Original Article

Evaluation of the Effect of Carvedilol in Preventing Right Ventricular Dysfunction in Breast Cancer Patients Receiving Anthracycline

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Abstract

Background: Today, it has been shown that it is possible for right ventricular (RV) wall motion abnormalities or RV functional disorders to occur during cancer treatment. Now, considering the effect of carvedilol on beta 1, 2, and alpha receptors and its antioxidant properties, it seems that it can prevent RV abnormalities. Therefore, the aim of this study was to investigate the possible protective effects of carvedilol in preventing RV dysfunction in patients with breast cancer treated with anthracyclines.

Materials and Methods: The present single-blind clinical trial study was performed on 23 patients with breast cancer that 12 of them received only the anthracycline antineoplastic doxorubicin (Adriamycin®) chemotherapy (control group) and 11 patients received carvedilol in addition to anthracycline. To evaluate the effect of carvedilol, patients underwent transthoracic echocardiography before intervention and 2 weeks after the end of treatment with anthracyclines.

Results: The two parameters of RV ejection fraction and RV fractional area change in the carvedilol group with a mean of 66.41% ± 8.10% and 51.85% ± 6.89% were slightly higher than the control group with a mean of 64.58% ± 6.83% and 50.48 ± 5.79%, respectively, which was not statistically significant ($P > 0.05$). In contrast, RV S wave tissue Doppler imaging (S-TDI) in the control group with a mean of 0.13 ± 0.02 m/s was significantly lower than the carvedilol group with a mean of 0.14 ± 0.02 m/s ($P = 0.022$).

Conclusion: According to the results of the present study, the effect of using carvedilol as a preservative on improving RV function was seen compared to the control group, although this difference was not statistically significant.

Keywords: Anthracycline, breast cancer, carvedilol, ejection fraction, right ventricle

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Introduction

Breast cancer is the most common type of cancer in women worldwide.[1] The rate of recovery from breast cancer has increased dramatically over the past 20 years, largely due to advances in cancer treatment.[2] However, many anticancer drugs used to treat patients with breast cancer may cause cardiac toxicity. Now, it is known that anthracycline-based chemotherapy is one of the most effective treatments of cancer, but is associated with a high incidence of cardiotoxicity and causes irreversible cardiac side effects up to 5%–20%, including cardiomyopathy, and therapeutic approaches have no effect on its improvement after incidence, and would be led to the death in more than 50% of cases.[3,4]

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Now, due to the poor prognosis of advanced cardiac dysfunction,[3] early detection of this disorder has received increasing attention to take appropriate intervention to prevent heart failure (HF). These interventions may include cardiac therapy (such as beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, and dexrazoxane), selection of alternative cancer regimens, or dose adjustment, and temporary cessation of cancer treatment.[5]

To date, there has been very little focus on the toxic effects of cancer treatment on the right ventricular (RV).[6] Due to the thinner structure of the RV with fewer myofibrils compared to left ventricular (LV), RV may be prone to damage from toxic cardiac therapy. Numerous studies have shown that RV wall motion abnormalities or dysfunctions occur during cancer treatment; however, this finding has not been confirmed.[7,8] The presence of RV dysfunction during myocardial toxicity and whether the disorder has different consequences than LV failure alone has not been studied yet. However, in many other heart diseases, RV dysfunction is associated with more adverse outcomes.[9,10]

To date, no direct study has been performed on the effect of carvedilol on the prevention of RV failure in patients with breast cancer treated with anthracyclines. Despite the fact that carvedilol, in addition to its impact on beta 1, 2, and alpha receptors, has antioxidant properties that have been proven in several animal studies, few studies have been performed on humans,[6,11] the aim of this study was to investigate the possible protective effects of carvedilol in preventing RV failure in breast cancer patients treated with anthracyclines.

Materials and Methods

The present study was a single-blind clinical trial. The population of the study included all patients with BC that were candidates for starting chemotherapy with anthracyclines (adriamycin) and were referred from the oncology ward to the cardiovascular ward of Taleghani Hospital in 2019. The sample size of 30 patients (15 patients per group) was randomly selected from the mentioned population at the confidence level of 95%, test power of 80%, and considering the incidence of cardiotoxicity following anthracycline and beta-blockers treatment to be equal to 23% and 80%, respectively.

Inclusion criteria were having breast cancer and being the candidate for the anthracycline antineoplastic doxorubicin (Adriamycin®) treatment, age of at least 18 years, diagnosis of invasive breast adenocarcinoma, need for adjuvant or neoadjuvant treatment, no menopause, and no history of hypertension.

