

Effects of Yoga in Managing Fatigue in Breast Cancer Patients: A Randomized Controlled Trial

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Abstract

Background: Cancer-related fatigue is widely prevalent in cancer patients and affects quality of life in advanced cancer patients. Fatigue is caused due to both psychologic distress and physiological sequel following cancer progression and its treatment. In this study, we evaluate the effects of yogic intervention in managing fatigue in metastatic breast cancer patients. **Methods:** Ninety-one patients with metastatic breast cancer were randomized to receive integrated yoga program ($n = 46$) or supportive therapy and education ($n = 45$) over a 3-month period. Assessments such as perceived stress, fatigue symptom inventory, diurnal salivary cortisol, and natural killer cell counts were carried out before and after intervention. Analysis was done using an intention-to-treat approach. Postmeasures for the above outcomes were assessed using ANCOVA with respective baseline measure as a covariate. **Results:** The results suggest that yoga reduces perceived stress ($P = 0.001$), fatigue frequency ($P < 0.001$), fatigue severity ($P < 0.001$), interference ($P < 0.001$), and diurnal variation ($P < 0.001$) when compared to supportive therapy. There was a positive correlation of change in fatigue severity with 9 a.m. salivary cortisol levels. **Conclusion:** The results suggest that yoga reduces fatigue in advanced breast cancer patients.

Keywords: Cortisol, fatigue, stress, supportive therapy, yoga

INTRODUCTION

The diagnosis and treatment of cancer can pose serious side effects and distress in cancer patients. This is more so when the cancer is at an advanced stage.^[1] Among these manageable treatment-related symptoms associated with distress include menopausal/vasomotor symptoms, pain, fatigue, and sleep disturbance. There is a wide prevalence in fatigue symptoms among breast cancer patients ranging from 70% to 100%.^[2,3] Cancer-related fatigue is perceived as being of greater magnitude, disproportionate to activity or exertion, and not completely relieved by rest, leaving the patient with an overwhelming and sustained sense of exhaustion.^[4] Fatigue is an umbrella term used to describe various sensations or feelings, and a variety of expressions of reduced capacity at physical, mental, emotional, or social levels.^[5]

Both physiological and psychosocial factors play a part in the development of fatigue. The physiological reasons for fatigue have been attributed to anemia, cancer therapy, nutritional

deficiency, electrolyte disturbances, pain, neuropathy, sarcopenia, and cachexia. The biopsychosocial model attributes fatigue to psychologic distress that is known to exacerbate fatigue due to other causes as well. Cancer-related fatigue is associated with psychosocial factors, such as anxiety and depression,^[6,7] difficulty in sleeping,^[8] full-time employment status,^[9] and low degrees of physical functioning.^[10] However, whether it is a cause or an effect of these factors is unknown. Fatigue is also linked to high amounts of other unmanaged symptoms, especially pain.^[11]

Perceived stress has been shown to be related to fatigue and treatment-related distress in cancer survivors.^[12] Several others studies have shown a direct link between stress, insomnia,

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How to cite this article: Vadiraja HS, Rao RM, Nagarathna R, Nagendra HR, Patil S, Diwakar RB, *et al.* Effects of yoga in managing fatigue in breast cancer patients: A randomized controlled trial. *Indian J Palliat Care* 2017;23:247-52.

Access this article online

Quick Response Code:



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DOI:
10.4103/IJPC.IJPC_95_17

fatigue, and diurnal salivary cortisol rhythms.^[13-16] Studies have shown that diurnal cortisol slope is an important predictor of survival in advanced breast cancer patients and is directly linked to depression.^[17] Peak cortisol levels are also known to cause soft tissue pains and fatigue as seen in fibromyalgia. The hypothalamo-pituitary axes dysregulation is known to cause this change in rhythm as seen in both fibromyalgia patients and those with cancer due to chronic stress and allostatic load.^[15,18]

