Original Article

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Subclinical Left Ventricular Dysfunction Prevention in Breast Cancer Patients after FAC Chemotherapy: A Carvedilol Trial

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Abstract

Objective: To assess the cardioprotective effects of Carvedilol in preventing subclinical left ventricular dysfunction (SLVD) in breast cancer patients after completing FAC chemotherapy.

Methods: This prospective study employed a quasi-experimental clinical trial conducted from September 2018 to May 2019. Breast cancer patients receiving FAC chemotherapy were divided into two groups: intervention (IG) and control (CG). The IG received Carvedilol 6.25 mg b.i.d., which was increased every three weeks until reaching a tolerated dose. The study evaluated changes in left ventricular global longitudinal strain (GLS) and the incidence of SLVD (GLS reduction ≥15% and GLS >-18%) 24 weeks after initiating the FAC regimen.

Result: Of the 81 women enrolled in the study, 31 were in the IG. No significant changes in GLS were observed during or after completing FAC chemotherapy in the IG, whereas the CG showed contradictory results. At the end of the follow-up period, the delta GLS reduction was lower in the IG (0.7; 95% CI -0.60, 3.60) compared to the CG (3.00; 95% CI -2.16, 4.19), with a p-value of 0.035. Similarly, the percentage reduction in GLS was 3.6% in the IG and 14.29% in the CG, resulting in a p-value of 0.05. The incidence rate of SLVD (GLS reduction ≥15% and GLS >-18%) was lower in the IG (41.9% and 25.8%) than in the CG (58% and 48%).

Conclusion: Carvedilol may have a cardioprotective effect in preventing the incidence of SLVD, as evaluated by GLS reduction and changes, in women with breast cancer after completing a full cycle of the FAC regimen.

Keywords: Breast cancer, carvedilol, chemotherapy, fluorouracil–adriamycin–cyclophosphamide, global longitudinal strain

Introduction

Breast cancer is the most prevalent form of cancer in women in Indonesia and worldwide.[1-3] According to GLOBOCAN statistics in 2018, breast cancer ranks as the fifth leading cause of death globally. It is estimated that approximately 2 million women have been diagnosed with breast cancer, resulting in 626,679 deaths.[4] In West Java alone, with a population of nearly 48 million residents, around 49.3% are women, and approximately 0.5% of these women have been diagnosed with breast cancer.[3] The systemic therapy for breast cancer includes chemotherapy and endocrine therapy. Anthracyclines-containing regimens, such as doxorubicin and epirubicin, are commonly used as adjuvant and neoadjuvant chemotherapy for breast cancer patients.[5-6] It is important to note that type 1 (irreversible) cardiotoxicity is primarily associated with anthracycline-containing chemotherapy regimens, particularly those with a dose-related effect, such as FAC.[5-7]

Cardiotoxicity due to anthracyclines can occur at a cumulative dose as low as 250 mg/m^2, and a decrease in left ventricular function can be observed at doses of 60-98 mg/m^2.[8-9]

The examination of myocardial deformation using echocardiography is an imaging technique that assesses subclinical dysfunction of the left ventricle, preferably evaluated using the Speckle Tracking Echocardiography (STE) technique. Global Longitudinal Strain (GLS) is a standard examination for SLVD, with predictive value for mortality and morbidity.[10,11] Carvedilol is chosen as a cardioprotective agent due to its antioxidant properties, which are the primary mechanism of cardiotoxicity caused by anthracyclines.[12] Despite supporting studies, Carvedilol has not been routinely used as a protective agent for anthracycline-induced cardiotoxicity in breast cancer patients. This study aims to evaluate the cardioprotective effect of Carvedilol in preventing the occurrence of SLVD in women with breast cancer undergoing FAC regimen chemotherapy.

Methods

This prospective study was a Quasi-Experimental clinical trial conducted at Dr. Hospital Hasan Sadikin Bandung from September 2018 to May 2019. The study included breast cancer patients who were scheduled to undergo six cycles of the FAC chemotherapy regimen, which was administered by oncologists. Prior to participation, all patients provided signed informed consent. The ethical committee board of Hasan Sadikin General Hospital granted approval for the cardio-oncology registry and this study, which were registered as no. LB.02.01/X.6.5/346/2018 and LB.04.01/A05/EC/222/VII/2018 respectively. Furthermore, data confidentiality was ensured throughout the research process.

