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Oxybutynin use as a hot flash reducer in breast cancer survivors in the use of tamoxifen: a pilot randomized clinical trial

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ABSTRACT

Introduction: Breast cancer is a heterogeneous disease in which genetic and environmental factors are involved. The most prevalent types are those expressing hormone receptors, consisting of 60% to 70% of all cases in developed countries. Therefore, the most common type of therapeutic approach is hormone therapy. Estrogen blockers, such as tamoxifen, and aromatase inhibitors, such as anastrozole, are the most prescribed medicines for these types of cancer. The purpose of this article was to assess the effects of once-daily oxybutynin 5 mg on frequency and severity of hot flashes in women with breast cancer using tamoxifen. **Methods:** A two-month double-blind, placebo-controlled, pilot randomized clinical trial in women with breast cancer using tamoxifen that were experiencing hot flashes. These women were treated daily with oxybutynin 5 mg (n=11) or a placebo (n=12). The co-primary outcome was to reduce, from baseline to month two, the frequency and severity of hot flashes symptoms. **Results:** Reductions in both frequency and severity of hot flashes were observed in women who received oxybutynin 5 mg/day compared to placebo, even though it was not statistically significant. Adverse effects reported by the oxybutynin arm were tachycardia and decrease in appetite (9.1%), and in the placebo arm were headaches (8.3%), xerostomia (16.6%), diarrhea (8.3%), and dry skin (8.3%). **Conclusions:** oxybutynin is a safe nonhormonal therapy for hot flashes in women with breast cancer using tamoxifen.

KEYWORDS: oxybutynin; breast cancer; tamoxifen; hot flashes.

INTRODUCTION

Breast cancer (BC) is a heterogeneous disease in which genetic and environmental factors are involved[1]. BC is a common cancer among women worldwide, and based on molecular and histological analysis, it should be divided into three groups: (i) estrogen receptor (ER^+) or progesterone receptor (PR^+) BC; (ii) human epidermal receptor 2 ($HER2^+$) BC; and (iii) triple negative (ER^-, PR^- $HER2^-$) BC. The classification is important since the treatment approaches are based in BC molecular characteristics[2,3]. The most prevalent types of BC are the ones expressing hormone receptors (HR), consisting of 60% to 70% of all BC cases in developed countries. Therefore, the most common type of therapeutic approach is hormone therapy[4]. Estrogen blocker, such as tamoxifen, and aromatase inhibitors, such as anastrozole, are the most prescribed medicines for these types of cancer[5].

Tamoxifen (TAM) is a selective estrogen receptor modulator regularly used in routine clinical practice for almost 40 years. This drug competes with estrogen for binding to the ER in BC that express ER[6,7]. Five years of adjuvant TAM therapy reduce BC recurrence risk by almost one half, with further long-term survival after ten years of treatment[8,9]. Although TAM is generally well-tolerated for pre- and perimenopausal women, hot flashes (HF), as other vasomotor side effects, can be a problematic toxicity for up to 78.0% of women in the long term[10,11]. Some studies have suggested that HF are an indicator of clinical effects[12-14], and Baxter et al.[15] showed an inverse relationship between endoxifen levels and HF severity.

Oxybutynin is an anticholinergic drug used to treat urinary frequency, incontinence, and overactive bladder[16]. A retrospective study suggested that oxybutynin could be used for women with refractory HF[17]. A previous clinical trial stablished that

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oxybutynin could be a well-tolerated drug option for women to treat HF with or without BC[18], even though anticholinergic medications can induce atropine-like symptoms, such as dry mouth, constipation, drowsiness, and blurred vision[19].

Therefore, the aim of this present study was to compare oxybutynin at a low dose of 5 mg once a day with placebo in treating HF with minimum adverse effects.

METHODS

Study design and participants

This was a randomized, prospective, double-blinded, placebo-controlled pilot clinical trial conducted at Hospital Regional de Presidente Prudente (HRPP), São Paulo state, Brazil. Eligible patients were adult women with BC history, treated in the HRPP, in use of TAM, regardless of the type of cancer treatment they had. TAM dose should be stable for at least 28 days, and treatment should continue during all the study period. $HER2^{+}$-directed therapy was allowed. Exclusion criteria were prior use of oxybutynin or contraindications to oxybutynin.

