Original Article

Comparative Evaluation of Captopril, Spironolactone, and Carvedilol Effect on Endothelial Function in Breast Cancer Women Undergoing Chemotherapy

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Abstract

Background: Breast cancer is the most prevalent malignancy in females which needs chemotherapy treatment. Studies demonstrated that anti-cancer agents used for chemotherapy in cancer patient causes endothelium dysfunction. Several researches showed the efficacy of angiotensin-converting enzyme inhibitors, Carvedilol and Spironolactone on improving endothelial function. This study aimed to evaluate the effect of the combination of Spironolactone, Carvedilol, and Captopril on endothelial function in breast cancer patients.

Materials and Methods: This study is a prospective Randomized Clinical Trial in breast cancer patients who underwent chemotherapy. Patients were divided into two groups who received the combination of Captopril, Spironolactone, and Carvedilol or standard regimen for 3 months during chemotherapy. Before and after intervention, ejection fraction (EF), E/A ratio and e' and flow-mediated dilation (FMD) properties were calculated and then compared.

Results: Fifty-eight patients with a mean age of 47.57 ± 9.46 years were evaluated. The mean FMD after the intervention is statistically different in case and controls (<0.001). E/A ratio and e' are not statistically different between groups after intervention. The mean EF was not statistically different between the two groups after intervention.

Conclusion: Prescribing combination of Carvedilol, Spironolactone, and Captopril in breast cancer patients undergoing chemotherapy can improve endothelial function and may have beneficial effects on diastolic function.

Keywords: Breast cancer, captopril, carvedilol, spironolactone

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Introduction

Breast cancer is the most prevalent malignancy in females and consists 3% of new cases of cancers annually.[1] In 2012, about 1.7 million new cases of breast cancer were diagnosed worldwide[2] higher morbidity and mortality were reported in developed countries that is may be due to the more availability of diagnosing and treating services.[3] Scientists estimated that about 90% of females with documented breast cancer will survive for 5 years or longer because of developing in diagnosing and treating breast cancer patients.[4]

Malignancies are associated with molecular changes in body structure and affected molecular pathways. Several biomarkers are associated with breast cancer according to recent studies including C-reactive protein, HER-2 receptors, and nitric oxide (NO).[5] One of the criteria for cancer invasion

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is its angiogenesis that is directly related to the level of NO in the peripheral system and the activity of NO synthase enzyme (NOS). In addition, NO is a vasodilatation mediator releasing agent from vascular endothelial cells that controls endothelium function and regulates blood supply.[6] Studies demonstrated that anti-cancer agents used for chemotherapy in cancer patients, causes endothelial dysfunction and have toxic effects on the vasculature.[7,8] Anti-cancer medications like Doxorubicin causes cyto-toxicity by producing free radicals which can lead to cardio-toxicity. In addition, this medication may have unfavorable effect on vascular walls and induce necrotic and apoptotic morphological changes in the vascular smooth muscles.[9] One of the other chemotherapy medications are anthracyclines.[7,8] Anthracyclines were used in solid and hematological malignancies and increased the survival rate from 30% to 70%. Anthracyclines may cause vascular endothelial dysfunction. The side effect of this medication is cumulative and lead to irreversible cardiotoxicity.[10,11]

Several researches showed the efficacy of angiotensin-converting enzyme inhibitors (ACE-I), Carvedilol, and Spironolactone on improving endothelial function. In heart failure patients using ACE-I increased Bradykinin and decreased oxidative stresses which can lead to improved endothelial function and adding Spironolactone to this regimen had beneficial effects.[12-15] Carvedilol has anti-oxidative activity that improves oxidative stress and endothelial functions.[16]

According to the effect of anti-cancer agents on endothelial dysfunction and reports of other studies on the effects of Carvedilol, ACE-I, and Spironolactone on improving endothelial function and lack of data about evaluating these three medications together, this study aimed to evaluate the effect of the combination of Spironolactone, Carvedilol, and Captopril on endothelial function in breast cancer females undergoing chemotherapy in Isfahan, the third populated province in Iran.

Materials and Methods

This study is a prospective open-label randomized clinical trial in breast cancer patients who received chemotherapy treatment in Seyed-Al-Shohada Hospital in Isfahan University of Medical Science (IUMS) from 2015 to 2016. Inclusion criteria were as followed: (1) newly diagnosed breast cancer patients at any stage, candidate for chemotherapy, (2) age between 30 and 70 years, (3) sinus rhythm in the electrocardiogram, (4) left ventricular ejection fraction (EF) ≥50 in echocardiography, and (5) patient's willingness to participate in this study. Exclusion criteria were history of previous myocardial infarction or coronary artery disorder, valvular disorder or cardiomyopathy, GFR ≤30 mm/min/1.73 m^2, treating with ACE-I, ARB or beta-blocker, sensitivity to the medications, systolic blood pressure ≤90 mmHg or heart rate ≤60 beat/min, atrial fibrillation rhythm that needed treating with anti-arrhythmia medications, pregnancy or unwillingness to participate in the study. Chemotherapy regimen was as follows: Docetaxel (taxotere) 100 mg/m^2, cyclophosphamide 600 mg/m^2 epirubicin (farmorubicin) 100 mg/m^2, per cycle according to physician judgment and clinical condition.