The inclusion and exclusion criteria before and after a complete cycle of chemotherapy were as stated in a previous study conducted by Martha *et al*.[12] The control group consisted of patients selected from the cardio-oncology registry at Hasan Sadikin General Hospital. After obtaining the control group data, patients who met the inclusion criteria were consecutively enrolled in the study as the intervention group. Both groups received six cycles of an intravenous FAC regimen over a period of 18 weeks. This regimen included 5-fluorouracil at a dose of 600 mg/m2, Adriamycin at a dose of 60 mg/m2, and cyclophosphamide at a dose of 600 mg/m2. One week before the administration of the FAC regimen, the intervention group was given Carvedilol at an initial dose of 6.25 mg b.i.d. The dose was gradually increased every three weeks until reaching the target dose of 25 mg b.i.d., or until the patient reached a tolerated dose. The criteria for achieving the tolerated dose were as follows: systolic blood pressure above 90 mmHg, pulse rate around 60 bpm, and serum creatinine level below 2.5 mg/dl. In case of symptomatic hypotension or bradycardia, the dose was reduced to the previous dose or the tolerated dose.

The clinical symptoms and 2D trans-thoracic echocardiography (TTE), including GLS, were compared at various time points (baseline, 3, 12, and 24 weeks after the first cycle) during chemotherapy in both groups. The incidence of SLVD was evaluated using GLS, with a criteria of delta GLS reduction ≥15% and GLS >-18%. The changes in GLS were also assessed and compared between the intervention and control groups at the end of chemotherapy. GLS measurements were obtained using TTE with the speckle tracking echocardiography (STE) method (%), and were analyzed by highly trained cardiologists using the General Electric (GE) Vivid 7, S-6, and T-8 echocardiography machine. The frame rate for image acquisition was set at 50–80 frames per second.

Standard echocardiographic parameters and 2D grayscale images were acquired over five cardiac cycles and evaluated at the end of the systolic phase, just before the aortic valve closed. Data evaluation was conducted offline using ECHOPAC software version 113. The statistical analysis of the study involved descriptive statistics and normality tests for the variables, employing either the Shapiro-Wilks or Wilcoxon test. Normally distributed data will be presented as means and standard deviations, while non-normally distributed data will be presented as medians and interquartile ranges. Unpaired T-tests, Chi-Square tests, or exact Fisher analysis were used to compare the intervention and control groups. Changes in GLS over time during chemotherapy were analyzed using Friedman's analysis. Alternatively, the unpaired t-test or Mann-Whitney test was employed to compare delta GLS, GLS reduction percentage, and the frequency of SLVD after a complete cycle of FAC chemotherapy between the control and intervention groups. A p-value ≤0.05 indicates a statistically significant difference between the two groups. Power analysis was

performed using G*Power version 3.1.9.6, and the calculations yielded approximately 90.7% (>80%). This level of statistical test ability allows for the detection of actual differences, with the Mann-Whitney U test exhibiting good strength in detecting differences between two groups with a d-effect size of 0.7. A significance level of 0.05 was employed.

The power analysis results indicate a strong likelihood of rejecting the null hypothesis in the presence of significant differences. The primary outcomes consisted of the incidence rate of new left ventricular systolic dysfunction, defined as a 15% reduction in LV GLS and LV GLS >-18%, as well as changes in LV GLS during chemotherapy. The secondary outcomes included changes in LVEF during chemotherapy and the incidence of cardiotoxicity at 24 weeks.

Results

Eighty-one patients were included in the study and were divided into intervention and control groups consisting of 31 and 50 patients, respectively. Figure 1 shows the patient enrollment process. Baseline age and GLS values in the two groups were found to be not significantly different, as shown in Table 1. The mean age of the study subjects in the intervention group was 49.35±9.891 years, while in the control group it was 47.20±7.907 years (p=0.283). Prior to chemotherapy, the median GLS in the intervention group was 19.4%, whereas in the control group it was 20.40% (p=0.600).

