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Efficacy of Escitalopram in Pain, Anxiety, and Depressive Symptoms of Patients with Breast Cancer: A Randomized Single-Blind Controlled Trial

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Abstract

Background: Pain, anxiety, and depression are common but often neglected problems in patients with cancer.
Objectives: Considering the importance and impact of anxiety and depression as common psychiatric symptoms in people with cancer, the present study aimed to assess the effectiveness of escitalopram in the reduction of pain, anxiety, and depression in patients with breast cancer.
Methods: This single-blind controlled trial was conducted on 32 patients diagnosed with breast cancer who were referred for modified radical mastectomy (2018-2019). The intervention group received daily oral capsules containing 10 milligrams of escitalopram for four weeks, while the control group received placebo capsules containing starch on a daily basis. Hospital Anxiety and Depression Scale (HADS) and Visual Analogue Scale were administered to the patients at the commencement of the study and four weeks after the intervention. In addition, at baseline examination, personality factors were assessed by the NEO Five-Factor Inventory-3 questionnaire.
Results: Based on the results, the scores of HADS anxiety, total HADS, and pain reduced after the intervention in the case group; however, the HADS depression score demonstrated a slight increase. A significant difference was observed between the case and control groups for HADS anxiety score after the intervention (P=0.01). The correlation of personality characteristics with HADS anxiety and depression subscales pointed out a significant negative correlation between the HADS depression score and conscientiousness (r=-0.40; P<0.05).
Conclusion: Due to minor side effects of escitalopram, this drug is suggested to be used for the reduction of anxiety symptoms and pain intensity in patients with breast cancer.

Keywords: Anxiety, Breast neoplasms, Depression, Pain

1. Background

Pain, anxiety, and depression are common but often neglected problems in patients with cancer (1,2). Advancements in cancer treatment have enabled these patients to live longer (3), and half of those who are diagnosed with cancer can expect to survive for at least 10 years (4). This definition of cancer as a long-term condition highlights the importance of the management of psychiatric disorders in patients diagnosed with malignancies (3,4). A systematic review of the prevalence of symptoms of depression and anxiety in long-term cancer survivors revealed the prevalence of depression (21.0%) and anxiety (21.0%) in these patients (5).

Breast cancer, which affects 2.09 million new cases and causes 627, 000 deaths annually, is recognized as the second most common malignancy and the fifth cause of cancer deaths worldwide (6). A review article demonstrated that this cancer is the first common cancer (24.4% of all cancers with an age-standardized incidence rate of 23.1 per 100,000 population) and the leading cause of cancer deaths among Iranian women (7). A previous study in the north of Iran revealed that 50.0% and 32.0% of patients with newly-diagnosed breast cancer had mild or severe anxiety; and 52.5% and 28.1% of cases had mild or severe depression, respectively (8).

Under-recognition and mismanagement of pain, anxiety, and depression can deteriorate the quality of life, patient's adherence to treatment, and treatment costs in patients with cancer (4). Some evidence has evaluated the efficacy of different modalities in the treatment of anxiety, pain, and/or depression in patients with malignancy, including breast cancer, in recent years (9-12).

Escitalopram as one of the most specific selective serotonin reuptake inhibitors (SSRIs) is used for the treatment of depression and anxiety disorders (13). Despite its efficacy, tolerability, and long-term effects, very limited clinical trials are available regarding the exclusive use of escitalopram for the treatment of patients with breast cancer (14).

2. Objectives

In light of the aforementioned issues, the present study aimed to assess the efficacy of this drug in the reduction of pain, anxiety, and depression symptoms in patients with breast cancer.

3. Methods

This single-blind randomized controlled trial was conducted on patients diagnosed with breast cancer who were referred for modified radical mastectomy to state hospitals in Babol, north of Iran, within six months (from 11/6/2018 to 5/5/2019). To find three units of difference in HADS scores of the two groups after the intervention, the sample size was estimated at 16 cases with the confidence level of 95% and the study power of 80%.