The sample size of this study was calculated 64 patients based on other similar studies[17,18] and statistical formula. Patients were selected based on simple randomized sampling methods and they gave written informed consent to participate in this study. Patients were divided into two groups by random allocation service. The first group received 12.5 mg Captopril every 12 h, 25 mg spironolactone daily, and 3.125 mg carvedilol every 12 h for 3 months during chemotherapy.[17-19] These medications were produced by pharmacological companies as followed: Captopril (Exir company, Boroujerd, Iran), Spironolactone (Pars Darou Company, Tehran, Iran), and Carvedilol (Pursina company, Karaj, Iran). The second group or control group received just standard treatment regimen. These medications in first group were administered 48 h before the first session of chemotherapy.

Patients were interviewed to collecting demographic data including age and gender. Before starting the intervention, brachial artery sonography for Basal brachial artery dimension (BBD) and flow-mediated dilation (FMD) test were performed for each patient, and echocardiography was done for evaluation of EF, E/A ratio and e'. Patients were evaluated every 2 weeks for hypotension, bradycardia, and other side effects of medications such as electrolyte disturbances. If patients showed any side effects, first they were treated and then excluded from the study. After the intervention echocardiography and FMD tests were repeated.

Echocardiography was done by Simpson methods and using Vividecho 3® echocardiogram. Vascular endothelial function can be characterized by FMD of the brachial artery which was measured by comparing the brachial artery diameter at rest to the diameter after increased forearm blood flow using B-mode scan and 7.5 MHz array transducer.[20] FMD was assessed in a patient's right arm in a supine position in a quiet room. At First patients rest for 10 min, then the brachial artery was imaged above the antecubital fossa in the longitudinal plane using B-mode ultrasound and the diameter of the brachial artery was measured continuously. A cuff was placed around the forearm above the antecubital fossa. After baseline arterial occlusion was induced by cuff inflation to at least 50 mmHg above systolic pressure for 5 min ($\geq 200_{mmhg}$). When the cuff was released FMD was calculated as the maximum precent increase in the diameter during hyperemia compared with the baseline diameter. These measurements were done for three times and its mean were calculated.[21]

Data for each participant before and after intervention were entered into SPSS 16 ((PASW Statistics for Windows, Version 16.0. SPSS Inc., Chicago, Illinois, USA) and then analyzed. For reporting quantitative and qualitative data we used mean ± standard deviation and number or percent, respectively. Data were analyzed using *t*-test and Chi-square tests. A two-sided α level of 0.05 was used to assess statistical

significance. This study was approved by the Regional Bioethics Committee of IUMS.

Results

Seventy patients were assessed for eligibility and 6 patients were excluded (4 patients did not met inclusion criteria and two patients declined to participate) the remaining 64 patients were randomized and divided into two groups. In the case group, 2 patients did not received intervention because of their unwillingness to continue participating in the trial. Four patients in cases were excluded because of discontinuing treatment due to their unwillingness without showing any side effects and finally, data of 58 patients were analyzed [Figure 1]. The mean age of participants was 47.57 ± 9.46 years (44.72 ± 8.26 years in the case group and 50.41 ± 9.46 years in the control group, $P = 0.2$). Other demographic feature has been described in Table 1.

The baseline mean FMD in case and control groups were 10.52 ± 3.80 and 9.29 ± 3.43, respectively, which was not statistically significant ($P = 0.2$). After finishing the intervention, the mean FMD in cases and controls was 9.85 ± 3.47 and 6.12 ± 3.17, respectively, which has statistically significant differences ($P < 0.001$). Univariate analysis of variance showed that mean FMD after intervention is statistically different in case and controls with considering the confound effects of other variables including age and type of chemotherapy treatment ($P < 0.001$) [Table 2].

We defined e'<7 and E < A as high probable Grade I of diastolic dysfunction. Before the intervention, none of the patients in cases and 4 patients in controls had grade I diastolic dysfunction and the others had normal diastolic function. After Intervention, evaluating participants showed that 14 patients in controls (48.27%) and 6 patients in cases (20.68%) had grade I diastolic dysfunction and Chi-square test showed these differences statistically significant ($P = 0.02$). Univariate analysis of variance with considering other confounding factors showed that having diastolic dysfunction is not statistically different between groups ($P = 0.33$) [Table 2].

