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Study On Cardioprotective Effect Of Enalapril In Patients With Breast Cancer On Doxorubicin Chemotherapy.

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ABSTRACT

Cancer patients receiving chemotherapy have an increased risk of cardiovascular complications. This limits the widespread use of lifesaving therapies, often necessitating alternate lower efficacy regimens, or precluding chemotherapy entirely.To determine the Cardioprotective effect of Angiotensin Converting Enzyme Inhibitor, Enalapril on Doxorubicin Induced Cardiotoxicity in breast cancer patients. The present study was carried out in the inpatients of Department Medical Oncology, Government Medical College, Omandurar, Government Estate, Chennai, Tamil Nadu, India. In the year 2021-2022. 60 female Breast cancer patients undergoing doxorubicin-based chemotherapy were included for the study. Patients with Left ventricular ejection fraction (LVEF) >50% were taken in to the study. Patients were allocated into two groups 30 in each. All the 60 patients treated with FAC Chemotherapy regimen (5-Fluorouracil 500mg/m^2, Doxorubicin 50mg/m^2, Cyclophosphamide 500mg/m^2) once in 3 weeks for 6 cycles. Test group received Tab. Enalapril 5 mg / once daily at bed time started after the 6th cycle of chemotherapy schedule and slowly titrated up to 10 mg once daily and continued for 6 months. Cardiac assessment was done by measuring Troponin I level at baseline,24 hrs after first dose of chemotherapy and at the end of the chemotherapyschedule (6th cycle). Cardiac function was also evaluated by serial measurement of Left ventricular ejection fraction (LVEF) and Fractional Shortening (FS) by echocardiogram at baseline, 3rd cycle, 6th cycle, 6th month and 9th month of the study.The mean LVEF at 9th month in Enalapril treated and control groups were 61.90 ±2.34 & 54.57 ± 5.86 respectively. At the end of 9th month the mean LVEF was maintained in Enalapril treated group than in control group from baseline line value which is statistically significant ($p < 0.001$).The mean FS at 9th month in Enalapril treated and control groups were 34.07.±2.21 & 28.97 ± 3.47 respectively. When FS is compared between these two groups Enalapril treated group showed significant improvement in FS than in control group ($P < 0.001$). Thus, we conclude that the prognostic role of TnI as an early marker of cardiotoxicity to find out the high-risk patients and Prophylactic Enalapril administration have been showed to preserve the left ventricular function & improved cardiac outcome. Thus, early treatment with Enalapril seems to prevent the development of late cardiotoxicity in patients undergone doxorubicin-based chemotherapy.

Keywords: Doxorubicin, Cardiotoxicity, Troponin I, Enalapril, Left ventricular ejection fraction, Fractional Shortening.

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INTRODUCTION

Breast cancer is the second most common cause of cancer in females in India , contributing to major cause of morbidity & mortality. Breast cancer can be treated by multimodality approaches like surgery, radiotherapy, chemotherapy & hormonal therapy. The different types of chemotherapy for carcinoma breast vary according to the stage whether prior surgery has been done or not. It may be adjuvant, neoadjuvant and palliative chemotherapy [1]. The drugs commonly used to treat breast cancer include cyclophosphamide, methotrexate, doxorubicin, 5 flurouracil, pacletaxel, docetaxel, carboplatin, trastuzumumab. Most chemotherapeutic agents are reported to cause severe adverse reactions and some of which lead to organ damage but these agents cannot be avoided in the treatment of cancer though side effects cannot be abolished [2]. Major limitations to the clinical efficacy of chemotherapy have been toxicity to the normal tissues of the body and the development of drug resistance. In the past decade, better understandings of molecular biology and pathways/targets have led to target specific therapy. This has resulted ina paradigm shift in the management of many cancers [3, 4]. Doxorubicin has been used as an efficacious antitumor antibiotic for many solid and haemopoietic malignancies. Doxorubicin (DOX), is an anthracycline antitumor agent, plays vital role in the management of breast cancer. However, dose-dependent increased risk of heart failure and dilated cardiomyopathy has restricted its clinical use [5].