Written informed consent was obtained from each participant, and the study protocol was reviewed and approved by the Research Ethics Committee of the HRPP and the Universidade do Oeste Paulista, under the CAAE 38839420.3.0000.5515.

Random assignment and masking

Women were randomly assigned to receive either 5 mg/day of the oxybutynin oral tablet formulation or a placebo, resulting in a 1:1 chance of receiving one or the other. The oxybutynin or placebo formulations were secretly prepared by a pharmacist who did not participate directly in the study. Web-based randomization was used, following the Pocock and Simon's dynamic allocation procedures[20]. Stratification factors included age, sex, cancer staging, treatment, HF duration, and HF frequency per day.

Procedures

During the first week of the study, treatment was assigned to groups, and a questionnaire was completed to establish baseline symptoms. The questionnaire Research Questionnaire for Breast Cancer Patients in use of Tamoxifen consists of 11 items that assess personal information, number of HF per day, intensity of HF, and side effects of oxybutynin such as xerostomia, headache, diarrhea, dysuria, and abdominal pain. These data were reassessed after 60 days of follow-up through telephone calls.

Outcomes

The primary outcome was the intrapatient reduction of the number and intensity of HF events, being the intensity assumed as grade 1 = mild; grade 2 = moderate; grade 3 = severe; and grade 4 = very severe. The secondary outcome included 2-month follow-up to evaluate the adverse effects of oxybutynin.

Statistical analysis

Applying a two-sided 5% significance level, 40 patients were designated for the study, from January to April 2021. After evaluation of eligibility, 27 patients were randomly allocated for the oxybutynin or placebo group (outlined in Figure 1). Categorical variables were expressed as proportions and continuous variables as means ± standard deviation. The groups were compared using chi-square (χ^2) test, and oxybutynin doses were compared against placebo applying the Fisher's exact test. Additionally, a logistic regression model was employed, and a statistical significance was defined as a p-value less than 0.05 ($p<0.05$). All statistical analyses were performed using GraphPad Prism version 9.0.0 (GraphPad Software, Boston, MA, 2020).

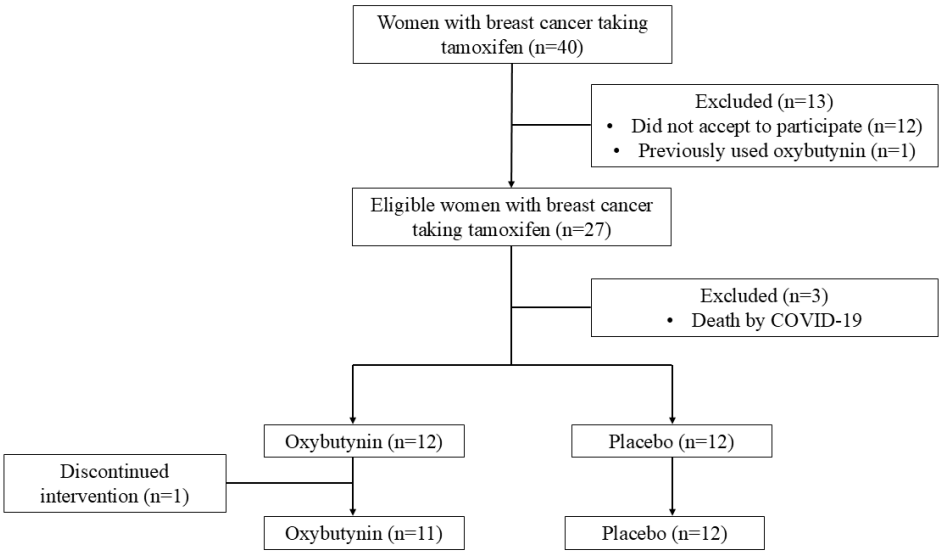


Figure 1. Study flow chart.