The patients were selected via the convenience sampling method. The inclusion criteria entailed 1) a recent diagnosis of breast cancer, and 2) having anxiety and/or depression symptoms based on the Hospital Anxiety and Depression Scale. On the other hand, the exclusion criteria were the history of elevated mood, suicidal thoughts, mental retardation, dementia, and current substance dependency. Demographic characteristics, including age, gender, level of education, place of residence, occupational status, and marital status, as well as comorbid illnesses, such as diabetes mellitus, thyroid gland, and cardiovascular disorders, were collected at the baseline examination.

The participants were randomly assigned to two groups. All of the patients in these two groups were in stage III of breast cancer and were referred for modified radical mastectomy. The intervention group received daily oral capsules containing 10 milligrams of escitalopram for four weeks, while the control group received placebo capsules containing starch. Placebo and escitalopram were filled into capsules of the same color and smell to execute a single-blind design. Both the case and control groups had free psychiatric visits during the study whenever they needed to. Moreover, in case of pain, they could receive ibuprofen 200 mg tablet up to three times a day. The patients were evaluated for primary research outcomes at the commencement of the study (before surgery) and four weeks after the surgery.

Primary outcomes were pain intensity, depression, and anxiety which were measured at the baseline examination and four weeks after the intervention. Pain intensity was measured by the Visual Analogue Scale (VAS); moreover, depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS). Furthermore, personality factors were assessed by the NEO Five-Factor Inventory-3 questionnaire. This 60-item questionnaire is used to assess the five main personality factors: neuroticism, extraversion, openness to experiences, agreeableness, and conscientiousness. The items were rated on a 5-point Likert scale ranging from strongly disagree to completely agree. People with a high score are prone to irrational beliefs, are less able to control their impulses, and are much less likely to cope with stress, as compared to others. The psychometric properties of the Persian version of this questionnaire have been approved in previous studies (15).

The VAS is one of the most widely used pain assessment instruments in the world. The scores of 1-3 indicate mild pain, 4-7 suggest moderate pain, and 8-10 signify severe pain (16). The HADS is a 14-item questionnaire employed for the assessment of anxiety (7 items) and depression symptoms (7 items). For each item, the participants are asked to indicate which of the four options (rated from 3-0 score) describes how they have been feeling in the past week. The scores of 0-7 indicate the absence of clinical symptoms of anxiety or depression, 8-10 are suggestive of mild anxiety or depression, and 11-21 signify symptomatic anxiety or depression (8).

The patients were interviewed, and these questionnaires were completed by a trained medical student. The obtained data were analyzed in SPSS software (version 16) using T-test, Chi-Square, Pearson's correlation coefficient, and ANOVA repeated measure. A p-value less than 0.05 was considered statistically significant. The current research was approved by the Ethics Committee of Babol University of Medical Sciences (ID: IR.MUBABOL.HRI.REC.1397.152) and was registered on the website of Iranian Clinical Trials with IRCT approval number: IRCT20150630022991N14. The study protocol is available at https://en.irct.ir/trial/34451.

4. Results

A total of 32 female patients admitted for mastectomy surgery within the age range of 35-68 years were recruited in the present study. Participant's information is presented in Figure 1. The mean age scores of the participants were reported as 50.2±9.4 and 49.7±9.1 years in the case and control group, respectively (P=0.879). A number of 22 subjects (68.8%) were living in urban areas, 27 (84.4%) cases had an educational level of primary to secondary school, 27 (84.4%) subjects were married, and 30 (93.8%) cases were housekeepers. Baseline demographic and clinical characteristics for the intervention and control groups are presented in Table 1. As illustrated in this table, these two groups had no significant difference in the baseline characteristics (P>0.05).

