy (p=0.01). The VAS scores decreased after radiotherapy as compared to before radiotherapy but there was no significant difference (p>0.05) in the patients in the pranayama and deep breathing exercise groups. In the fourth week, the VAS score of the pranayama (3.0) and deep breathing exercise (3.0) groups decreased in comparison to the VAS scores of the control group (5.0) and this decrease was more significant in the deep breathing group compared to the control group (p=0.04). In the fifth week of radiotherapy, although the VAS score of the control group (4.5) was higher in comparison to the pranayama (3.0) and deep breathing exercise (3.0) groups, there was no statistically significant difference (p>0.05) (Figure 3).

Table 2. Comparison of the patients’ intra-group and inter-group total PFS and subdimension scores before and after radiotherapy (n=60)
In both the intra-group and inter-group comparison of all three groups no statistically significant difference in PFS total and subdimension scores before and after radiotherapy was found (p>0.05) (Table 2).

There was no statistically significant difference in terms of insomnia VAS score of the pranayama and deep breathing exercises group before and after radiotherapy (respectively p=0.007, p=0.027). However, in the third week of radiotherapy, the insomnia VAS scores of the pranayama and deep breathing exercise groups showed a statistically significant decrease when compared to the control group (p=0.03). In the fourth week of radiotherapy, the pranayama group showed a statistically significant decrease in VAS scores compared to the control and deep breathing exercise groups (p=0.009). (Figure 4).

Table 3. Comparison of the patients’ intra-group and inter-group total PSQI and subdimension scores before and after radiotherapy (n=60)
| PSQI subdimensions       | Control Group | Pranayama | Deep Breathing | Inter-group |
|--------------------------|--------------|-----------|----------------|-------------|
|                          | Median       | Median    | Median         | Kw P        |
|                          | (minimum-maximum) | (minimum-maximum) | (minimum-maximum) |            |
| Subjective Sleep Quality |              |           |                |             |
| Before radiotherapy      | 1.0 (0-2)    | 1.0 (0-2) | 1.0 (0-3)      | 0.60 0.73   |
| After radiotherapy       | 1.0 (0-3)    | 1.0 (0-2) | 1.0 (0-2)      | 4.01 0.13   |
| **Intra-group Zb p**     | -2.00 0.04   | -1.001 0.31 | -2.12 0.003 |             |
| Sleep Latency            |              |           |                |             |
| Before radiotherapy      | 1.0 (0-3)    | 1.0 (0-3) | 2.0 (0-3)      | 1.96 0.37   |
| After radiotherapy       | 1.0 (0-3)    | 1.0 (0-3) | 1.5 (0-3)      | 5.88 0.053  |
| **Intra-group Z p**      | -1.06 0.28   | -1.66 0.09 | -0.57 0.56 |             |
| Conventional Sleep Activity |              |           |                |             |
| Before radiotherapy      | 1.0 (0-3)    | 3.0 (0-3) | 1.5 (0-3)      | 2.44 0.29   |
| After radiotherapy       | 1.0 (0-3)    | 2.0 (0-3) | 1.5 (0-3)      | 0.06 0.96   |
| **Intra-group Z p**      | -0.41 0.67   | -1.44 0.15 | -0.1 0.91 |             |
| Sleep disorder           |              |           |                |             |
| Before radiotherapy      | 1.0 (0-3)    | 1.0 (0-2) | 1.0 (0-2)      | 0.14 0.93   |
| After radiotherapy       | 1.0 (0-2)    | 1.0 (0-2) | 1.0 (0-2)      | 1.39 0.49   |
| **Intra-group Z p**      | -1.41 0.15   | -0.70 0.48 | -1.41 0.15 |             |
| Use of sleeping medication |            |           |                |             |
| Before radiotherapy      | 0.0 (0-3)    | 0.0 (0-3) | 0.0 (0-3)      | 1.06 0.58   |
| After radiotherapy       | 0.0 (0-3)    | 0.0 (0-3) | 0.0 (0-3)      | 0.47 0.78   |
| **Intra-group Z p**      | -1.00 0.31   | -1.00 0.31 | -1.34 0.18 |             |
| Daytime Dysfunction      |              |           |                |             |
| Before radiotherapy      | 0.0 (0-2)    | 1.0 (0-3) | 1.0 (0-2)      | 4.34 0.11   |
| After radiotherapy       | 1.0 (0-3)    | 1.0 (0-2) | 1.0 (0-3)      | 4.72 0.09   |
| **Intra-group Z p**      | -2.94 0.003  | -0.08 0.93 | -0.83 0.40 |             |
| Total                    |              |           |                |             |
| Before radiotherapy      | 6 (1-16)     | 9 (2-16)  | 7 (1-15)       | 1.62 0.44   |
| After radiotherapy       | 8 (2-16)     | 7.5 (1-12)| 8.5 (2-15)     | 0.88 0.64   |
| **Intra-group Z p**      | -1.86 0.06   | -1.76 0.07 | -0.115 0.90 |             |

*aKruskal Wallis  
bWilcoxon Test

The comparison of the intra-group mean scores before and after radiotherapy showed that the PSQI subjective sleep quality negatively increased in the control group after radiotherapy when compared to before (p=0.04). In the deep breathing exercise group, subjective sleep quality positively increased after radiotherapy when compared to before (p=0.03). The study showed that daytime dysfunction negatively increased after radiotherapy in the control group (p=0.003) but the intra-group and inter-group
comparison showed no statistically significant difference in mean PSQI total scores and mean subdimension scores before and after radiotherapy (Table 3).