RESULTS

Baseline characteristics of the total cohort

In the present study, 40 patients who underwent BC treatment and were on TAM use between January and April 2021 were enrolled. After applying the inclusion and exclusion criteria, 27 patients were eligible for the study. Unfortunately, three patients died of COVID-19; therefore, 24 cases were randomly assigned (1:1) to oxybutynin or placebo treatment arm. Subsequent to this enrollment, one patient allocated in the oxybutynin treatment arm discontinued the intervention.

A statistical difference was found between the mean age in the oxybutynin and placebo groups. Meanwhile, all other baseline characteristics were well balanced, such as the proportion of postmenopausal state, ethnicity, tumor, node, and metastasis (TNM) status, and HF intensity. Table 1 describes the baseline characteristics of all patients.

Hot flashes reduction and adverse effects

HF scores and intensity reduction are presented in Table 2 and Figure 2. Patients on each arm, oxybutynin and placebo, achieved reductions in HF scores, being 60.3% and 33.4%, respectively. However, this difference was not statistically significant (p=0.13). Oxybutynin also reduced HF intensity in the analyzed women, but it was not statistically significant (p=0.19) when compared to placebo. Although the calculated relative risk (RR) showed a protection from oxybutynin to HF intensity in these patients, it was also not statistically significant, being RR=0.65 and 95% confidence interval (CI) 0.78–1.98.

Table 3 shows the adverse effects reported by the patients of each arm. Interestingly, more women in placebo arm reported anticholinergic adverse effects such as xerostomia, headache, diarrhea, and dry skin. Even though only one woman reported tachycardia and decrease in appetite in the oxybutynin arm, there was no statistically significant difference between the two

Table 1. Baseline characteristics of the study population.

	Total (n=24)	Oxybutynin (n=12)	Placebo (n=12)	p-value
Mean age, y±SD (range)	51.5±5.50 (34–62)	51.8±3.46 (48–59)	51.2±7.15 (34–62)	**0.02**
Menstrual state (%)				
Premenopausal	2 (8.3)	0	2 (16.6)	0.48
Postmenopausal	22 (91.7)	12 (100)	10 (83.4)	
Ethnicity (%)				
White	15 (62.5)	7 (58.3)	8 (66.7)	0.99
Nonwhite	9 (37.5)	5 (41.7)	4 (33.3)	
TNM status				
T status (%)				
Tis	2 (8.3)	0	2 (16.6)	0.49
T1	9 (37.5)	5 (41.7)	4 (33.4)	
T2	10 (41.7)	5 (41.7)	5 (41.7)	
T3	3 (12.5)	2 (16.6)	1 (8.3)	
T4	0	0	0	
N status (%)				
N0	14 (58.3)	7 (58.3)	7 (58.3)	0.45
N1	6 (25.1)	2 (16.7)	4 (33.4)	
N2	2 (8.3)	2 (16.7)	0	
N3	2 (8.3)	1 (8.3)	1 (8.3)	
HF intensity (%)				
Mild	1 (4.2)	0	1 (8.3)	0.30
Moderate	8 (33.3)	6 (50.0)	2 (16.6)	
Severe	8 (33.3)	3 (25.0)	5 (41.7)	
Very severe	7 (29.2)	3 (25.0)	4 (33.4)	

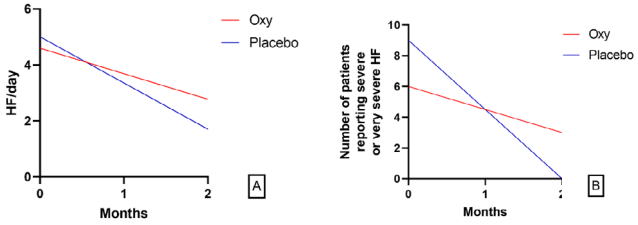
Nonwhite: black, brown, yellow, and indigenous ethnicity; TNM: tumor, node, and metastasis; HF: hot flashes.

groups in adverse effects (p=0.37), showing that oxybutynin was well tolerated at this dose.