The mean EF in case and control group before intervention were 62.06 ± 2.50 and 61.55 ± 2.70, respectively ($P = 0.54$) and these variables after intervention were 61.89 ± 2.80 and 61.03 ± 2.45, respectively ($P = 0.36$) [Table 2].

No electrolyte disturbances, hypotension, or bradycardia were reported by the oncologist during every 2 weeks of follow up.

Discussion

This study evaluated the effect of Carvedilol, Captopril, and Spironolactone on endothelial and diastolic function in breast cancer patients which demonstrated that administrating Carvedilol, Spironolactone, and Captopril together in patients with breast cancer who undergoing chemotherapy can improve endothelial function and diastolic dysfunction.

We revealed that prescribing Carvedilol, Captopril, and Spironolactone together in breast cancer patients can significantly improve their endothelial function. Endothelium is considered as a dynamic organ that lines the entire vascular system and controls vascular function by responding to different hormones, neurotransmitters, and vasoactive factors.[22] Endothelium releases vasoactive factors like NO that is endothelium-dependent vasodilator which produced

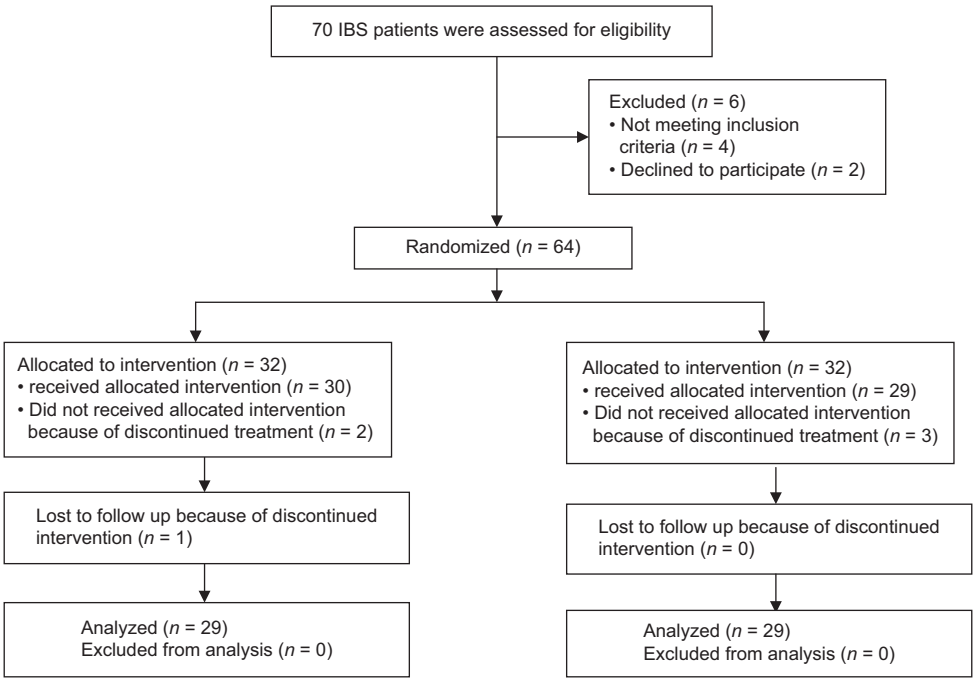

Figure 1: Consort diagram of selecting participants

Table 1: Baseline characteristics of patients

Variable	Cases ($n=29$), n (%)	Controls ($n=29$), n (%)
Age	44.72±8.26	50.41±9.46
Diabetes mellitus	1 (3.44)	1 (3.44)
Hypertension	2 (6.89)	3 (10.34)

Table 2: The mean flow mediated dilation and incidence of diastolic dysfunction in cases and controls

Variable	Cases	Controls	*P*
FMD			
Before intervention	10.52±3.80	9.29±3.43	0.2
After intervention	9.85±3.47	6.12±3.17	<0.001*
EF			
Before intervention	62.06±2.50	61.55±2.70	0.54
After intervention	61.89±2.80	61.03±2.45	0.36
E'			
Before intervention (e'), *n*			
<7	4	25	0.69
>7	0	26	
After intervention (e'), *n*			
<7	14	15	0.02*
>7	6	23	