The number of subjects with cardiovascular risk factors in the two groups was similar. The prevalence of obesity was 25.8% in the intervention group, whereas it was 34.0% in the control group (p=0.641). The hypertension rate in the intervention group was 45.2%, compared to 28.0% in the control group (p=0.114). Only 3.2% of patients in the intervention group had diabetes mellitus, whereas the prevalence was 12.0% in the

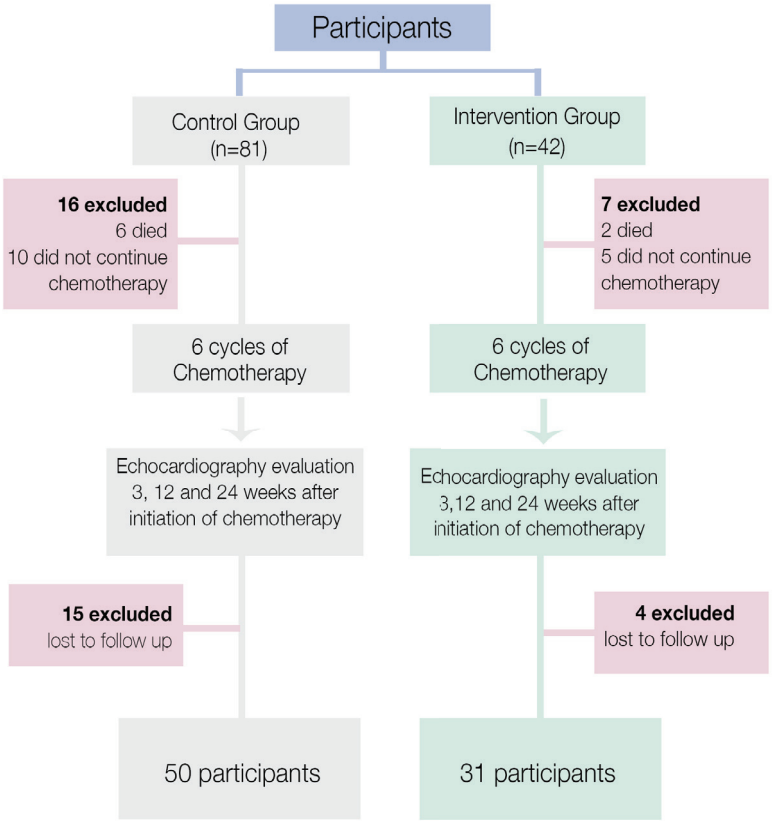

Fig. 1 Patient's Enrolment. The CG were Patients from Cardio-oncology Registry at Dr. Hasan Sadikin General Hospital. Following the CG enrollment, Consecutive Patients were Assigned as IG

Table 1 Study Characteristics

Baseline Characteristics	Participant n=81	Group		P-value
		Intervention n=31	Control n=50	
[a]Age (Year), mean ± SD	48.02±8.7	49.35±9.9	47.20±7.9	0.283[a]
[a]Body Mass Index, n (%)				
18.5–22.9 kg/m^2	19 (23.4%)	8 (25.8%)	11 (22,0%)	0.435[a]
23.0–24.9 kg/m^2	21 (25.9%)	7 (22.6%)	14(28.0%)	
25.0–29.9 kg/m^2	25 (30.9%)	8 (25.8%)	17(34%)	
>29.9 kg/m^2	16 (19.8%)	8 (25.8%)	8(16%)	
Risk Factors, n (%)				
Obesity	41 (50.7%)	16 (51,6%)	25 (50%)	0.888[b]
Hypertension	28(34.6%)	14 (45,2%)	14 (28,0%)	0.114[b]
Hypertensive Heart Disease	0(0.0%)	0(0.0%)	0(0.0%)	1.000[b]
Smoking	0(0.0%)	0 (0,0%)	0 (0,0%)	1.000[b]
Diabetes Mellitus	7 (8.6%)	1 (3,2%)	6 (12,0%)	0.242[c]
Dyslipidemia	6(7.4%)	3(9.7%)	3(6.0%)	0.670[c]
Family CHD History	4(4.9%)	2 (6.5%)	2 (4.0%)	0.635[c]
GLS (%)				
Median	-20.0	-19.4	-20.4	0.600[d]
Range (min-max)	-28.50–(-10.30)	-24,80–(-16.20)	-28,50–(-10.30)	
LVEF (%)				
Median	69.0	69.0	69.5	0.925[d]
Range (min-max)	48.0–81.0	55.0–80.0	48.0–81.0	

