Original Research Article

Role of nebivolol in anthracycline-induced cardiotoxicity

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ABSTRACT

Background: Anthracyclines are extensively used in the treatment of breast cancer. However, these therapeutic agents are responsible for chemotherapy-induced cardiotoxicity. Aim of this study was to assess the effect of use of prophylactic nebivolol for the prevention of anthracycline-induced cardiotoxicity in breast cancer patients.
Methods: This was a prospective, randomized, single-blind, and placebo-controlled trial involving 80 participants with breast cancer, scheduled to undergo chemotherapy with doxorubicin. Patients were randomly divided into two groups: the nebivolol group (n=40) to receive nebivolol 5 mg daily and the placebo group (n=40) to receive placebo. All patients were evaluated with baseline Electrocardiogram (ECG) and echocardiography prior to treatment, and at the 6-month follow-up. Echocardiography included 2D echocardiography, colour doppler and tissue doppler imaging.
Results: The study groups had comparable baseline echocardiographic variables. At the 6-month echocardiographic follow-up, there were no changes of statistical significance in any 2D echocardiographic variables in either group. However, there were minimal reductions of 0.4% in left ventricular ejection fraction in the nebivolol group (62.2±4.4% to 61.9±4.2%, p=0.75) and 1.6% in the placebo group (62.8±3.6% to 61.8±3.2%, p=0.18). Doppler examinations also did not reveal any statistically significant changes in variables such as peak A velocity, peak E velocity, E/A ratio, isovolumic relaxation time, and isovolemic contraction time in either group.
Conclusions: Prophylactic use of nebivolol treatment may possess cardioprotective properties against anthracycline-induced cardiotoxicity in breast cancer patients although not statistically significant in this study.

Keywords: Anthracycline, Beta-blockers, Cardiotoxicity, Echocardiography, Left ventricular ejection fraction, Nebivolol

INTRODUCTION

Breast cancer is a global health concern. It is the most prevalent cancer in urban India and the second most prevalent cancer in rural India. Thus, its contribution towards a quarter of all female cancers in the country is not surprising. Moreover, recent years have witnessed an increased incidence of breast cancer in younger women, particularly in their thirties and forties.[1-3]

Anthracyclines are commonly used in the treatment of breast cancer as they possess a broad range of antineoplastic properties and have proven to improve survival from 30-70%.[4] Unfortunately, despite extensive use of these chemotherapeutic agents in the eradication of malignant cells, the pitfalls of these chemotherapeutic agents are dose-related, cumulative, and irreversible cardiotoxicity.[5] This disadvantage of anthracyclines of simultaneously inducing toxicity is a widely established limitation. Thus, it is neither unusual nor surprising for anthracyclines to cause cardiotoxicity associated with unfavorable short and long-term toxicity, thus impeding long-term clinical benefits. Further, resultant myocyte injury gives rise to decline in Left Ventricular (LV) function and heart failure during or towards the end of the

course of therapy. More serious implications include severe patient morbidity and even mortality.[6]

Nebivolol a highly cardio-selective beta-blocker with antioxidant, anti-apoptotic and vasodilator properties have been used to treat hypertension and heart failure.[7,8] However, scant literature on placebo-controlled clinical trials concerning the use of prophylactic nebivolol in preventing anthracycline-induced cardiotoxicity exists.[5] Thus, this study was designed to assess the protective effect of nebivolol.

METHODS

Study design and patient population

A prospective, randomized, single-blind, placebo-controlled study was conducted. This study includes breast cancer patients who were planned to receive chemotherapy with doxorubicin at tertiary-care center during the period from August 2016 to August 2017. Patients with underlying LV dysfunction prior to chemotherapy, history of coronary arterial disease, earlier chemotherapy or radiotherapy, and patients who failed to give consent for the study were excluded. Accordingly, 80 consecutive patients were selected randomly and divided into two groups: the nebivolol group (n=40) to receive nebivolol 5 mg daily and the placebo group (n=40) to receive placebo.

