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Effect of Citalopram and Aspirin on Hot Flashes and Quality of Life in Premenopausal Women with Breast Cancer: A Randomized Double-blind Clinical Trial

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Abstract

Introduction: Over 70% of Iranian breast cancer patients are reported to have experienced an earlier menopause after chemotherapy. Due to the high and prevalent appearance of amenorrhea, this study focused on the efficacy of citalopram plus aspirin, compared to citalopram plus a placebo on cancerous women with chemotherapy-induced amenorrhea symptoms in premenopausal stages.

Methods: In this randomized clinical trial study, 32 participants were randomly allocated to treatment (receiving citalopram and aspirin), and 28 to control (receiving citalopram and placebo) groups. Participants were selected from patients referring to Breast Cancer Research Center of ACECR, and Seyyed-o-Shohada Hospital in Isfahan, Iran. To assess their functional, physical, emotional and socio-familial well-being, as well as their hot flashes, Functional Assessment of Cancer Therapy-General questionnaires were used, while the effect of treatment was measured using paired t-test and Wilcoxon signed-rank test.

Results: The means of participants' ages were 45.03 ± 5.1 and 44.7 ± 5.3 in treatment and control groups, respectively. Hot flashes decreased in both groups to a statistically significant degree, while no significant differences were observed in functional and socio-familial well-being of participants before and after the treatment. The treatment group also displayed significantly improved emotional and physical well-being statuses after the treatment.

Conclusions: The study demonstrated that premenopausal women undergoing chemotherapy for breast cancer experience disturbing symptoms such as hot flashes, and lower emotional and physical well-being, which can largely be treated with citalopram and aspirin. Relevant specialists and physicians could thus prescribe this drug regimen to alleviate these major symptoms.

INTRODUCTION

Around half of Iranian women with breast cancer are below 50 years, and over 70% of them are reported to have experienced an earlier menopause after chemotherapy [1, 2]. The side effects of chemotherapy vary depending on the type and dosage of drugs, as well as the length of the treatment, and they do not occur similarly in different people. Among younger women, menstruation cycle change is one of the most common side effects of chemotherapy, followed by amenorrhea and infertility [3]. As defined by World Health Organization (WHO) and Stages of Reproductive Aging Workshop (STRAW), menopause is 12 months of amenorrhea with follicle-stimulating hormone (FSH) levels exceeding 40 mIU/mL [4]. Menopausal symptoms arise from reduced hormone secretion that occurs naturally among women of 45 to 55 years old [5], and mainly include hot flashes, vaginal dryness, sleep disorders, night sweats, and mood disorders. Menopausal women

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therefore undergo numerous physical and mental difficulties in this process [6]. Hot flashes are particularly irritating problems that affect around 75% of women at this stage, and their treatment is a common clinical challenge. One of the solutions is hormone replacement therapy (HRT) that effectively decreases vascular kinetic symptoms by 80 to 90%, yet many patients are reluctant toward such a treatment. The findings published by the Women Health Initiative (WHI) showed that HRT could lead to an invasive breast cancer, and many thus resort to non-hormonal treatments [7].

Other symptoms of menopause include emotional changes, such as irritability, sadness, nervousness, despair and dissatisfaction, as well as increased risk of sleep disorders, cardiovascular complications, diabetes and osteoporosis. That would affect functional well-being, particularly for fulfilling duties or enjoying recreational activities [8]. Menopause also compromises physical well-being, causing itching, skin dryness, vaginal dryness, metrorrhagia, and painful intercourse, which in turn leads to the patient's further irritability and deficient socio-familial well-being. For instance, she could face relationship problems with her partner and lose the emotional support of her family. Hot flashes are among the most prevalent symptoms among menopausal women that undergo chemotherapy. It is, however, impossible to treat them with estrogen or progesterone, since 80% of such patients have estrogen receptors and need to employ non-hormonal agents such as clonidine, sertraline, or venlafaxine [7, 9].