Cardiotoxicity may compromise the efficacy of chemotherapy and affecting the quality of life & survival of the patients undergoing cancer chemotherapy. Risk factors for doxorubicin induced cardiotoxicity are cumulative dose above 550 mg/m^2, more than 60yrs of age, dosing schedule, mediastinal radiotherapy, previouscardiac disease, hypertension, female sex and combined chemotherapy with known cardiotoxic agents like cyclophosphamide, trastuzumab etc. [6]. Multiple mechanisms may contribute to the development of chemotherapy induced cardiotoxicity. However free radicals formation and oxidative stress to the heart appears to be an important cause of apoptosis and cardiomyocyte damage [7] Doxorubicin induced Cardiotoxicity may develop during and delayed years after the treatment schedule with doxorubicin. Acute cardiotoxicity may manifest as tachyarrhythmia, pericarditis, myocarditis and even heart failure, can develop within weeks to months following treatment. Chronic cardiotoxicity may manifest as severe left ventricular dysfunction, dilated cardiomyopathy and chronic heart failure months to years after treatment which is not response to conventionaltreatment and become irreversible. Hence patients undergoing anthracycline treatment need serial measurements of LVEF, Fractional shortening by echocardiography [8] prior to, during and after treatment to assess the left ventricular function andcardiotoxicity. Cardiac Troponin I is one of the marker for early myocardial insult has been used to monitor doxorubicin induced cardiotoxicity. An elevation in plasma troponin I level following cancer chemotherapy may be an important tool to predict the poor cardiological outcome in patients with breast cancer. Adjustment in doxorubicin dose is the main approach to prevent the development of cardiac dysfunction. A certain number of patients still develop severe cardiac dysfunction at doses less than 550 mg/m^2 [9]. Iron chelating agent dexrazoxane and analogues of anthracycline like epirubicin, idarubicin has been used to protect patients with evidence of early cardiotoxicity at medium doses of doxorubicin. Few studies found thatdexrazoxane eventhough reduce the cardiotoxicity, may also reduce the antitumor efficacy of anthracyclines ·Angiotensin Converting Enzyme Inhibitors (ACEI) like captopril,enalapril have been traditionally used to delay the deterioration of left ventricular function in many different clinical settings including doxorubicin induced cardiomyopathy [10]. Hence, ACE inhibitors may be useful in preventing doxorubicin induced cardiotoxicity by minimizing oxidative stress and limiting left ventricular remodeling. Many experimental animal model data's found & suggest that the Renin-Angiotensin System (RAS) plays a vital role in the formation and progression of doxorubicin-induced cardiotoxicity [11]. Hence ACEIs like enalapril has been used to prevent & treat the anthracycline-induced cardiotoxicity. So, patients, who are more prone to develop cardiotoxicity in future after exposure to doxorubicin, could have been prevented by prophylactic administration of ACEIs.

MATERIALS AND METHODS

The study was undertaken in breast cancer patients who undergone doxorubicin based chemotherapy, to find out the cardio protective effect ofenalapril on doxorubicin induced cardiotoxicity by serial monitoring of Left Ventricular Ejection Fraction, Fractional Shortening by echocardiogram and serum Troponin I level.60 adult female breast cancer patients on doxorubicin based chemotherapy, divided into two groups, each group comprising 30 patients after satisfying the inclusion and exclusion criteria.

Inclusion Criteria

- Breast cancer patients of age between 20 – 65 yrs. irrespective of tumour size, and stage of the disease undergoing doxorubicin based chemotherapeutic regimen.
- Gender – Female.
- Subjects willing for the study.

Exclusion Criteria

- Age more than 65 years.
- Male breast cancer patients.
- Pregnant & lactating women
- Patient with H/o hypersensitivity to Enalapril.
- Known case of bilateral renal artery stenosis
- Left Ventricular Ejection Fraction < 50 % by echocardiogram
- Ongoing therapy with ACE inhibitors & angiotensin receptorblockers
- Patients with hypertensive, ischemic and valvular heart disease and uncontrolled hypertension.
- Patients with systolic blood pressure less than 90 mmHg
- Patients with hepatic dysfunction - As evidenced by symptomatic liver disease or abnormality in liver function tests.
- Patient with Chronic kidney disease (Creatinine Clearance ≤ 60 ml/min.)
- Patient with elevated serum potassium level ≥ 5meq/ l.
- Previous participation in a similar study.