Among patients that started the study, only one in the oxybutynin arm was excluded from the analyses since she stopped taking the medication, reporting having unbearable dizziness.

DISCUSSION

TAM is a well-established medication used for the treatment of ER+ BC, leading to a significant reduction in deaths when in the adjuvant setting, and reducing by 34.0% the incidence of ER+ BC in women at high risk of developing the disease[21,22]. This prodrug needs to undergo hepatic metabolism by CYP2D6 to activate its metabolites 4-hydroxytamoxifen and endoxifen, both with a much higher level of affinity for ER than TAM itself[15]. Elevated endoxifen plasma levels suggest that this metabolite is clinically more important in TAM efficacy than 4-hydroxytamoxifen[23]. However, the use of TAM can be associated with adverse effects such as HF in approximately 80.0% of patients[24]. Additionally, it is believed that the conversion of TAM to endoxifen is the cause of HF, and it is also assumed as a biomarker of efficacy[15].



HF: hot flashes; Oxy: oxybutynin.

Figure 2. Hot flashes scores (A) and intensity (B) reduction by oxybutynin and placebo.

Table 2. Reduction in hot flashes score and intensity from baseline to month 2.

HF measure	Oxy Baseline (n=12)	Oxy Month 2 (n=11)[a]	p*	Placebo Baseline (n=12)	Placebo Month 2 (n=12)	p†	Mean (SD) reduction Oxy (% of reduction)	Mean (SD) reductionPlacebo (% of reduction)	p††	RR (95%CI)
HF score (%)										
I	0	7 (63.6)		2 (16.7)	11 (91.7)		1.81±1.01 (60.3)	3.33±2.99 (33.4)	0.13	1.21 (0.78–1.98)
II	7 (58.3)	3 (27.3)		5 (41.6)	1 (8.3)					
III	4 (33.4)	0	>0.99	1 (8.3)	0	**0.04**				
IV	0	0		2 (16.7)	0					
V	1 (8.3)	1 (9.1)		2 (16.7)	0					
HF intensity (%)										
Mild	0	6 (54.5)		1 (8.3)	9 (75.0)		(54.5)	(83.3)	0.19	0.65 (0.87–5.56)
Moderate	6 (50.0)	2 (18.2)	0.40	2 (16.6)	3 (25.0)	**<0.01**				
Severe	3 (25.0)	2 (18.2)		5 (41.7)	0					
Very severe	3 (25.0)	1 (9.1)		4 (33.4)	0					

[a]One patient in the oxybutynin arm was excluded from this analysis since she stopped taking the medication because of reported dizziness.
HF: hot flashes; Oxy: oxybutynin 5 mg/day; HF score: I = 1 to 2 HF/day, II = 3 to 4 HF/day, III = 5 to 6 HF/day, IV = 7 to 8 HF/day, V = 9 to 10 HF/day; RR: relative risk; 95%CI: 95% confidence interval; p*: p-value from the difference between the reduction of HF score and HF intensity of oxybutynin 5 mg/day from baseline to month 2; p†: p-value from the difference between the reduction of HF score and HF intensity of placebo from baseline to month 2; p††: p-value from the difference between the reduction of HF score and HF intensity of oxybutynin 5 mg/day and placebo.

Table 3. Self-reported adverse effects from baseline to month 2.

Adverse effects	Oxy (%) (n=11)	Placebo (%) (n=12)	p-value	RR (95%CI)
Headaches	0	1 (8.3)	0.37	0.44 (0.64–5.56)
Xerostomia	0	2 (16.6)		
Diarrhea	0	1 (8.3)		
Dry skin	0	1 (8.3)		
Tachycardia	1 (9.1)	0		
Decrease in appetite	1 (9.1)	0		

Oxy: oxybutynin 5 mg/day; RR: relative risk; 95%CI: 95% confidence interval.