Analyzed by [a]T-test, [b]Chi-Square, [c]exact Fisher, [d] Mann Whitney

Table 2 Time-to-time GLS and LVEF Score Changes During Chemotherapy in the Intervention And Control Group

Variable	GLS Score (%)				P-value	LVEF (%)				p-value
	Pre	3 weeks	12 weeks	24 weeks		Pre	3 weeks	12 weeks	24 weeks	
Intervention group (n=31)										
Median	-19.4	-19.0	-18.8	-19.2	0.161[a]	69.0	68.0	66.0	64.0	0.018*
Range (min-max)	-24.8-(-16.2)	-24.9-(-15.4)	-22.5-(-14.9)	-24.9-(-4.2)		55.0-80.0	53.0-83.0	58.0-75.0	28.0-78.0	
Control group (n=50)					0.0001[a]*					0.0001*
Median	-20.40	-19.63	-18.80	-17.40		69.5	67.5	65.5	62.5	
Range (min-max)	-28.5-(-10.3)	-26.9-(-11.2)	-23.0-(-9.6)	-24.10-(-5.3)		48.0-81.0	49.0-79.0	50.0-82.0	25.0-76.0	

[a]Analyzed using Friedman test. * Statistically significant (p<0.05)

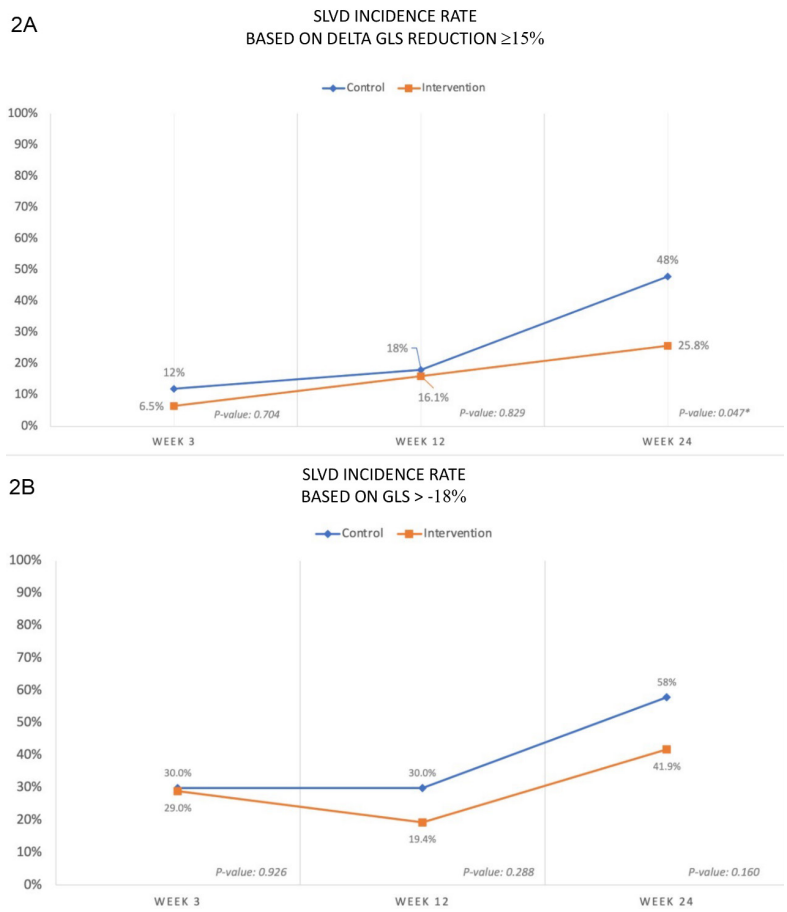

Fig. 2 Significant Different of Subclinical LV Dysfunction Incidence Rate; (2A) Based on GLS reduction of ≥15%, there were significantly a smaller number of SLVD in IG and based on GLS >-18% (2B) more patients with SLVD were detected in CG compared to IG

control group (p=0.242). The percentage of patients with a family history of CAD was 6.5% in the intervention group and 4.0% in the control group (p=0.635). Neither group had any subjects with smoking as a risk factor. Both groups were ethnically Indonesian, with the majority being Sundanese, followed by some Javanese and Melayu patients.