Methodology

60 Breast cancer patients undergoing doxorubicin contain chemotherapy either post operatively as adjuvant therapy or preoperatively as neoadjuvant therapy, admitted in the department of medical oncology were included for the study. The investigations like complete haemogram, blood sugar, blood urea, serum Creatinine, serum Bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), Alkaline Phosphatase (ALP), Serum Proteins, Electrocardiogram (ECG), serum electrolytes were done. A baseline assessment of plasma troponin I (TnI) level was measured by ELISA method. Left ventricular ejection fraction (LVEF) & Fractional Shortening (FS) were measured by echocardiogram. Patients with LVEF >50% were taken in to the study. Patients were allocated into two groups. Each group comprising 30 patients.

Group I (Control - Without Enalapril)

- Inj. Doxorubicin 50mg/m^2 intravenously once in 21 days for 6cycles
- Inj. Cyclophosphamide 500mg/m^2 intravenously once in 21days for 6cycles.
- Inj.5-Fluorouracil 500mg/m^2 intravenously once in 21 days for 6cycles.

Group II (Enalapril)

- Inj. Doxorubicin 50mg/m^2 intravenously once in 21 days for 6 cycles,
- Inj. Cyclophosphamide 500mg/m^2 intravenously once in 21 days for 6 cycles
- Inj. 5-Fluorouracil 500mg/m^2 intravenously once in 21 days for 6 cycles.
- Tab. Enalapril 5 mg / once daily at bed time started after the 6^{th} cycle of chemotherapy schedule and slowly titrated upto 10 mg once daily and continued for 6 months.

Cardiac assessment was done by measuring Troponin I level at baseline, 24 hrs after first dose of chemotherapy and at the end of the chemotherapy schedule (6th cycle). Cardiac function was also evaluated by serial measurement of LVEF and FS by echocardiogram at baseline, 3^{rd} cycle,6^{th} cycle, 6^{th} month and 9^{th} month of the study.

Visit 1 [Baseline]

Patients were reviewed after one week of screening and they underwent the Following:

- Obtained informed written consent.
- Recorded height, weight and calculated BSA.
- Performed physical examination.
- Measured vital signs - Pulse rate, Blood pressure as per method described above.
- Performed a detailed systemic examination
- Obtained blood samples for laboratory tests [Blood sugar, blood urea, serum Creatinine, Serum electrolytes, Liver function tests, Hb%, Troponin I] and urine sample for albumin, Sugar and deposits.
- Evaluated the left ventricular ejection & fractional shortening by ECHO.
- Dispensed the study drug to the test group for every 21 days for a period of 6 months after end of doxorubicin schedule and instructed the patient to take enalapril and explained about the dose and time ofintake.
- Informed about the possible adverse reactions to drug therapy and were given the investigator's details for reporting.
- The date of treatment initiation was documented and the patients were advised not to take any medication without the knowledge of the invigilator.
- The subjects were asked to bring the utilized drug strips during their next visit to ensure their compliance.

Subsequent Visits

During subsequent visits,

- Patients were reviewed once in 21 days.
- The patients were enquired about the wellbeing.
- Used strips of the study medication dispensed during previous visit were collected and checked.
- Recorded blood pressure and pulse and systemic examination wasperformed.
- The patients were assessed for any adverse events.
- The study drug was given for the 3 weeks.
- After the end of 6th month, all the clinical tests performed during theinitial visit were repeated.

End Of The Study

At the end of 9th month all investigations were done during the initial recruitment were repeated, and ECHO was also performed to assess the left ventricular ejection fraction and fractional shortening. The treatment efficacy was monitored with echocardiography assessment. The tolerability of the drugs was monitored by assessing adherence to treatment, serum potassium levels and any adverse reactions noticed either by the patients or by the invigilator.

Statistical Analysis

The data were analyzed with SPSS statistical software package (Version 16.0 SPSS Inc., Chicago, USA). The results were analyzed using Student's "independent" t test for between the groups and Student's "paired" t test for within the group. $P < 0.05$ will be considered as statistically significant.