Evidence suggests that pain, fatigue, and depression are frequently undertreated. Patients and health-care providers have reported depression and persistent lack of energy as the aggressiveness of therapy has been increased and/or the underlying malignancy has worsened.^[19] Cancer symptom management would benefit if an integrated intervention plan existed for a cluster of symptoms based on a clear understanding of which symptoms are likely to cluster, when clustering is likely to occur, and how a symptom cluster affects patient outcomes at different stages of treatment. Most of these symptom clusters are influenced by patients' perception, awareness, education, mood states, and can be explained through various biologic, psychological, behavioral, and sociocultural mechanisms that constitute a symptom interaction network and symptom experience.^[20] The experience of multiple simultaneous symptoms has a synergistic effect on symptom distress.^[21]

Management of symptoms, therefore, requires a holistic approach that integrates behavioral and mind-body strategies, this is more so emphasized in earlier studies that have shown several stress reduction and mind-body approaches to reduce distressful symptoms and mood states in cancer patients.

Several studies have shown psychotherapeutic interventions such as supportive therapy, counseling, social support, and cognitive behavior therapy to reduce fatigue in cancer patients.^[14,22-25] Several other studies have shown exercise, physical activity, and energy conservation therapy to reduce fatigue in cancer survivors.^[10,26,27] Mind-body interventions such as yoga have been shown to reduce fatigue in early breast cancer survivors during treatment.^[28-30] Our earlier studies with yoga showed reduction in fatigue in early breast cancer patients undergoing radiotherapy.^[31,32] Earlier studies with yoga intervention are varied with different types of yogic intervention and duration. However, there is a paucity of studies showing effects of yogic intervention in reducing fatigue in advanced breast cancer patients.^[33,34]

In this study, we evaluated the effects of an integrated yoga program versus supportive therapy on perceived stress, fatigue in patients with advanced breast cancer. We also evaluated the relationship between fatigue and cortisol rhythms in metastatic breast cancer.

METHODS

In this study, 91 patients with metastatic breast cancer were recruited to participate in a trial comparing integrated yoga program with education and supportive therapy sessions from

January 2004 to June 2007. Institutional Review Board of the participating institution approved the study. The participants were recruited if they satisfied the selection criteria and gave written consent to participate in the study. Patients were included in the study if they were diagnosed to have metastatic breast cancer and were between 30 and 70 years of age and had adequate performance status (ambulatory >50% of time). Patients were excluded from the study if they had brain metastases, underwent chemotherapy treatment with exception of bisphosphonate therapy, were pregnant or lactating, on hydrocortisone medications, participated in clinical trials involving investigational new drugs, etc., This was a prospective, two-arm, randomized controlled study comparing integrated yoga program with supportive therapy with randomization done using computer-generated random numbers and opaque envelopes with group assignments. More details regarding study procedure are mentioned elsewhere.

Sample size

The sample size was calculated based on an earlier study with Mindfulness Based Stress Reduction Program (MBSR) that had shown a modest effect size (ES = 0.38) on EORTC QLC30 global quality of life measure.^[35] Based on an ES of 0.38 for ANOVA between factor effects with $\alpha = 0.05$ and $\beta = 0.2$, the sample size thus required was 44 in each group. Considering dropouts, we recruited 46 patients in each group.

There were 65 study completers of yoga ($n = 42$) and supportive therapy ($n = 33$) in the study.

Interventions

The intervention group received "integrated yoga program" and the control group received "supportive counseling sessions" both imparted as individual sessions over a 3-month period. We developed an integrated yoga module comprising various practices that include asana (postures), pranayama (regulated nostril breathing), yogic relaxation in supine (shavasana), meditation, self-appraisal, and counseling. Practices such as pranic energization technique (positron emission tomography - observing the flow of energy or prana through the body), cyclic meditation - combination of postures and relaxation techniques done keeping eyes closed, and mind sound resonance technique (chanting of mantras verbally and mentally) were some of the specific techniques used in cancer patients. Details of both the interventions are given elsewhere (Raghavendra *et al.*, 2009).^[36,37]

Outcome measures

At the initial visit before randomization, demographic information, medical history, clinical data, intake of medications, investigative notes, and conventional treatment regimen were ascertained from all consenting participants. The outcome measures ascertained could be grouped into the following categories:

Perceived stress scale

Perceived stress levels were assessed using perceived stress scale^[38] questionnaire. This self-rated scale includes 14 items

scored on a 5-point scale. This scale was used to assess the degree to which participants appraise their daily life as unpredictable, uncontrollable, and overwhelming over the last month. This has a reliability of 0.85.^[38]

Fatigue symptom inventory

The fatigue symptom inventory (FSI), developed in the United States in 1998, is a 14-item self-report measure designed to assess the intensity (4 items), daily pattern (1 item), and duration of fatigue (2 items), as well as its impact on quality of life (7 items).^[39,40] Twelve items consist of 11-point Likert-type scale (0 = not at all fatigued; 10 = extremely fatigued) and 1 item is composed of the number of days in the past week the patients felt fatigued. However, one item related to daily pattern of fatigue provides qualitative information and is not included in the total fatigue score. The higher the total fatigue score, the more severe the level of fatigue. The scale development process involved a review of literature on fatigue in cancer patients and on chronic fatigue in general. Thus, the scale was intended to be used to compare fatigue in various groups of patients and normal healthy populations. Based on two previous studies, Cronbach's alpha coefficients of the subscale of FSI of impact on quality of life ranged from 0.93 to 0.95.^[39,40] The FSI has also demonstrated test-retest reliability, construct validity, divergent validity, convergent validity, and discriminant validity.^[39]

RESULTS

Ninety-one metastatic breast cancer survivors (group mean age: 50.54 years \pm 8.53 years) registered in hospital-based cancer registry of Bangalore Institute of Oncology were recruited for this study. The sociodemographic characteristics of the study sample were similar across groups.

Fatigue severity

Analysis of covariance on postmeasures using baseline fatigue severity score as a covariate showed a significant difference between groups with better decrease in fatigue severity in yoga compared to control group [F(1,61) = 32.55, $P < 0.001$, ES - 1.4, Percentage change (PC) - 61.15%]. Paired-sample t -test done to assess within-group change showed a significant decrease in fatigue severity in yoga group only ($t = 6.7$, $P < 0.001$) and not in the control group ($t = -0.05$, $P = 0.96$) [Table 1].

Fatigue frequency

Analysis of covariance on postmeasures using baseline fatigue frequency score as a covariate showed a significant difference between groups with better decrease in fatigue frequency in yoga compared to control group [F(1,61) = 17.81, $P < 0.001$, ES - 1.1, PC - 52.64%]. Paired-sample t -test done to assess within-group change showed a significant decrease in fatigue frequency in yoga group only ($t = 5.8$, $P < 0.001$) and not in the control group ($t = 0.33$, $P = 0.74$) [Table 1].

Fatigue interference

Analysis of covariance on postmeasures using baseline fatigue interference score as a covariate showed a significant difference between groups with better decrease in fatigue interference in yoga compared to control group [F(1,61) = 28.36, $P < 0.001$, ES - 1.3, PC - 72.6%]. Paired-sample t -test done to assess within-group change showed a significant decrease in fatigue interference in yoga group only ($t = 5.5$, $P < 0.001$) and not in the control group ($t = -0.36$, $P = 0.72$) [Table 1].

Fatigue diurnal variation

Analysis of covariance on postmeasures using baseline fatigue diurnal variation score as a covariate showed a significant difference between groups with better decrease in fatigue diurnal variation in yoga compared to control group [F(1,61) = 13.65, $P < 0.001$, ES - 0.9, PC - 52.33%]. Paired-sample t -test done to assess within-group change showed a significant decrease in fatigue diurnal variation in yoga group only ($t = 3.8$, $P < 0.001$) and not in the control group ($t = -1.18$, $P = 0.24$) [Table 1].

Perceived stress score

Nonparametric Mann-Whitney test done to assess between-group changes showed significant difference between groups with better decrease in self-report perceived stress in yoga compared to control group ($z = -2.49$, $P = 0.01$, ES - 1.4, PC - 32.57%). Nonparametric Wilcoxon test done to assess within-group change showed significant decrease in self-reported perceived stress in yoga group only ($z = -3.46$, $P = 0.001$) not in the control group ($z = -0.62$, $P = 0.54$) [Table 2].