Exclusion criteria included impossibility of RV function assessment, history of chemotherapy or radiation therapy, HF symptoms, previous diagnosis of cardiomyopathy, history of coronary artery diseases, moderate to severe mitral and aortic disease, and atrial fibrillation, using beta-blockers, ACE Inhibitors, and ARB drugs.

It should be noted that the patients' treatment regiments were the following:

All patients included in the study received all 4 sessions of the chemotherapy course 100%. Adriamycin with the mean of 55 mg/m^2 (minimum 50 – maximum 60 mg/m^2) per session. Adriamycin total dose in 4 sessions – 200–240 mg/m^2. Cyclophosphamide the mean of 550 mg/m^2 (minimum 500–maximum 600 mg/m^2) per session. Cyclophosphamide total dose in 4 sessions - 2000–2400 mg/m^2.

All eligible patients underwent routine laboratory tests and transthoracic echocardiogram prior to randomization. If the patient met the eligibility criteria, she was included in the study.

After obtaining the ethical approval of ethics committee of Shahid Beheshti University of Medical Sciences in Tehran (Code: IR.FBMU.MSP.REC.1397.804) and obtaining written consent from patients, patients were randomized using a computerized randomization in three random blocks (up to dividing participants into two groups of 15).

At the beginning of the study, all demographic information including age, body mass index, previous underlying diseases, human epidermal growth factor receptor 2 (HER2), and other received drugs were recorded.

In the first group, treatment was started with carvedilol 10 days before the beginning of chemotherapy with a dose of 3.125 mg twice daily, which was then 12.5 mg, with a maximum dose of 25 mg every 12 h if the patient tolerates, continued until 10 days after the end of chemotherapy. Carvedilol administration was continued until the end of chemotherapy.

In the second group, as a control group, only the usual treatment with anthracycline (Adriamycin) chemotherapy was performed.

RV echocardiographic indices (including fractional area change (FAC), S wave tissue Doppler imaging (S-TDI) and RV ejection fraction (RVEF)) were measured once at the beginning of the study and then 2 weeks after the end of treatment with anthracyclines.

In order to observe the conditions of the blind study, the cardiologist (researcher) was not aware of the allocation of patients in the two groups to perform cardiac echocardiography and recorded only the results of echocardiographic indices without knowing the type of the therapeutic intervention.

These measured echocardiographic indices were calculated as follows:

Fractional area change

It is a volumetric method used to measure RVEF that requires close observation of RV performance, with FAC <35% estimated to be Abnormal. Its value was calculated through the formula of FAC = (RV end-diastolic area − RV end-systolic area)/end-diastolic area.

S wave tissue Doppler imaging

S-TDI, measured in the annulus tricuspid, which S ware <9.5 cm/s is Abnormal.

Right ventricular ejection fraction

In the present study, RVEF was measured by the Simpson Method, which values below 45% were considered to be Abnormal.

It is necessary to mention that 7 of 30 patients (4 in the Carvedilol group and 3 in the control group) were excluded from the study due to their nonreferral for follow-up regarding their cardiac status after chemotherapy [Figure 1].

Finally, the collected data were entered into SPSS software (version 25; SPSS Inc., Chicago, Ill., USA). Data were reported as mean ± standard deviation or *n* (%). Chi-square test was used to compare the frequency distribution of qualitative variables between the two groups. Due to the small samples in each group and the result of Kolmogorov–Smirnov test based on abnormal data distribution, Man–Whitney test was used to compare the mean of quantitative variables between the two groups, and to compare the mean of quantitative variables before and after the intervention, Wilcoxon test was used in each group. In all analyzes, a significance level of <0.05 was considered.

Results

The present study was performed on 23 patients with breast cancer with a mean age of 47.35 ± 4.89 years in the two groups treated with anthracycline chemotherapy (control group: 12 people) and anthracycline chemotherapy with Carvedilol (Carvedilol group: 11 people). In addition to breast cancer, 30.4% of patients had other conditions, such as high blood pressure, diabetes, hypothyroidism, and hyperlipidemia. In addition to receiving breast cancer medications, 26.1% of them also took other medications, including levothyroxine and atorvastatin. There was no significant difference between the two groups in terms of age, BMI, comorbidities, and use of other drugs ($P > 0.05$) [Table 1].