A comparison of changes in GLS scores during chemotherapy is presented in Table

Table 3 GLS Changes Before and After Chemotherapy in Intervention and Control Groups

Variable	Group		P-Value
	Intervention	Control	
Delta GLS score (%) Median Range (min-max)	0.70 -3.60-17.20	3.00 -4.30-12.60	0.035[a]
GLS reduction percentage (%) Median Range (min-max)	3.6 (2.9-17.5)	14.29 (10.7-20.8)	0.05[a]

Note: [a]Analysis using Mann Whitney

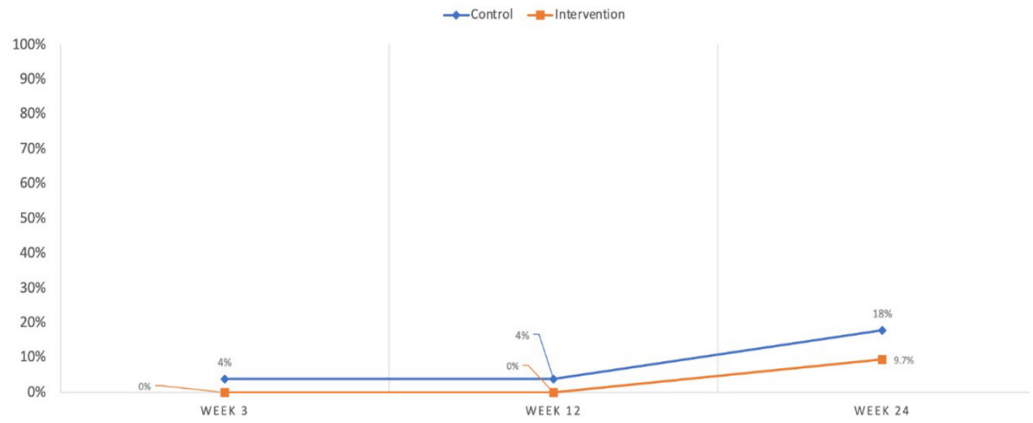

Fig. 3 Incidence of Cardiotoxicity. The IG Had Lower Incidence of Cardiotoxicity at Week 24 Compared to CG

2. There was no significant reduction in GLS observed during chemotherapy in the intervention group (IG). However, in the control group (CG), there was a significant decrease in GLS during chemotherapy. The values gradually declined from a median of -20.4% (-28.5-(-10.3) %) at baseline to -19.6%, -18.8%, and -17.4% (-24.1-(-5.3) %) at 3, 12, and the completion of chemotherapy, respectively. Both the IG and CG experienced a reduction in LVEF during chemotherapy, but the values remained within normal limits, and there was no significant difference between the two groups (Table 2). At the end of chemotherapy (Table 3), the median delta GLS showed a less significant reduction in the IG at 0.70% (95% CI–0.60, 3.60) compared to the CG at 3.00% (95% CI–2.16, 4.19) (p=0.035). Additionally, the percentage of GLS score reduction was lower in the IG (3.62%) compared to the CG (14.29%) (p=0.05), as shown in Table 3.

The incidence of patients with a reduction in GLS of ≥15% was significantly lower in the intervention group (IG) than in the control group (CG) (Figure 2a). At three and twelve weeks after initial chemotherapy, there was no significant difference in the percentage of patients with a delta GLS of ≥15% between the intervention and control groups. However, a significant difference was observed between baseline and 24 weeks' GLS; 25.8% of the IG and 48% of the CG experienced a reduction in GLS of ≥15%. Additionally, a smaller number of patients in the IG developed subclinical LV dysfunction 24 weeks after chemotherapy initiation. Figure 2b showed a significant increase in patients with subclinical LV dysfunction evaluated by GLS >-18%. A total of 41.9% of patients in the IG and more than half in the control group (58%) experienced SLVD at the end of chemotherapy. During chemotherapy, only 5 (12%) patients achieved the maximum dose of Carvedilol, 26 (62%) were on 12.5 mg bid, and 11 (26%) were on 6.25 mg bid.