The HADS and pain score of the two groups before and after the intervention is displayed in Table 2. Based on this table, HADS anxiety, total HADS, and

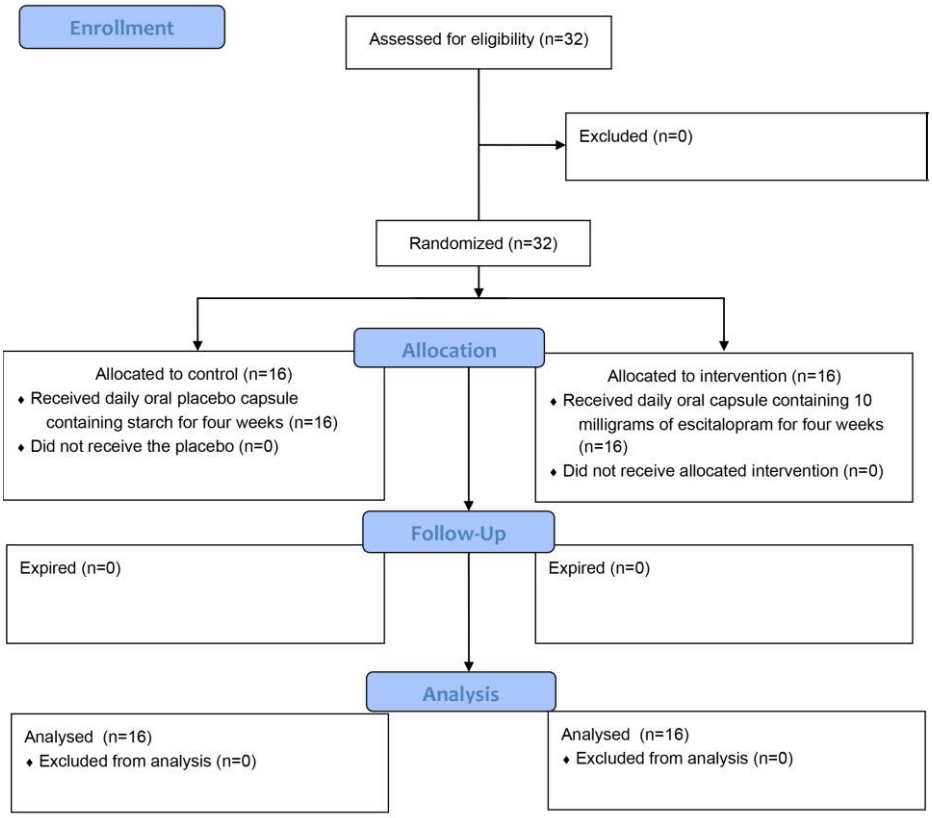

Figure 1. Flow diagram of the participants

pain score reduced after the intervention in the case group; however, HADS depression score demonstrated a slight increase. In the control group, HADS depression and pain score decreased, and HADS anxiety and total HADS increased. A significant difference was detected between the case and control groups in HADS anxiety score after the intervention (P=0.01). No significant difference was observed between the case and control groups in HADS depression score (P=0.18), total HADS (P=0.06), and pain score (P=0.32). Personality factors of the two study groups at baseline examination are presented in Table 3. This table indicated that these two groups had no significant differences in the personality factors (P>0.05), except for openness to experience (P=0.02). The correlation of personality factors with HADS anxiety, depression, and severity of pain in the intervention and control groups at baseline assessment and after the intervention is illustrated in Table 4 A significant negative correlation was observed between the HADS depression score and conscientiousness when post-intervention values were compared with the baseline measures (r=-0.40;.

Table 1. Baseline demographic and clinical characteristics for the two study groups

Variable	Intervention group Number (Percent) n=16	Control group Number (Percent) n=16	P-value
Mean age (year)	50.2±9.4	49.7±9.1	0.879
Living region			
Urban	13 (81.25)	9 (56.25)	0.127
Rural	3 (18.75)	7 (43.75)	
Level of education			
Illiterate	2 (12.50)	1 (6.25)	0.831
Primary to secondary school	13 (81.25)	14 (87.50)	
College education	1 (6.25)	1 (6.25)	
Marital status			
Single	1 (6.25)	1 (6.25)	
Married	14 (87.50)	13 (81.25)	0.386
Widowed	0 (0.00)	2 (12.50)	
Divorced	1 (6.25)	0 (0.00)	
Occupation			
Housekeeping	15 (93.75)	15 (93.75)	0.999
Others	1 (6.25)	1 (6.25)	