Bivariate relationships

There was a significant positive correlation between changes in fatigue severity with change in 9 a.m. cortisol levels,

Table 1: Comparison of fatigue symptom inventory scores using GLM repeated measures ANOVA between yoga and control groups

Outcome variables	Yoga (n=33), mean (SD)			Control (n=31), mean (SD)			Effect size (Cohen's d)	(Y-C) percentage
	Pre	Post	Percentage	Pre	Post	Percentage		
Fatigue severity	17.18 (9.14)	6.76***.††† (7.13)	60.65	17.94 (6.95)	18.03 (9.05)	-0.50	1.4	61.15
Fatigue frequency	8.70 (4.83)	3.70***.††† (4.07)	57.47	9.52 (3.96)	9.06 (5.78)	4.83	1.1	52.64
Interference	23.27 (16.90)	7.64***.††† (9.47)	67.17	25.61 (16.06)	27.0 (18.34)	-5.43	1.3	72.60
Diurnal variation	3.00 (1.35)	1.82**.*††† (1.74)	39.33	2.77 (1.12)	3.13 (1.20)	-13.00	0.9	52.33

††† $P < 0.001$ for between-group change using ANCOVA. ** $P < 0.01$, *** $P < 0.001$ for within-group change using paired t -test. GLM: Generalized linear model, SD: Standard deviation

indicating the stress reduction benefits of yogic intervention [Table 3].

DISCUSSION

The results from this study demonstrate a significant reduction in fatigue frequency, severity, interference, and diurnal fatigue variability in yoga group compared to supportive therapy intervention. There was also a significant decrease in perceived stress in yoga group compared to supportive therapy group. These findings are similar to earlier observations in early breast cancer patients with mindfulness-based^[29] stress reduction and Iyengar yoga.^[33]

Perceived stress

The results suggest an overall decrease in perceived stress scores with time in both the studies. In our study, yoga intervention reduced perceived stress by 32.6% (ES = 1.4) compared to control group. There is growing evidence that perceived stress has a major impact on the initiation and progression of disease, i.e., cardiovascular disease and chronic pain syndromes^[41,42] by downregulating the immune system, it is observed that greater perceived stress positively predicted salivary cortisol levels.^[43]

Fatigue symptom inventory

In this study, there was a significant decrease in fatigue (61.2%, ES = 1.4), fatigue frequency (52.6%, ES = 1.5), fatigue interference (72.6%, ES = 1.3), and diurnal variation (52.3%, ES = 0.9) in yoga group compared to controls on FSI. Our results are in contrast to earlier studies that have shown a modest decrease in fatigue (5.7% following MBSR intervention on Profile of Mood States–fatigue subscale^[35] and 6.4% on Functional Assessment of Chronic Illness Therapy fatigue scale in a study by Moadel *et al.*^[44] This could be because of inadequacy of the subscale to measure various dimensions of fatigue^[35] and use of yogic intervention in early-stage cancer patients where fatigue would not have been a main concern^[44] contrary to our study where fatigue was

measured in advanced breast cancer patients using a specific FSI. Fatigue is an important symptom in cancer patients that directly affects functional quality of life. Apart from clinical conditions that affect fatigue such as infections, anemia, and pain, progressive disease itself causes fatigue as a part of cancer cachexia through release of inflammatory cytokines. Therefore, managing fatigue is also an indication of clinical improvement in the patient’s condition. The decrease in fatigue seen with our study and consequent reductions in morning salivary cortisol and improvement in natural killer (NK) cell counts support this understanding.