A large group of women treated for breast cancer experience amenorrhea, while many of the available medical treatments for such symptoms either lack adequate efficacy, or interfere with the cancer treatments. Hot flashes are more serious for women with breast cancer, who are seldom treated with hormone therapy for their problem [10]. There are a number of non-hormonal drugs to relatively decrease hot flashes, such as venlafaxine, clonidine, paroxetine, gabapentin, etc. However studies haveshown that some selective serotonin re-uptake inhibitors (SSRIs) used to control hot flashes, such as paroxetine or fluoxetine, interfere with tamoxifen and promote the recurrence risk of breast cancer [11]. However, not all SSRIs interfere with tamoxifen in this regard. In this study, citalopram was used as an SSRI, which showed a favorable effect on vascular kinetic symptoms, and recent findings attest its impact on hot flashes and depression as well [12-14]. Aspirin was employed in this study to alleviate vascular kinetic symptoms, in order to assess both its effect on other menopausal symptoms and its promoting influence on citalopram. The effect of aspirin has previously been studied in a number of researches, and has been confirmed to be positive [15, 16]. Considering the importance of premature menopause resulting from chemotherapy, reported in over 70% of women with breast cancer, this study focused on the efficacy of a drug regimen of citalopram plus aspirin, compared to citalopram plus a placebo on cancerous women with CIA symptoms. The present study considers the effect of the two mentioned drug regimens on hot flashes, as well as physical, social, emotional and functional well-being.

METHODS

Patients and Sample Size

In this randomized double-blind clinical trial, 60 patients were randomly divided into treatment and control groups, 32 and 28 participants respectively. The sample volume was calculated using the sample volume calculation formula for clinical trials, assuming 0.05 for type I error and 80% as the statistical power, as well as reduced hot flash frequency by 55% in the treatment and 36 % in the control groups. Participants were selected from patients referring to BCRC, ACECR and Seyyed-o-Shohada Hospital in Isfahan. The population included non-menopausal women with breast cancer who had undergone chemotherapy and were experiencing amenorrhea as a result. The criteria for excluding patients from the study comprised chronic physical diseases (such as heart, kidney, lung or liver deficiencies), diagnosed mental disorders (such as affective disorders, schizophrenia or major cognitive disorders), taking psychotherapeutic medications, taking other medications that interfere with the drugs being studied, pregnancy, taking letrozole, and comorbidity.

Intervention

The participants were randomly allocated to treatment and control groups, the former receiving citalopram and aspirin, and the latter citalopram plus a placebo. Citalopram is a lipophilic medicine prescribed for mental disorders, such as depression, and is absorbed rapidly through the gustatory system. Aspirin was provided in a single dose of 80 mg, which entailed no adverse effects among the participants. Citalopram was offered in a single dose of 20 mg.

Measurement

The Functional Assessment of Cancer Therapy - General (FACT-G) scale was used for measuring the quality of life sub-items, evaluating 28 items across four domains: social/family (7 items); physical (7 items), emotional (5 items); and functional (7 items) well-being [17]. In addition, hot flash was measured by the Functional Assessment of Cancer Therapy-Endocrine Symptom (FACT-ES, version 4) questionnaire, translated from English into Farsi at BCRC. Menopausal symptoms including hot flashes were also assessed by this questionnaire.

The information required for accepting patients into the population were collected through a face-to-face interview by a pharmacist, who would also fill the questionnaires. The interview with each patient lasted around 15 minutes in average. The FACT-G and FACT-ES ques-

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tionnaires for each participant in the two groups were filled in two stages (before and after taking the regimen) with a three-month interval.

The research plan for this study was registered and approved by the Ethics Committee of the Pharmacy Faculty of Islamic Azad University and BCRC, ACECR. The procedure included an initial oral presentation of the general principles and objectives of the study for the qualified participants, followed by the participant signing a consent document for participation in the study and granting the researchers permission to access each patient's hospital reports and medical history.

Statistical Analysis

After the completion of the questionnaires by the participants, the statistical analysis was done. A paired t-tests were used under a normality assumption in order to assess the desired intervention effect. Moreover, Wilcoxon and nonparametric Mann-Whitney U tests were employed to measure changes in hot flashes before and after the intervention. Randomization was achieved in this study through a simple random method, and blinding was guaranteed by keeping the researchers uninformed about the method of allocating participants to each group and the designated codes. All descriptive and interpretive analyses were conducted by SPSS software version 21, at a significance level of 0.05.

RESULTS

The participants' mean age for both groups is 44.86 years. The mean age for the control group (receiving citalopram and placebo) is 44.7 with a standard deviation of 5.1, and for the treatment group (receiving citalopram and aspirin) it is 45.03 with a standard deviation of 6.3. According to the results of independent t-test for the age variable, the participants had been uniformly distributed into control and treatment groups (Table 1).

The results of the t-test depicted that no significant differences were observed in functional and socio-familial well-being of the participants before and after the treatment ($P < 0.05$). The treatment group, however, displayed significantly improved emotional ($P = 0.02$) and physical ($P = 0.04$) well-being after the treatment (Table 2). No significant statistical differences were observed in the control group before and after the treatment. Figure 1 shows the mean changes in control and treatment groups before and after the treatment.