Table 2. Hospital Anxiety and Depression Scale score of the case and control groups before and after the intervention

Variable	Intervention group (n=16)		Control group (n=16)		P value
	Mean	SD	Mean	SD	
HADS anxiety score					
Before the intervention	10.93	3.58	7.56	2.60	0.01
After the intervention	6.50	2.12	8.56	2.50	
HADS depression score					
Before the intervention	11.93	2.61	11.68	2.33	0.18
After the intervention	12.25	2.08	11.56	2.60	
Total HADS score					
Before the intervention	22.87	4.92	19.25	3.60	0.06
After the intervention	18.75	2.59	20.12	3.84	
Pain Score					
Before the intervention	4.50	2.44	4.00	1.89	0.32
After the intervention	2.93	2.51	2.18	1.55	

HADS: Hospital Anxiety and Depression Scale

Table 3. Scores on personality factors at baseline examination for the two study groups

Personality factors	Intervention group (n=16) Mean±SD	Control group (n=16) Mean±SD	P-value
Neuroticism	39.06±6.28	39.58±7.16	0.52
Extraversion	45.50±3.70	47.06±4.83	0.31
Openness to experiences	46.87±3.20	47.06±4.68	0.02
Agreeableness	44.81±3.79	45.50±4.72	0.38
Conscientiousness	47.12±2.44	46.31±3.21	0.18

Table 4. correlation of personality factors with hospital anxiety and depression scale anxiety and depression subdomains and severity of pain for the two study groups

Personality characteristics	HADS-anxiety						HADS-depression						Severity of pain					
	Intervention group		Control group		Total		Intervention group		Control group		Total		Intervention group		Control group		Total	
	Baseline	After the intervention	Baseline	After the intervention	Baseline	After the intervention	Baseline	After the intervention	Baseline	After the intervention	Baseline	After the intervention	Baseline	After the intervention	Baseline	After the intervention	Baseline	After the intervention
Neuroticism	-0.15	-0.19	0.11	0.16	-0.05	0.02	-0.01	0.21	-0.15	-0.26	-0.08	-0.07	-0.14	0.05	0.41	0.01	0.11	0.03
Extraversion	-0.20	-0.26	-0.13	0.04	-0.22	0.01	0.32	0.41	-0.41	-0.44	-0.08	-0.14	-0.22	-0.20	-0.26	0.05	-0.25	0.01
Openness to experiences	0.01	-0.28	-0.50*	-0.30	-0.21	-0.25	0.53*	0.48	-0.10	-0.18	0.16	-0.04	-0.49	-0.11	-0.36	-0.09	-0.40	-0.09
Agreeableness	-0.46	-0.44	0.14	-0.06	-0.19	-0.16	-0.01	-0.22	-0.36	-0.37	-0.19	-0.03	-0.29	0.08	0.15	0.26	-0.08	0.21
Conscientiousness	-0.31	-0.15	0.08	0.06	-0.02	-0.07	0.08	-0.22	-0.48	-0.55*	-0.20	-0.40*	-0.16	0.02	-0.07	-0.02	-0.09	-0.03

*P<0.05

P<0.05). The patients receiving escitalopram reported no serious drug side effects following the intervention.

5. Discussion

As evidenced by the results of the present study, escitalopram significantly reduced the anxiety symptoms in patients with breast cancer; however, its effect on depression symptoms was not significant. Moreover, although the intensity of pain decreased in both groups after four weeks, the difference between the intervention and control groups was not significant. Furthermore, no serious adverse side-effect was reported in patients who received this medication. Lydiatt et al. suggested that preventive use of escitalopram could reduce the risk of depression symptoms by more than 50% in non-depressed patients treated for head and neck cancers (17). In the same context, Schillani et al. reported that the use of SSRIs could be effective in palliative care of patients with cancer. It not only relieves depression symptoms but also improves mental adaptation to cancer (18).