Most did not achieve the maximum dose because their heart rate was around 60 bpm. At the end of chemotherapy, cardiotoxicity occurred in 3 patients of the IG (9.7%) and 9 patients of the CG (18.0%). There were no severe adverse effects, and no patient was excluded due to adverse effects. Several patients experienced cardiotoxicity at weeks 3, 12, and 24, as seen in Figure 3. The incidence of cardiotoxicity increased over time to a rate of 9.7% at 24 weeks.

Discussion

This study revealed that patients in the intervention group had a significantly lower incidence of subclinical left ventricular dysfunction. This was demonstrated by a reduced occurrence of GLS reduction ≥15%, a notable increase in the percentage of patients with GLS >-18%, and less delta GLS changes at 24 weeks after chemotherapy. These results indicate the potential efficacy of carvedilol 6.25 mg twice daily in preventing subclinical left ventricular dysfunction in breast cancer patients undergoing anthracycline chemotherapy. The control group had a higher rate of subclinical LV dysfunction and

cardiotoxicity compared to the intervention group. Additionally, the number of patients with delta GLS ≥15% and GLS > -18% increased during chemotherapy and reached a significant level 24 weeks after initiating the first cycle of chemotherapy in the control group. Previous studies have suggested cut-offs ranging from >10-15% for delta GLS score reduction to predict the occurrence of cardiotoxicity.[7-10]

This result is in line with the expert consensus and position paper, which suggests that a GLS ≥15% could be a predictive value for cardiotoxicity.[13]. These findings are consistent with previous studies indicating that Carvedilol can prevent a decline in left ventricular systolic function in breast cancer patients undergoing chemotherapy with anthracycline-containing regimens (11,14). The FAC regimen is currently one of the first-line options for managing breast cancer and carries a five-fold higher risk of cardiotoxicity compared to other regimens.[5,6] Carvedilol is a non-selective, third-generation beta-blocker that inhibits both beta one and two receptors. It also exhibits alpha-one insulating properties, resulting in peripheral vasodilation.[15,16] Moreover, Carvedilol has antioxidant effects, including inhibition of electron transport enzymes such as 5,5-dimethylprolin-1-oxidase and 2-methyl-nitrosopropane, as well as lipid peroxidase and neutrophil O2 release inhibitors. These effects help preserve the body's natural antioxidants, such as glutathione and vitamin E, and other antioxidant protective systems.[15] Consequently, Carvedilol is the preferred agent for releasing neutrophil O2, preserving the body's natural antioxidants (glutathione or vitamin E) and other antioxidant protective systems.[15]

It may have potential cardioprotective effects due to increased free radicals resulting from anthracycline, which is considered the primary mechanism of anthracycline-induced cardiotoxicity.[11] Most of the patients in this study were administered Carvedilol 12.5 mg b.i.d, which already demonstrated a significant reduction in GLS and LVEF compared to the control group. This suggests that the achieved tolerated dose may have a cardioprotective effect by preventing SLVD in the intervention group. Previous trials of carvedilol in heart failure patients typically reached 75% of the maximum dose with varying levels of tolerability. A study by Farahani MM *et al*. revealed that the maximum tolerated dose of carvedilol in the intervention group was 12.5 mg twice a day in non-metastatic HER2 breast cancer patients undergoing trastuzumab treatment. This dose was effective in preventing GLS decline and may also reduce systolic and diastolic function impairment based on echocardiographic findings. The study showed significant changes in the GLS variable in the control group ($p<0.0001$) but not in the carvedilol group ($p=0.080$).17 GLS evaluation is advantageous over LVEF assessment as it detects changes at an earlier stage. Therefore, GLS evaluation could be beneficial for preventing chemotherapy-induced cardiotoxicity.[9]

This study found that the intervention group's GLS did not decrease during chemotherapy over time, whereas the control group did experience a decrease. The mean delta GLS reduction was significantly greater in the control group (3%) compared to the intervention group (0.7%), $p=0.035$. In this study, the mean cumulative dose of anthracycline was 565.85±65 mg/m^2. A previous study conducted by Elitok *et al*.[18] in 2014 demonstrated that administering Carvedilol to breast cancer patients could prevent the reduction of strain imaging evaluated by Tissue Doppler Imaging (TDI) in the intervention group, particularly with small cumulative doses (≤240 mg/m^2). In 2016, Beheshti *et al*.[19] conducted a similar study comparing changes in systolic function in 70 breast cancer patients undergoing chemotherapy with an anthracycline.The baseline LVEF did not differ from LVEF after chemotherapy in both the Carvedilol and control groups. The TDI examination in the control group (placebo) revealed a decrease in strain and strain rate in the septal, lateral basal, inferior basal, and anterior basal segments (all p-value <0.001) compared to baseline. No strain changes were observed in the Carvedilol group.