RESULTS

Totally 60 female breast cancer patients, 30 in each group were recruited for the study. All the 60 patients were followed up to the end ofthe study. There was no drop out from the study.

Among the 60 female patients who completed the study, the age related distribution were as follows, In the enalapril group 16.6% patients were in the age group 30-39 years, 20% patients were in the age group 40-49 years, 30% patients were in the age group 50-59 years, 33.3% patients were in the

age group > 60 years.

In control group (without Enalapril) 16.6% patients each were in the age group 30-39 and 40-49 years, 33.3% patients each were in the age group50-59 and > 60years. The majority of patients belonged to > 60 years of age(33.3%) in both the groups.

The mean age of the patients in the control group was 53.33 ± 9.58 years.

The mean age of the patients in enalapril group was 52.13 ± 9.80 years.

Table 1: Age distribution of the participants

Age (years)	Number of patients	
	Control group	*Enalapril group*
30 – 39	5	5
40 – 49	5	6
50 – 59	10	9
>60	10	10
Total	**30**	**30**

Baseline Parameter

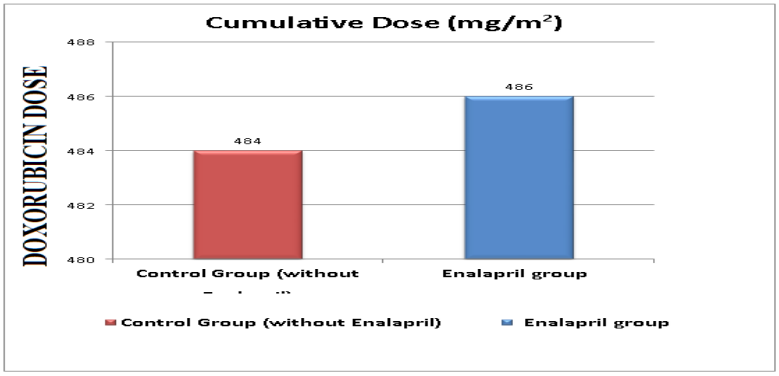
The following table shows the baseline characteristics of the patients in theboth group included in the study.

Table 2: Baseline characteristics of the participants

PARAMETER	Mean ± SD	
	Control Group (Without Enalapril)	Enalapril Group
Age (years)	53.33 ± 9.58	52.13 ± 9.8
BSA (m^2)	1.61 ± 0.12	1.62 ± 0.09
Number of chemotherapy cycles	6	6
Cumulative doses of doxorubicin	484 ± 36.93	486± 28.35
Baseline Heart rate	87.56 ± 10.32	89.02 ± 11.63
Baseline Systolic BP (mm Hg)	124.14 ± 13.52	128.06± 11.17
Baseline Diastolic BP (mm Hg)	81.23 ± 7.92	80.42 ± 9.07
Baseline Troponin I (ng/ml)	0.29 ± 0.14	0.25 ± 0.13
Baseline LVEF (%)	61.63 ± 2.98	61.45± 2.82
Baseline Fractional Shortening (%)	33.73 ± 2.22	34.03 ± 2.27

Cumulative Doxorubicin Dose

Figure 1: Mean cumulative doxorubicin dose



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The mean cumulative doxorubicin dose of the study subjects at the end of the chemotherapeutic schedule (6th cycle) in Enalapril group and control group were 486 ± 28.35 and 484 ±36.93 respectively which is statistically not significant.

Troponin I

Troponin I was used to categorize the high risk group as an early marker of myocardial injury. Plasma troponin I was measured using ELISA technique. After standardization the cut off value was determined as 1 ng/ml. The value > 1ng /ml was considered as early myocardial injury.

Average Troponin I value at baseline in Enalapril & control group was 0.25± 0.13 & 0.29± 0.14 ng/ml respectively. Within 24 Hrs of Doxorubicin infusion Troponin I level were elevated to 0.67± 0.60 & 0.63± 0.59 ng/ml in both the groups.

At the end of the chemotherapy schedule mean Troponin I value were 0.64±0.55 & 0.77±0.73 in both the groups respectively. 23.3% of patients in both the groups showed persistent elevation of Troponin I level and were more prone for cardiotoxicity and those subjects were considered as High risk groups.