All patients received 6 cycles of chemotherapy, a mean of every 3 weeks. All patients were evaluated with baseline ECG and echocardiography prior to treatment and at the 6-month follow-up. The study was approved by the Institutional Ethics Committee.

Echocardiography

All patients were echocardiographically evaluated prior to chemotherapy and at 6 months using Philips HD15 system (Philips; Amsterdam, The Netherlands). The probe frequency was 2.5 MHz. Transthoracic echocardiographic evaluations by 2D echocardiography, colour doppler and Tissue Doppler Imaging (TDI) were performed. All measurements were performed according to the recommendations of the American Society of echocardiography.[9]

Left Ventricular End-Diastolic Dimensions (LVEDd) and Left Ventricular End-Systolic Dimensions (LVESd) were measured from M-mode and Left Ventricular Ejection Fraction (LVEF) was calculated by Simpson's method. For trans mitral pulsed Doppler examinations, peak velocities of early (E) and late diastolic flow (A), the E/A ratio, Isovolumic Relaxation Time (IVRT), and Isovolemic Contraction Time (IVCT) were measured. Diastolic functions were evaluated according to changes in mitral inflow parameters whereas systolic dysfunction was defined as LVEF <50%.

Statistical analysis

Continuous variables are expressed as mean±SD and categorical variables as frequencies and proportions. An independent t-test of difference between two means was used to compare different parameters under study between the two groups. The p value <0.05 was considered as statistically significant. Statistical analysis was performed using Microsoft Excel and in silico project support for life sciences.

RESULTS

Baseline characteristics of the study population

Total of 104 patients were assessed for study eligibility. Out of these, 24 were found to be ineligible. Of these 24 patients, 5 were ineligible due to age >70 years, 6 declined study participation, and 13 were ineligible due to existing co-morbidities. Thus, 80 patients were enrolled into the study. Of these 80 patients, 40 were randomly assigned to the nebivolol group and 40 were randomly assigned to the placebo group. The study flow is illustrated in (Figure 1).

Table 1: Baseline characteristics of the study population.

Variables	Nebivolol (n =40)	Placebo (n =40)	p value
Age (years)	48.6±8.4	49.2±9.8	NS
BMI (kg/m^2)	23.2±3.2	24.9±2.3	NS
Number of chemotherapy cycles	6.0	6.0	NS
Total doxorubicin dose (mg/m^2)	448.0±12	436.0±10.0	NS
2D echocardiographic variables			
Baseline LVEF (%)	62.2±4.4	62.8±3.6	NS
Baseline LVDD (mm)	46.4±5.3	45.5±4.6	NS
Baseline LVSD (mm)	30.4±5.0	30.8±4.7	NS
Doppler variables			
Baseline peak E velocity (cm/s)	74.2±16.4	70.8±15.6	NS
Baseline peak A velocity (cm/s)	68.8±13.4	68.8±13.0	NS
E/A ratio	1.08±0.2	1.03±0.2	NS
IVRT (MS)	64.3±18.9	62.7±16.1	NS
IVCT (MS)	59.6±19.6	61.3±18.7	NS

p= ns (<0.05 considered statistically significant).
Data expressed as mean ± SD or percentage.
BMI = body mass index; LVEF = left ventricular ejection fraction; LVDd = left ventricular end-diastolic diameter; LVSd = left ventricular end-systolic diameter; NS = not significant; IVRT = isovolumic relaxation time; IVCT = isovolemic contraction time

The study groups had comparable demographics such as age (48.6±8.4 vs. 49.2±9.8 years) and body mass index (23.2±3.2 vs. 24.9±2.3 kg/m^2) for the nebivolol and

placebo groups, respectively. The nebivolol and placebo groups received cumulative doxorubicin doses of 448.0 ± 12.0 and 436.0 ± 10.0 mg/m^2, respectively.