In this study, GLS was calculated using the 2-D STE technique, which detects subclinical myocardial damage and is unaffected by the patient's position. A study by Avila *et al*.[20] and Beheshti *et al*. showed no significant changes in LVEF between the carvedilol group and the control group following chemotherapy with an anthracycline-containing regimen.[19] However, the use of carvedilol resulted in a significant reduction in troponin levels and diastolic dysfunction.[20] This study showed a 5% decrease in LVEF in the intervention group and a 7% decrease in the control group. Both groups experienced a decrease in LVEF, although it remained within the normal

limit, and there was no substantial difference in chemotherapy completion compared to baseline. In this study, the adriamycin cumulative dose exposure was 556.65±89 in the intervention group and 573±51 in the control group (p>0.4). Previous studies have shown that the benefits of carvedilol in preventing cardiotoxicity are more significant in studies with higher cumulative doses or more accompanying risk factors. [11, 14]

In the study by Jhorawat *et al.*,[21] the prophylactic use of carvedilol protected the systolic functions of the left ventricle in patients receiving anthracycline. Similarly, in a study by Huang *et al.*,[22] the prophylactic use of carvedilol had no impact on the early asymptomatic decrease in LVEF but appeared to reduce the frequency of clinically overt cardiotoxicity and prevent ventricular remodeling.

In this study, nearly half of the population had hypertension, with 45% in the intervention group and 28% in the control group. The percentage of breast cancer patients with diabetes mellitus risk factors was 3.2% in the intervention group and 12% in the control group. Subjects with a family history of coronary heart disease accounted for 4% in the intervention group and 6.5% in the control group. Carvedilol was administered as a cardioprotective agent in this study, regardless of cardiovascular disease risk. There were no significant differences in CVD risk factors between the intervention group and the control group.

After the administration of carvedilol, there was a lower incidence of SLVD with a similar CVD risk profile between the groups. This suggests that a cardio-protective agent may be necessary for every patient who undergoes chemotherapy with an anthracycline regimen, regardless of their risk score. This result differs from the recently published SUCCOUR trial that was just published.[23] The trial revealed that there was no difference between GLS-guided and LVEF-guided evaluation at 1 and 3 years after cardioprotective administration in breast cancer patients given an anthracycline regimen. However, the GLS cut-off used in the study (<12% reduction) for cardio-protection was lower than the SLVD cut-off used in most societies, including this study. Additionally, the cardiac function may have recovered to baseline after more than a year of follow-up in the SUCCOUR trial, compared to the 24 weeks in this study.

This study had several limitations, including a small sample size, the absence of randomization, and being conducted at a single center. Furthermore, several patients were excluded due to discontinuation of chemotherapy or being lost to follow-up. Additionally, the patient demographic data was not explained in detail, which could have provided more specificity to the research findings, particularly regarding the variability in the study's outcome. The intervention group did not receive a uniform dose of carvedilol due to individual variability in medication tolerance, and data on the number of doses administered were not available. Although a protective effect of carvedilol administration against subclinical LV dysfunction during chemotherapy was observed, the long-term impact remains unpredictable due to the follow-up period. Advanced research could be conducted to assess the effect of the dosage given to individuals.

In conclusion, this study demonstrates that carvedilol administration during chemotherapy may have a cardioprotective effect in preventing the incidence of subclinical LV dysfunction and GLS changes. The intervention group exhibited a significantly lower reduction in delta GLS and fewer new cardiotoxicity events compared to the control group, 24 weeks after initiating FAC regimens. Thus, carvedilol administration with GLS evaluation during chemotherapy may be necessary in preventing subclinical LV dysfunction.

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