*FMD and e' after intervention were statistically different between two groups. FMD: Flow mediated dilation, EF: Ejection fraction, E': Early diastolic mitral annular tissue velocity

by the NOS enzyme.[23] Endothelial dysfunction is an early marker for atherosclerosis in patients with malignancies and several studies demonstrated the effects of medications on improving this function.[24,25] Captopril is an ACE-I placed on the endothelium to affect angiotensin II and bradykinin activity and NO synthesis.[26] ACE-I had two activity including inhibition of Ang II formation and bradykinin breakdown and the effects of ACE-I on endothelial function is maybe due to these two mechanisms.[27] Yavuz *et al*. demonstrated that ACE-I can improve FMD in patients with cardiovascular diseases and the FMD was changed from 8 to 14.[28] Khan *et al*. demonstrated that the beneficial effect of ACE-I on endothelial function is because of increasing bradykinin in the vascular wall and decreasing oxidative stresses.[29] The effects of beta-blockers on endothelium function were assessed in a previous study and reported that third generation of beta-blockers like Carvedilol have beneficial effects on the endothelial function which is due to eliminating oxidative stresses.[30-32] In a study on diabetic patients prescribing Carvedilol, improved FMD in the brachial artery.[30] In addition, researches illustrated that using beta-blockers in combination with ACE-I can significantly improve vascular health which can lead to improve endothelial function.[33] Spironolactone is an Angiotensin antagonist that inhibits NO release. There are studies that demonstrated the effect of Spironolactone on endothelial function by decreasing bioactivity of NO in tissue and its inverse relation with arterial compliance which may be related in part to NO.[34,35] Generally, Spironolactone improves NO activity that can cause endothelial dysfunction.[14] These three medications used in our trial have their specific effects on improving endothelial function and most of the study evaluated their effects on endothelial function separately and there are limited studies that assessed these effects together. This study suggested that prescribing these medications together maybe had additive effects in improving endothelial function. For further researches, it is better to compare long-term effect after 6 months for evaluation of its primary effect for prevention of diastolic and systolic dysfunction.

In the current study, patients were treated with Cyclophosphamide, Taxstere, and Farmorubicin. Studies demonstrated that Taxotere is a potent and potentially specific inhibitor of endothelial cell migration and angiogenesis.[36] During the early phases of treating with cyclophosphamide, endothelial damage was induced which occurs a little earlier than suppression of the immune system.[37] Farmorubucin can induce endothelial dysfunction and endothelial cell injuries during cancer treatment.[38] Chemotherapy agents are associated with significant abnormalities in diastolic function because of its cardiac damage.[39] The incidence of anthracycline-induced cardiotoxicity varies depending on medications and its cumulative doses. Free radical formation is generally accepted as the main mechanism for prescribing the effect of these anti-cancer agents on cardiac toxicity.[40]

Comparing the incidence of diastolic dysfunction using Chi-square revealed significant increase in diastolic dysfunction incidence in control group, but univariate analysis with considering other confounding factors did not show significant differences. The number of patients with grade I diastolic dysfunction at the first of study was zero in cases and 4 in controls and lack of presence of diastolic dysfunction in cases maybe affect these outcomes. In addition, diastolic dysfunction defines by several criteria in combination together that but only e'<7 and E < A was considered in this study, which may be does not illustrate exact diastolic dysfunction. Overall there are limited studies evaluated the effect of these medications on diastolic dysfunction. One study on 83 breast cancer patients illustrated that prescribing Spironolactone maintains diastolic and systolic function.[11] Another study reported that Captopril can improve diastolic dysfunction by decreasing blood pressure. Another study on diastolic heart failure patients demonstrated that Carvedilol can improve diastolic dysfunction.[41]

Our results indicated that prescribing these medications did not have any effects on EF. In another study prescribed Carvedilol and Enalapril for patients with leukemia showed that a combination of these medications can prevent EF reduction in these patients.[42] Another study demonstrated that using Spironolactone in patients undergoing chemotherapy can prevent from decreasing EF.[11] Maybe the difference between our findings and these studies is related to the smaller sample size. For better evaluation, larger sample size is needed.

This study has a strength that evaluates the effect of Carvedilol, Captopril and Spironolactone in combination to each other

that other studies evaluated these medications separately. Other strength is evaluating these effects on breast cancer patients who are at risk of endothelial dysfunction and diastolic dysfunction due to chemotherapy medications.

There were although some limitations. This study was performed on 58 breast cancer patients that are not enough to generalize these outcomes to the population. EF was measured by M mode methods, although there are other available methods with better sensitivity and specificity including Simpson and speckle tracking. For future researches, it is better to use these methods for better evaluation.

Conclusion

Carvedilol, Spironolactone, and Captopril in breast cancer patients undergoing chemotherapy can improve endothelial function and may have beneficial effects on diastolic dysfunction.

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Conflicts of interest

There are no conflicts of interest.

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