Table 3: Patients with Persistent Troponin I Elevation

Timing of Troponin I	No of patients with persistent Troponin I Elevation	
	Control group	Enalapril group
24 hrs after doxorubicin	9 (30%)	8 (26.7%)
End of CT schedule	7 (23.3%)	7 (23.3%)

Table 4:Plasma Troponin I values in both the groups

Timing of Tn I tested	Troponin I value (ng/ml) (mean ±SD)				
	Control Group	Enalapril Group	T value	df	P value
Baseline	0.29± 0.14	0.25± 0.13	-0.960	58	0.341
24hrs after first dose	0.63± 0.59	0.67± 0.60	0.257	58	0.798
6th cycle	0.77±0.73	0.64±0.55	-0.724	58	0.472

*Significant if $P < 0.05$

Ejection Fraction

Ejection Fraction is an important parameter to evaluate left ventricular function in doxorubicin induced cardiotoxicity. Hence Left ventricular function was monitored by serial measurement of Ejection Fraction with the help of Echocardiogram. The mean LVEF between groups were compared at baseline, 3rd, 6th cycle, 6th and 9th month of the study.

The mean LVEF at baseline, 3rd cycle and 6th cycle in both the groups were 61.47 ± 2.82 & 61.63 ± 3.02; 58.8± 3.16 & 58.87±3.50; 56.63 ± 4.10 & 56.83 ± 3.76 respectively. Comparison of LVEF between these groups were statistically not significant on "independent" t test. But within their respective groups they were statistically significant on students "paired" t test. The mean LVEF at 6th month in Enalapril treated group and control group were 60.20 ± 2.87 and 55.93 ± 4.33 respectively. Comparison of LVEF between these two groups showed that Enalapril treated group showed statistically significant improvement in LVEF than in control group($P < 0.05$).

The mean LVEF at 9th month in Enalapril treated group and control group were 61.90 ±2.34 & 54.57 ± 5.86 respectively. Comparison of LVEF between these two groups showed that Enalapril treated group showed statistically significant improvement in LVEF than in control group ($P < 0.05$).

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Table 5: Changes in Left ventricular ejection fraction

Timing of ECHO	LVEF (%) MEAN ± SD						
	Control Group		Enalapril Group		T value	df	p value
Baseline	61.63	± 3.02	61.47	± 2.82	-0.221	58	0.619
3rd Cycle of CT	58.87	± 3.50	58.80	± 3.16	-0.077	58	0.819
6th Cycle of CT	56.83	± 3.76	56.63	± 4.10	-0.197	58	0.969
6th Month	55.93	± 4.33	60.20	± 2.87	4.493	58	0.023*
9th Month	54.57	± 5.86	61.90	±2.34	6.362	58	0.001*

*Significant P <0.001

Fractional shortening is another important parameter to evaluate left ventricular function in doxorubicin induced cardiotoxicity. Hence in this study, left ventricular function was monitored by serial measurement of Fractional Shortening with the help of M mode Echocardiogram. The mean FS between groups were compared at baseline, 3rd ,6th cycle, 6th and 9th month of the study. The mean FS at baseline, 3rd cycle and 6th cycle in both the groups were 34.03 ± 2.31 & 33.73± 2.56 ; 32.23 ± 2.10 & 31.90 ± 2.31; 30.77 ± 2.90 &30.63 ± 2.51 respectively. When a change in FS was compared between these groups, they were not significant statistically on "independent" student's t test. But within their respective groups they were statistically significant on student's "paired" t test. The mean FS at 6th month in Enalapril treated group and control group were 32.87 ± 2.53 and 29.60 ±2.55 respectively. On comparing FS between these two groups Enalapril treated group showed significant improvement in FS than in control group (P <0.001).The mean FS at the end of study (9th month), in Enalapril treated group and control group were 34.07 ±2.21 & 28.97 ± 3.47 respectively. When FS is compared between these two groups Enalapril treated group showed significant improvement in FS than in control group (P <0.001).