HF are the subjective and transitory sensation of heat, flushing, and excessive sweating in the face and chest, and it generally occurs as a result of decreased estrogen or increased gonadotropin concentrations[24-27]. Furthermore, other reported precipitators include psychological stress, hot weather, alcohol, and caffeine[28]. The physiological and molecular mechanism of HF is still unknown[29]; however, it is known to be triggered by a small elevation in core body temperature that induces activation of the sympathetic nervous system by peripheral vasodilation and increased activity of sweat glands. It is believed that this mechanism is associated with the response of the hypothalamus to decreased estrogen levels and the modulation of serotonin and noradrenalin[30]. Thus, HF can result in sleep disturbance, headache, irritability, and in reduced quality of life[31].

Pharmacologically, the most used medications are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), megestrol, clonidine, and gabapentin. However, there is a frequent association of these drugs with weight gain, and it is not frequent that patients become refractory to treatment, even after the most effective agents, like SSRIs[32]. Therefore, in the need of new medications to improve quality of life, oxybutynin emerges as a plausible drug since it is an anticholinergic agent that can interfere with the postjunctional effects of acetylcholine on smooth muscle, causing smooth muscle relaxation of the bladder and blood vessels[33,34]. Oxybutynin presents selectivity for the M3 and M1 muscarinic subtypes, which can be found in the brain, and this central effect may diminish the thermostat level and sweating threshold, reducing HF severity and frequency[32].

In this work, oxybutynin 5 mg/day was administered to BC women using TAM for two months (8 weeks). Although this concentration did not differ statistically from placebo, it was possible to see that it actually reduces the number and intensity of HF/day. These results partially corroborate Leon-Ferre et al.[18], who also investigated oxybutynin 5 mg/day and 10 mg/day versus placebo for HF reduction in women with or without BC, using TAM or not, and found that these two doses of oxybutynin were efficient in decreasing HF in those women. There were some differences in the methodology applied, such as the period the oxybutynin was administered. The authors administered the doses for six weeks, twice a day (2.5 mg twice a day and 5 mg twice a day), finding statistical difference between placebo and both doses. Simon et al.[35] also evaluated oxybutynin versus placebo, in the dose of 15 mg once a day, for 12 weeks in postmenopausal women, and found statistical difference in HF reduction in women treated with oxybutynin, besides the improvement in sleep quality, sleep disturbance, and the global sleep index.

In our study, women in the placebo arm reported more anticholinergic adverse effects than in the oxybutynin arm, although one patient discontinued the study since she felt severe dizziness. Adverse effects of anticholinergic drugs, such as xerostomia, constipation or diarrhea, decrease in appetite, dizziness, and dry eyes and skin are expected. But our study showed that a low dose of oxybutynin for a short period presented very tolerable adverse effects.

One important advantage of oxybutynin over SSRIs and SNRIs is that oxybutynin does not interfere with CYP2D6, since this enzyme is important for TAM metabolism. The use of this enzyme, and its consequent inhibition, can decrease endoxifen plasma levels; studies are still debating if this inhibition can interfere with TAM anticancer efficacy[36-39].

Although the sample size is adequate for a pilot study, the small cohort and short duration are limitations for the results. And although the dose needs to be adjusted, the short duration showed a preclusion of long-term safety of oxybutynin for BC patients in use of TAM. A new study with an expanded casuistic is going to be conducted with registration in the Brazilian Registry of Clinical Trials.

CONCLUSIONS

Oxybutynin is a safe nonhormonal therapy option for hot flashes in women with breast cancer in use of tamoxifen. More studies are needed to better adjust the dose and period of oxybutynin for higher efficacy.

AUTHORS' CONTRIBUTIONS

BFM: Conceptualization, Data curation, Investigation, Methodology, Writing - original draft. MGO: Conceptualization, Data curation, Investigation, Methodology, Writing - original draft. VTO: Conceptualization, Data curation, Investigation, Methodology, Writing - original draft. LEK: Formal analysis, Project administration, Supervision, Validation, Writing - review & editing. SUS: Conceptualization, Formal analysis, Validation, Writing - original draft. RSS: Conceptualization, Project administration, Supervision, Writing - review & editing.

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