**Discussion**

The medical treatment of cancer-related fatigue, which leads to negative effects on quality of life and daily life activities, is very limited. Previous studies have shown that nonpharmacological methods can be effective in the management of fatigue [13-18]. There are studies showing that breathing exercises are effective in reducing fatigue in cancer patients [14, 25, 34, 47, 48]. Devi et al. determined that deep breathing exercises reduced fatigue in patients receiving radiotherapy [42].

In this research the degree of fatigue has increased in the controlled group thorough the end of the treatment (5th week) compared to the start of the radiotherapy. In both the trial groups, the degree of fatigue decreased at the end of the treatment compared to the start of the radiotherapy but there was no statistical significance. The lack of significance is thought to be caused by the fact that in the paranayama and breathing exercises group there were both patients with fatigue and without fatigue at the beginning of the study even though the degree of fatigue decreased. If only with patients with fatigue had been included I, the study would have been more effective therefore it is suggested that only the patients with fatigue must be included in the upcoming studies.

However, what distinguishes this study from other studies is that the breathing exercises were carried out individually accompanied by an observer. It is thought that the patients were more willing to do the breathing exercises and to perform these more efficiently because they were only 10 minutes and because the sessions were accompanied by an observer.

Disturbed sleep patterns and sleep problems can also be observed with fatigue in patients undergoing radiotherapy. Sleep disorders may cause patients to experience fatigue during the day, which negatively affects quality of life and creates difficulties in performing activities of daily life and maintaining social roles [9, 12, 49]. In the current study, both pranayama and deep breathing exercises significantly reduced insomnia at the end of treatment in the group comparison of insomnia severity. Mustian et al. determined that yoga practice involving pranayama, was effective in relieving insomnia in breast cancer patients who had completed treatment [36].

There have been no studies showing that only the pranayama or the breathing exercises increase the quality of sleep in the patients receiving radiotherapy even though it has been stated that the pranayama breathing exercises help decrease sleep disorders.

Both pranayama and deep breathing exercises are easy to learn. They can be used individually or as a group at anytime and anywhere and are exercises that can be done without creating stress on the person and without consuming too much energy [14, 42, 47, 48].
It is thought that the mind relaxes and parasympathetic activity is stimulated during the deep breathing exercises by focusing on breathing and therefore theses exercises are effective in improving the quality of sleep. In this study it has been found that each of the different deep breathing exercises (pranayama and deep breathing techniques) have been effective in decreasing the fatigue and improving the quality of sleep but none predominates the other.

In this context, the patients participating in the study stated that they easily learned the exercises and that they were willing to continue the exercises in the future. In the current study, a quiet environment and no special equipment other than a chair were required for the application, and no side effects developed during or after the application.

The limitations of the research: the study has been conducted in one hospital for a duration of 10 minutes under observation after 25 sessions of radiotherapy. The fact that the exercises were done under observation and one to one is the strong point of the study. However the fact that whether patients have continued with the exercises at home is unknown constitutes a weak point. The study has been conducted on the patients receiving radiotherapy for breast cancer. So the results obtained are only related to the patients with breast cancer. In this study, feedback related to fatigue and sleep quality is only based on self-feedback and that is another limitation of the study.

**Conclusion**

The study determined that fatigue and sleep problems exist in breast cancer patients before radiotherapy and that these symptoms increased with radiotherapy treatment. In this study, both pranayama and deep breathing exercises were found to be effective in reducing fatigue and reducing insomnia, even when performed for a short time (10 minutes a day). In line with these results, we suggest conducting studies with widespread pranayama and deep breathing exercises, which are easy to learn, do not require a lot of energy/effort and can be done easily anytime and anywhere in oncology clinics and to conduct further studies on the use of breathing exercises of different lengths and durations in the prevention and treatment of fatigue and insomnia in breast cancer and other types of cancer.

**Declarations**

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**Conflicts of interest** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethics approval:** Procedures performed in this study were in accordance with the 1964 Helsinki Declaration and its later amendments and in accordance with the ethical standards of the institutional review board and independent ethics committee.
Consent to participate for publication: All participants gave written informed consent prior to enrolment and randomisation.

Availability of data and material and code availability: The authors have full control of all primary data, material and code availability and agree to allow the journal to review their data if requested.

Authors' contributions: Fatma Gündogdu: Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Writing - original draft, Writing - review & editing, Visualization. Sema Koçaklı: Conceptualization, Methodology, Formal analysis, Investigation, Writing - review & editing

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**Figures**
Figure 1

CONSORT scheme of the study
| Pranayama Group Breathing Exercises                                      | Deep Breathing Group Breathing Exercises                                |
|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Step One: Focusing on breathing (1 minute)                              | Step One: Focusing on breathing (1 minute)                              |
| Step Two: Alternative nasal breathing (3 minutes)                      | Step Two: Chest breathing (3 minutes)                                  |
| Step Three: Refreshing breath (3 minutes)                              | Step Three: Diaphragmatic breathing (3 minutes)                        |
| Step Four: Humming bee breath (2 minutes)                              | Step Four: Pursed lip breathing (2 minutes)                             |
| Step Five: Focusing on breathing (1 minute)                            | Step Five: Focusing on breathing (1 minute)                            |

**Figure 2**

Breathing exercises used in the study

![Breathing exercises chart](image)

**Figure 3**

Distribution of patients' fatigue VAS scores by follow-up

![Fatigue scores chart](image)
Figure 4

Distribution of patients' insomnia VAS scores by follow-up

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplememntaryappendix1.doc
- Supplememntaryappendix2.doc
- Supplememntaryappendix3.doc