In addition, a significant negative correlation was detected between the HADS depression score and conscientiousness; and other personality characteristics had no significant correlation with HADS anxiety, depression, and pain intensity after the intervention. In contrast with the result of the present research, Chen et al. assessed the effect of personality traits on anxiety in patients with primary glaucoma and concluded that neuroticism was positively correlated with anxiety. Moreover, they reported that openness, conscientiousness, agreeableness, and extraversion had a significant negative correlation with anxiety (19). Kaplan et al. assessed the correlation of social anxiety with

personality traits in a study conducted on 1,200 subjects and concluded that individuals with higher extraversion and less neuroticism reported less social anxiety. They also found that social anxiety was negatively correlated with openness, conscientiousness, and agreeableness (20). Along the same lines, Bienvenu et al. concluded that higher neuroticism could predict the incidence of anxiety and depression symptoms. They believe that depression, general anxiety, and neuroticism might have common genetic factors that are initially manifested by neurotic presentations, and consequently, a complete syndrome of general anxiety and depression occurs (21). In their meta-analysis study, Malouff et al. reported that patients with anxiety or depression had a higher degree of neuroticism and lower degrees of extraversion, agreeableness, and conscientiousness; nonetheless, this correlation was not observed with openness (22). Schrier reported that people with anxiety or depression symptoms might typically have higher neuroticism and extraversion, as well as lower agreeableness and conscientiousness (23).

This discrepancy between the results of the present study and those obtained in the aforementioned articles can be attributed to the small sample size of the research, study duration, or assessment tools (20). We used the HADS questionnaire for the assessment of anxiety and depression, and we might have had different results if we had examined the patients through a structured interview. A variety of factors affect the development of depression and anxiety in people with cancer. In general, this considerable disparity in the results of different studies can be justified by the following factors: individual characteristics (including age, gender, ethnicity, marital status, sexuality, disability, religion, biological factors, and comorbid disorders), sociodemographic factors (such as level of education, occupation, household income, social support, and health care system), characteristics of cancer (such as stage, grade, type of cancer, symptoms, curability, and recurrence), previous psychological factors, and cancer treatment aspects (1).

Pain intensity had no significant correlation with personality characteristics. Contrary to the findings of the current study, Naylor et al. detected a significant correlation between conscientiousness and chronic pain (24). Pour Mozaffari et al. pointed to a significant association of severe pain, neuroticism, social support, and strategies for coping with functional disability in patients with rheumatoid arthritis (25). Jalilvand Qazvini et al. represented that people with higher extraversion had a positive attitude, passion, and higher involvement in activities; moreover, they are interested in interacting more with others which increases their capacity to tolerate severe pain. Agreeable people with chronic pain who experience stressful events and negative emotions are expected to cope much better with severe pain regardless of levels of stress. It has been demonstrated that people with higher conscientiousness are less depressed, less fearful of pain, and more qualified to deal with pain (26). This difference might be due to the measurement tool. In the current study, the pain intensity was assessed by VAS which has been represented as the most common measure for the assessment of pain intensity in cancer research (27). The patients who are diagnosed with cancer might need to be visited medically for different purposes. The questionnaires used for the assessment of symptoms and treatment management of these patients should be specific and not time-consuming (28).

Among the notable limitations of this study, we can refer to the small sample size and short duration of follow-up. Therefore, it is recommended to conduct a larger study with longer duration of follow-up to compare the efficacy of escitalopram with other antidepressants.

6. Conclusion

Due to the minor side effects of escitalopram, this drug is suggested in patients with breast cancer. Since the effect of this medication is not significantly correlated with personality characteristics, except conscientiousness, it can be used for a wide range of patients without any limitation.

Footnotes

Authors' contribution: NN, EZ, ZH, AA, and SM contributed to the conception and design, as well as the acquisition, analysis, and interpretation of data. SM drafted the article. All authors have read the manuscript, revised it critically for important intellectual content, and approved the final version of the article to be published.

Conflicts of Interest: The authors declare that they have no conflict of interest**.**

Ethical Approval: The present study was approved by the Ethics Committee of Babol University of Medical Sciences (ID: IR.MUBABOL.HRI.REC.1397.152). All participants provided a written informed consent form to participate in the research.

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Informed consent: All participants were informed of personal characteristics or clinical details to be published in this study.

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