On the other hand, the evaluation of RV function showed that the three parameters of RVEF, RV FAC, and RV S-TDI of right ventricle before the intervention were not significantly different between the two groups ($P > 0.05$). Two weeks after the end of treatment with anthracyclines, although RVEF and RV FAC were higher in the Carvedilol group with a mean of 66.41 ± 8.10% and 51.85 ± 6.89%, respectively than the control

Table 1: Baseline characteristics of patients in the two groups

Characteristics	Carvedilol (*n*=11), *n* (%)	Control (*n*=12), *n* (%)	*P*
Age; year	45.56±4.95	49.00±3.97	0.101
BMI; kg/m^2	24.56±3.60	25.31±4.36	0.684
Other medications			
Levothyroxine	3 (27.3)	1 (8.3)	0.570
Atorvastatin	0	2 (16.7)	
Comorbidity			
Hypertension	1 (9.1)	1 (8.3)	0.405
Diabetes	0	1 (8.3)	
Hypothyroidism	1 (9.1)	2 (16.7)	
Hyperlipidemia	0	1 (8.3)	
HER2			
Positive	1 (9.1)	2 (16.7)	0.660
Negative	8 (90.9)	9 (83.3)	

HER2: Human epidermal growth factor receptor 2, BMI: Body mass index

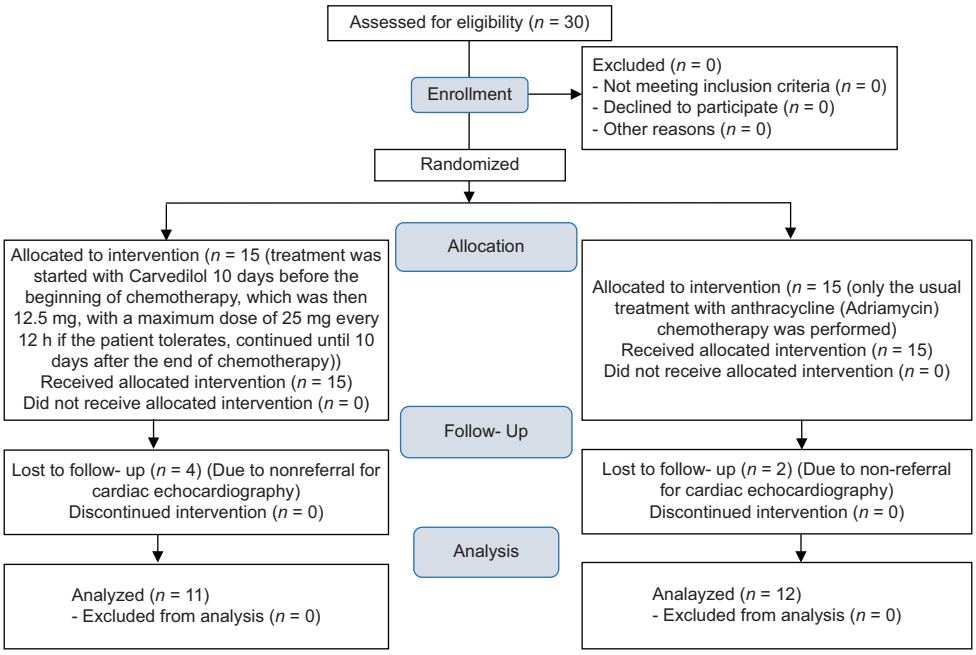

Figure 1: CONSORT flowchart of patients

group with a mean of 64.58 ± 6.83% and 50.48 ± 5.79%, this difference was not statistically significant ($P > 0.05$). In contrast, RV S-TDI in the Carvedilol group with the mean of 0.14 ± 0.02 m/s was significantly higher than the control group with the mean of 0.13 ± 0.02 m/s ($P = 0.022$). In addition, the changes of these three parameters after the intervention compared to before were not significant in either group ($P > 0.05$) [Table 2].

Discussion

The results of the present study showed that 2 weeks after the end of treatment with anthracyclines, the mean of RVEF and RV FAC in the carvedilol group was higher than the control group, but there was no significant difference between the two groups; however, these two parameters were normal in both groups.

The mean of RV S-TDI in the Carvedilol group was significantly higher than the control group, but it was normal in both groups.

In this regard, Zamani *et al*. evaluated the protective effect of Carvedilol on anthracycline-induced cardiomyopathy in patients with breast cancer and lymphoma and it was shown that prophylactic administration of carvedilol at a dose of 12.5 mg/day may significantly prevent LV systolic and diastolic dysfunction in patients receiving anthracycline chemotherapy.[12] Although this study differs from the present study in terms of therapeutic dose of carvedilol, the results have consistence.