Considering the frequency of the hot flashes among the participants of the two groups, significant changes were observed in terms of decreased intensity of hot flashes after the treatment in both groups, especially in the treatment group (Table 3). The results of the Wilcoxon test for hot flash intensity as the variable pointed to significant changes ($P < 0.05$) before and after the intervention ($P < 0.0001$).

Moreover, the results of Mann-Whitney U test between the two groups before the intervention displayed no significant changes, yet the hot flash intensity ($P < 0.05$) was significantly differed afterwards between the two groups ($P = 0.003$).

Table 1: Age Distribution in the Treatment and Placebo Groups

Group Parameter	Treatment (n = 28)	Placebo (n = 32)	P value
Age	44.7 ± 5.3	45.03 ± 5.1	0.31

Data in table are presented as Mean ± SD.

Table 2: Mean Scores of Quality of Life Sub-items in Treatment and Placebo Groups

Quality of life sub-items	Citalopram and Aspirin (n=28)	P value	Citalopram and Placebo (n=32)	P value
Physical well-being		0.04		0.41
Before	11.29 ± 8.3		13.62 ± 5.34	
After	16.89 ± 7.7		14.22 ± 5.75	
Social/Family well-being		0.83		0.21
Before	18.64 ± 4.68		17.06 ± 4.53	
After	17.42 ± 6.44		17.53 ± 4.24	
Emotional well-being		0.02		0.06
Before	7.29 ± 5.36		12.69 ± 3.17	
After	15.4 ± 3.89		13.34 ± 3.27	
Functional well-being		0.85		0.21
Before	17.06 ± 3.03		16.65 ± 3.85	
After	17.17 ± 6.86		17.53 ± 5.2	

Data in table are presented as Mean ± SD.

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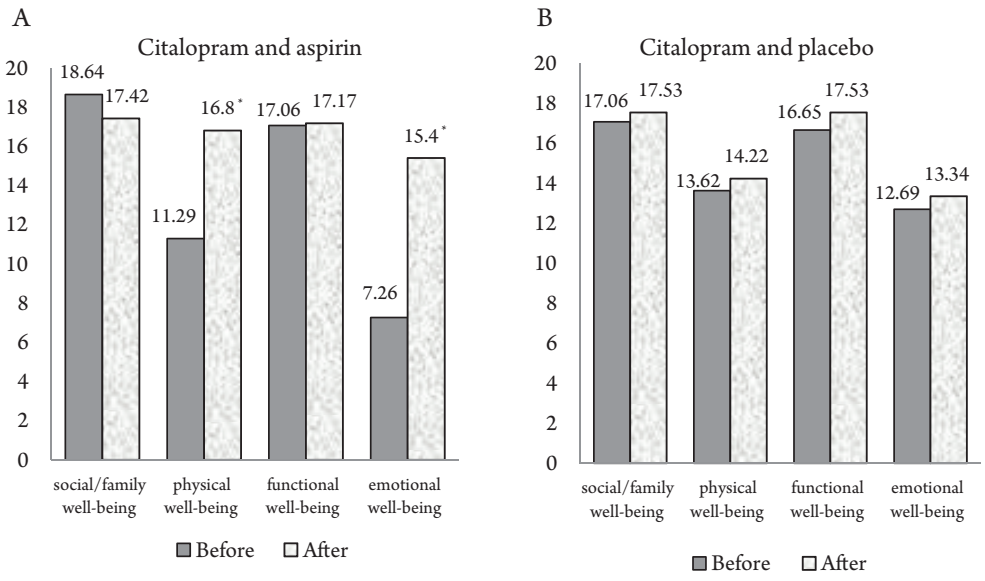

Figure 1: Bar Chart of Mean Scores of Quality of Life Sub-items in A) Treatment and B) Placebo Groups

Table 3: Hot Flash Intensity in Two Groups

Hot flash intensity	Not at all	A little	Very much	P value
Citalopram and Placebo				0.000
Before	0	4 (12.5)	28 (87.5)	
After	3 (9.4)	16 (50)	13 (40.60	
Citalopram and Aspirin				0.000
Before	0	0	25 (100)	
After	1 (3.8)	18 (59.3)	7 (26.9)	

Data in table are presented as No. (%).