Baseline echocardiographic variables were also comparable for LVEF (62.2 ± 4.4 vs. 62.8 ± 3.6%), Left Ventricular Diastolic Diameter (LVDd) (46.4 ± 5.3 vs. 45.5 ± 4.6 mm), and Left Ventricular Systolic Diameter (LVSd) (30.4 ± 5.0 vs. 30.8 ± 4.7 mm) for the nebivolol and placebo groups, respectively. The baseline characteristics of the study population are detailed in (Table 1).
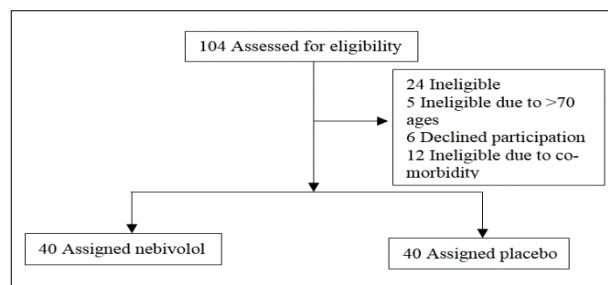

Figure 1: study flow diagram.

Table 2: Comparison of 2D echocardiographic and doppler variables in nebivolol and placebo group before and after chemotherapy.

	Nebivolol (n=40)			Placebo (n=40)		
	Baseline	Post chemotherapy	p value	Baseline	Post chemotherapy	p value
2d echocardiographic variables						
LVEF (%)	62.2 ± 4.4	61.9 ± 4.2	0.75	62.8 ± 3.6	61.8 ± 3.2	0.18
LVDD (MM)	46.4 ± 5.3	46.8 ± 4.4	0.71	45.5 ± 4.6	47.2 ± 4.8	0.10
LVSD (MM)	30.4 ± 5.0	30.6 ± 4.6	0.85	30.08 ± 4.7	31.6 ± 4.6	0.14
Doppler variables						
Peak E velocity (CM/S)	74.2 ± 16.4	72.4 ± 14.6	0.60	70.8 ± 15.6	68.6 ± 14.6	0.51
Peak A velocity (CM/S)	68.8 ± 13.4	67.5 ± 12.6	0.65	68.8 ± 13.0	66.9 ± 14.4	0.53
E/A ratio	1.08 ± 0.2	1.07 ± 0.2	0.82	1.03 ± 0.2	1.02 ± 0.2	0.82
IVRT(MS)	64.3 ± 18.9	62.6 ± 16.8	0.67	62.7 ± 16.1	60.4 ± 18.4	0.55
IVCT (MS)	59.6 ± 19.6	64.4 ± 22.3	0.30	61.3 ± 18.7	60.2 ± 18.5	0.79S

$p<0.05$ considered statistically significant.
Data expressed as mean $\pm$ SD or percentage.
LVEF = left ventricular ejection fraction; LVDd = left ventricular end-diastolic diameter; LVSd = left ventricular end-systolic diameter; IVRT = isovolumic relaxation time; IVCT = isovolumic contraction time

Comparison of echocardiographic variables in nebivolol and placebo group pre and post chemotherapy

Post chemotherapy, there was no statistically significant change in LVEF (62.2 ± 4.4 to 61.9 ± 4.2 %, p=0.75) and (62.8 ± 3.6 to 61.8 ± 3.2, p=0.18), LVDd (46.4 ± 5.3 to 46.8 ± 4.4 mm, p=0.71) and (45.5 ± 4.6 to 47.2 ± 4.8, p=0.10), and LVSd (30.4 ± 5.0 to 30.6 ± 4.6 mm, p=0.85), and (30.08 ± 4.7 to 31.6 ± 4.6 mm, p=0.14), for the nebivolol and placebo groups, respectively.

Doppler imaging variables also did not differ with any statistical significance between groups post chemotherapy. Comparison of 2D echocardiographic and Doppler variables in nebivolol and placebo group before and after chemotherapy (Table 2).