The results of a clinical trial done by Guglin *et al*. to evaluate the efficacy of lisinopril versus carvedilol in preventing cardiac toxicity of trastuzumab in breast cancer patients indicated that those receiving anthracycline and being actively treated with an angiotensin-converting enzyme inhibitor or beta-blockers are less disturbed compared to those taking trastuzumab and placebo. They also stated that in patients with HER2-positive breast cancer treated with trastuzumab, both lisinopril and carvedilol prevented heart diseases in patients receiving anthracycline, which is consistent with the present study.[13]

Table 2: Determination and comparison of mean right ventricular ejection fraction, right ventricular fractional area change, and right ventricular S wave tissue Doppler imaging before and after intervention in the two groups

Variables	Time	Carvedilol ($n=11$)	Control ($n=12$)	P^a
RVEF; %	Before intervention	61.15±9.73	59.47±7.39	0.674
	After intervention*	66.41±8.10	64.58±6.83	0.421
P^b		0.176	0.203	
FAC; %	Before intervention	46.10±9.57	48.06±6.92	0.613
	After intervention*	51.85±6.89	50.48±5.79	1.00
P^b		0.093	0.308	
S-TDI; m/s	Before intervention	0.13±0.02	0.12±0.01	0.096
	After intervention*	0.14±0.02	0.13±0.02	0.022
P^b		0.106	0.959	

*After intervention: 2 weeks after the end of treatment with anthracyclines, [a]Used of Mann-Whitney test to compare the mean of variables between the two groups, [b]Used of Wilcoxon test to compare the mean of variables after intervention compared to before in each of the two groups. FAC: Fractional area change, S-TDI: S wave tissue Doppler imaging, RVEF: Right ventricular ejection fraction

On the other hand, a meta-analysis study showed that statins, in addition to anti-inflammatory and fat-reducing effects, have antioxidant and pleiotropic properties. According to the results of this study, pretreatment with statins in cancer patients undergoing anthracycline chemotherapy may prevent anthracycline-induced cardiomyopathy and LV ejection fraction (LVEF) reduction. This increases the use of statins as a drug for the prevention and treatment of cardiovascular diseases.[11] Although the use of statins to prevent anthracycline-induced cardiomyopathy differs from the present study, it is in accordance with anthracyclines-induced LVEF reduction.

Contrary to the present study, Calleja *et al*. showed that RV FAC was significantly lower in patients with cardiac toxicity than in the control group.[14]

In another study to evaluate the preventive effect of Carvedilol use through SI in a patient with anthracycline-treated breast cancer (ANT), it was found that both LVEF and fraction shortening were normal in all patients before and after ANT treatment. Although the initial parameters of SI were similar between the groups, in the control group compared to the Carvedilol group, there was a significant decrease in the peak systolic action of the basal wall and lateral basal.[15] In fact, these results indicate that Carvedilol has a protective effect on ANT-induced cardiac toxicity, which is consistent with the present study.

The report by Kalay *et al*. also suggested that while the E velocity in the Carvedilol group decreased, the E velocity and E/A ratio decreased significantly in the control group. As a result of the preventive use of carvedilol in patients taking anthracyclines, LV systolic and diastolic function can be protected.[16] Regarding the overall outcome and systolic and diastolic criteria, it agrees with the present study but there is contrary in terms of E velocity.

Finally, it can be stated that although the strength of this study was the evaluation of the effect of Carvedilol on the prevention of anthracycline-induced cardiac toxicity on RV function indicators in patients with breast cancer, the small sample size, sample missing in the follow-up of patients' cardiac status are among the limitations of this study, so it is suggested to do future studies with larger sample sizes on different types of cancers considering the other cardiac and chemotherapy drugs to attribute more reliable results.

Conclusion

According to the results of the present study, RVEF and FAC parameters of the right ventricle were lower in the control group as compared with the Carvedilol group after

the intervention. However, the mentioned finding was not significant. In contrast, the S-TDI parameter of the right ventricle was significantly lower in the control group as compared with the carvedilol group after the intervention. Therefore, it can be stated that the use of carvedilol with the dose and method described in this study will reduce the chances of anthracycline-induced cardiac toxicity on the RV function. However, this protective effect is not complete and requires further research in this area.

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Conflicts of interest

There are no conflicts of interest.

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