DISCUSSION

This study focused on the efficacy of medical regimen of citalopram plus aspirin, compared to citalopram plus a placebo on cancerous women below the age of 50 that experienced CIA symptoms. Review of the related literature confirmed this study to be the first to consider the simultaneous effect of citalopram and aspirin on hot flashes, as well as the patients' functional, physical, emotional and socio-familial well-being.

Hot flashes were relatively alleviated in the two groups after the treatment, which was particularly significant for the group treated with citalopram plus aspirin. Considering the significant difference observed for the simultaneous effects of these two drugs on hot flashes, it could be concluded that the efficacy of citalopram plus aspirin is higher than citalopram alone. Other studies had previously established the separate positive effects of citalopram and aspirin on reducing hot flashes [18-22]. Therefore, if these drugs could separately alleviate hot flashes, their simultaneous use was expected to leave a higher impact. One study rejected the effect of citalopram plus fluoxetine on reducing hot flashes [23, 24], and another considered citalopram for treating women with breast cancer histories. These women experienced a minimum of 14 hot flashes per week. The 21 participants in that study received 10 mg of citalopram per day for a week, and then 20 mg per day for the next three weeks. Their hot flashes had decreased after four weeks [18].

Studies have also pointed to the positive impact of aspirin on reducing hot flashes. Patients who experienced hot flashes arising from niacin were treated with aspirins, in order to control the prostaglandin it was taken 30 minutes before using niacin [15, 16].

Kalay et al. (2007) studied 254 menopausal women with breast cancer histories that had avoided HRT. These women had a minimum of 14 hot flashes per week. For this study, participants were divided into four groups of 57 patients, while 83 patients received placebos. Group 1 received 10 mg of citalopram per day from the second to the seventh week; group 2 received 10 mg of citalopram per day for the second week, and 20 mg per day from the third to the seventh week; group 3 received 10 mg of citalopram per day for the second week,

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20 mg per day for the third week, and 30 mg per day from the fourth to the seventh week; group 4 received placebos. Hot flashes in the four groups were reduced by 49%, 50%, 55% and 23%, respectively. The participants that received citalopram during the study also experienced improvements in their professional performance, sleeping, moods and life quality as a whole. This study also recommended citalopram as a treatment for hot flashes [19].

Another research compared the separate impacts of citalopram and venlafaxine on hot flashes, and found citalopram to be more effective in this respect [20]. The study on hot flashes due to niacin intake proved that aspirin taken with niacin would decrease hot flashes and general body temperature [25]. The present study also depicted the positive effect of citalopram alone and taken together with aspirin.

The emotional well-being of the two groups after being treated with citalopram also showed significant changes in mean values compared to those before the intervention. Thus, it was shown that taking citalopram and aspirin can positively affect emotional health disorders such as depression. Studies conducted in other countries have also highlighted the significant impact of citalopram on emotional well-being, compared to taking placebos [26, 27], while similar studies have recommend the use of SSRIs for similar purposes [28, 29]. Aspirin was not studied separately for its effect on emotional well-being, and this study focused on its combined impact with citalopram.

Considering the mean values calculated, the physical well-being of participants in the control group did not change tangibly before and after the intervention, yet the treatment group showed improved physical well-being afterwards. One could therefore conclude that taking these drugs together would positively affect physical well-being among the patients. Studies on physical well-being, however, do not favor choosing SSRIs [30, 31]. Citalopram alone can improve physical well-being among patients, but its positive impact is promoted if taken together with aspirin. The social well-being of the participants in both groups before and after the intervention showed no significant differences, which rejects the impact of citalopram alone or with aspirin on social well-being. Furthermore, no previous research was found to have studied this aspect.

The participants in the two groups depicted no significant differences in terms of functional well-being, and it can be concluded that citalopram and aspirin did not influence the functional well-being. In a similar study, an SSRI taken with a hypnotic drug was effective in treating sleep disorders resulting from hot flashes [32]. Sleeping plays a crucial role in functional well-being; thus citalopram and aspirin together would not be an effective regimen to deal with sleep disorders. Other studies found pairing an SSRI with a hypnotic drug effective on sleep shortages associated with hot flashes [32].

One limitation for this study was sickness and low spirits of the patients, which made it difficult to communicate with them. It was also impossible to increase the number of participants due to the stipulated time frame for the study. The participants were supposed to answer the questionnaires within the given time. This study showed that women undergoing chemotherapy for breast cancer have irritating symptoms including hot flashes and impaired emotional well-being, which can be largely resolved using citalopram and aspirin along with the required chemotherapy program. Therefore, simultaneous use of citalopram and aspirin can be recommended and prescribed by specialists to reduce and resolve these symptoms.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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