Adherence to intervention and outcomes

Adherence to intervention was good in our study with 80% attending 24 supervised sessions. There was a significant improvement in quality of life and decrease in 9 p.m. cortisol level in individuals with good adherence to intervention (attending >20 classes). Adherence to intervention in control group was 100%, as they had to invariably meet the counselors before appointment with their oncologists. This also explains why earlier studies did not have similar effects, as the number of sessions was very limited (9–12 sessions).^[45,46]

It may be hypothesized from these results that distress decreases with time in cancer patients, use of stress reduction interventions only augments this process and that, patients with initially high distress and high cortisol levels would probably take a longer time for attenuation of such high cortisol levels than those with lesser distress or cortisol profiles. These observations are important as hypothalamic-pituitary-adrenal (HPA) axes dysregulation in terms of diurnal salivary cortisol rhythm was found to be an important predictor for survival in advanced breast cancer patients.^[17] The changes in stress response patterns and appraisal could have contributed to reductions in cortisol and distress seen with our intervention. The reduction in perceived stress seen with our intervention further offers support for this mechanism. An elevated level of cortisol

Table 2: Comparison of scores for anxiety, depression, and perceived stress scores using ANCOVA between yoga and control groups with respective baseline measure as a covariate

Outcome variables	Yoga (n=35), mean (SD)			Control (n=31), mean (SD)			Effect size (Cohen’s d)	(Y-C) percentage
	Pre	Post	Percentage	Pre	Post	Percentage		
Perceived stress score	16.49 (8.93)	10.09 (7.25)***†††	38.81	21.16 (5.01)	19.84 (6.19)	6.24	1.4	32.57

***P<0.001 for within-group change using paired t-test. †††P<0.001 for between-group change using ANCOVA. SD: Standard deviation

Table 3: Bivariate relationships between changes in measures of stress, fatigue, salivary cortisol, and natural killer cell counts following intervention in yoga group using Pearson’s correlation analysis

Outcome variable	600 cortisol level	900 cortisol level	2100 cortisol level	Mean diurnal cortisol level
Perceived stress	-0.09	0.09	0.29	0.20
Fatigue severity	-0.28	0.53**	-0.19	-0.38
Fatigue interference	0.26	-0.24	0.08	-0.14
Fatigue frequency	0.22	-0.36	-0.06	-0.27
Fatigue diurnal variation	-0.14	-0.06	0.21	-0.08

is known to have immunosuppressive effects and is largely responsible for the downregulation of immune function because of stress. Reduction seen in cortisol levels in our study offers further support for improvements in immune functioning (NK cell counts) seen in our study in yoga group (32.4%, ES = 0.5) as also seen with our earlier study.^[47] The combination of physical postures, breathing exercises, relaxation, and meditation could have helped attenuate cortisol levels through stress reduction and exercise effect as earlier studies have documented quality of life and biological benefits in cancer patients after moderate exercise.^[48,49] Various components of yoga intervention are known to have a calming effect and correct the autonomic imbalance^[50-52] and HPA axes disturbances^[35] that prelude stress responses. Overall, the reduced psychological stress and cortisol following yoga program could be attributed to stress reduction rather than mere social support and education in conformity with earlier studies.^[53]

The ability to “unwind” after stressful encounters, i.e., the ability to return to ones neuroendocrine baseline influences the total burden that the stressors place on the individual.^[54] Decrement in NK cell counts has been found to be an important predictor for survival in advanced breast cancer. Catecholamines and glucocorticoids have been shown to rapidly and markedly affect the distribution of NK cells among different immune compartments (e.g., spleen, liver, lungs, circulating blood, marginating pool of blood, etc.),^[55,56] and it may be hypothesized that changes in these hormone levels and NK cell counts could be one of the mechanisms of action of our intervention.

Larger randomized controlled trials are needed to further validate the findings and effects of yoga intervention on HPA axes dysregulation.

CONCLUSION

In summary, our yoga-based intervention was effective in reducing psychological morbidity, distressful symptoms, toxicity, and improving the quality of life in early breast cancer patients undergoing conventional cancer treatments. This was probably facilitated through stress reduction and helping the cancer patients to cope better with their illness at various stages of their conventional treatment. However, larger randomized controlled trails with structured psychiatric interventions as controls are needed to further validate our findings.

Acknowledgments

Central Council for Research in Yoga and Naturopathy, Ministry of AYUSH, Govt of India

Financial support and sponsorship

This study was supported with grants from the Central Council for Research in Yoga and Naturopathy, Ministry of AYUSH, Government of India.

Conflicts of interest

There are no conflicts of interest.

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