DISCUSSION

Present study was conducted to determine whether nebivolol treatment had any beneficial effects in the reduction of anthracycline-induced cardiotoxicity in breast cancer patients. Earlier preclinical studies have proven nebivolol to be beneficial in the reduction of

cardiotoxicity.[10,11] However, such a benefit was not observed in this study.

In this study, although no statistically significant changes were observed in LVDd and LVSd post chemotherapy in both groups, minimal reduction was observed in LVEF from baseline to 6 months (0.4% in the nebivolol group and 1.6 % in the placebo group. This study may be closely compared to another study. Similarly, Kaya et al, did not observe any changes in echocardiographic variables LVDd and LVSd post chemotherapy in the nebivolol group.[5] However, they also reported reduction in LVEF after chemotherapy (1.8% in the nebivolol group and 9.1% in the placebo group). These findings of LVEF perseverance are highly suggestive of cardioprotective properties of nebivolol.

In line with findings, the study by Cochera et al, did not report any statistically significant changes in echocardiographic variables.[12] However, TDI detected changes in myocardial velocities suggestive of LV deformation and Speckle Tracking Imaging (STI) detected altered ventricular deformation suggestive of decreased systolic function. Their observations provide evidence of short-term prevention of occurrence of

anthracycline-induced cardiotoxicity with nebivolol. Earlier studies hint at the possibility of cardioprotective properties of nebivolol. However, larger randomized, long-term studies are required to validate this hypothesis.

In 2003, heart failure incidences of 5%, 16%, and 26% for cumulative doxorubicin doses of 400, 500, and 550 mg/m^2 were reported, respectively.[13] These findings resulted in an amendments towards the cumulative anthracycline dose to 400 from 450 mg/m^2.[14] Doxorubicin-induced left ventricular dysfunction or congestive heart failure usually occurs in patients receiving >550 mg/m^2. In this study, doxorubicin doses were low yet sufficient enough to induce cardiotoxicity in both nebivolol and placebo groups (448±12 mg/m^2 and 436±10 mg/m^2, respectively). This may be the reason none of the patients developed clinical heart failure or significant left ventricular dysfunction (LVEF <50%) at the end of the study.

Potential justification for the discrepant findings may be that prior studies may have had a patient population receiving higher doses of anthracyclines and higher prevalence of cardiovascular co-morbidities, which could in turn contribute to a favorable effect of beta-blockade.[5] Moreover, given that the reduction in LVEF in the placebo group in this study was less than originally anticipated, the power of the study to detect between group differences was reduced. Accordingly, the apparent lack of effect of nebivolol on LVEF may also be due to inadequate statistical power and does not rule out a beneficial effect of beta-blockade. Finally, author cannot rule out the possibility efficacy of an alternative beta-blocker or a higher dose of this studied beta-blocker.

Anthracyclines continue to serve as the backbone of chemotherapeutic regimes for breast cancer despite their cardiotoxic effects. Unfortunately, their replacement with other chemotherapeutic agents is therapeutically infeasible. Moreover, deprivation of anthracyclines may limit drug dosage, reduce tumor response, or unfavorably impact patient survival.

The present study had a few limitations, the main limitation was enrollment of a limited number of patients. Secondly, study report lacked follow-up data beyond the adjuvant therapy period.

Thirdly, author evaluated the protective effect of nebivolol only on early cardiotoxic effects of chemotherapy and not late-term effects of chemotherapy. Thus, future studies with a larger study population and larger study duration are needed.

CONCLUSION

Prevention of anthracycline-induced cardiotoxicity is an important clinical problem. The use of prophylactic nebivolol in breast cancer patients may protect LV function. Although not statistically significant in this study, nebivolol treatment may protect the myocardium against anthracycline-induced cardiotoxicity in breast cancer patients. Although nebivolol administration did play any significant role, large randomized clinical trials are warranted.

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