Table 6: Changes in the Fractional Shortening

Timing of ECHO	FS (%) MEAN ± SD				
	Control Group	Enalapril Group	t value	df	P value
Baseline	33.73 ± 2.26	34.03 ± 2.31	0.508	58	0.613
3rd Cycle of CT	31.90 ± 2.31	32.23 ± 2.10	0.585	58	0.561
6th Cycle of CT	30.63 ± 2.51	30.77± 2.90	0.199	58	0.843
6th Month	29.60 ± 2.55	32.87 ± 2.53	4.978	58	0.001*
9th Month	28.97 ± 3.47	34.07 ±2.21	6.776	58	0.001*

*Significant P <0.001

Percentage Of Reduction LVEF & FS Over The Study Period

At the end of the chemotherapy schedule (6th cycle), LVEF fell by 7.87% (56.63 ± 4.1) and 7.8% (56.83 ± 3.76)in both the groups from the baseline LVEF (61.47 ± 2.82 & 61.63 ± 3.02) respectively . Afterintervention with enalapril, at 6th month the average LVEF was reduced by 2.06% (60.20± 2.87) and at the end of the study it was above the baseline (61.9±2.34). In control group, at 6th month the average LVEF was reduced by 9.2% (55.93 ± 4.33) and at the end of the study it had fell to 11.4% (54.57 ± 5.86) from the baseline value.

At the end of the chemotherapy schedule (6th cycle), FS fell by 9.4 % (30.77±2.9) and 9.2% (30.63 ± 2.51) in both the groups from the baseline FS (34.03±2.31 & 33.73±2.26) respectively. After intervention with enalapril, at 6th month the average FS was reduced by 3.3% (32.87 ± 2.53) and at the end of the study it had reached above (34.07 ±2.21) the baseline value. In control group, at 6th month the average FS was reduced by 12.2% (29.60 ± 2.55) and at the end of the study it had fell to 14.1 % (28.97 ± 3.47)from the baseline value.

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Table 7: Percentage of Reduction LVEF over the study period

EjectionFraction	Control group		Enalapril group	
	Mean LVEF	%of reduction	Mean LVEF	%of reduction
Baseline	61.63± 3.0	0 %	61.47± 2.8	0 %
3rd cycle	58.87±3.5	↓4.5%	58.8 ± 3.16	↓4.3%
6th cycle	56.83± 3.7	↓7.8%	56.63 ± 4.1	↓7.8 %
6th month	55.93 ± 4.33	↓9.2%	60.20± 2.87	↓2%(↑5.9%)
9th month	54.57± 5.86	↓11.4%	61.90±2.34	0% (↑8.5%)

Table 8: Percentage of reduction FS over the study period

EjectionFraction	Control group		Enalapril group	
	Mean FS	%of reduction	Mean FS	%of reduction
Baseline	33.73±2.26	0 %	34.03±2.31	0 %
3rd cycle	31.9±2.31	↓5.4%	32.23±2.1	↓5.2%
6th cycle	30.63 ± 2.5	↓9.2%	30.77±2.9	↓9.4 %
6th month	29.6 ± 2.55	↓12.2%	32.87 ± 2.53	↓3.3%(↑6.3%)
9th month	28.97 ± 3.47	↓14.1%	34.07 ±2.21	0% (↑9.6%)

Subclinical Toxicity

Tough clinical manifestations of doxorubicin induced cardiotoxicity manifest when its cumulative dose exceeds > 450 mg/m^2, sub clinical,asymptomatic cardiotoxicity increases by adding each dose of doxorubicin. Sub clinical toxicity defined as more than 10% reduction of LVEF and fractional shortening from its baseline value during serial echocardiogram evaluation.
In this study

Table 9: No. of patients with LVEF < 50% & FS < 25%

Timing ofECHO	No. of patients with LVEF < 50% & FS < 25%			
	Control group		Enalapril group	
End of CT	3	(10%)	2	(6.7 %)
End of study	6	(20%)	0	(0%)

Table 10 No. of patients with > 10 % reduction in LVEF & FS

Timing of ECHO	No. of patients with > 10 % reduction in LVEF & FS			
	Control group		Enalapril group	
End of CT	7	(23.3%)	7	(23.3%)
End of study	11	(36.7%)	1	(3.3%)

Table 11: Cardiac events during entire study period

EVENTS	Total	ControlGroup	EnalaprilGroup
ECG changes (Non specific)	11	8	3
Arrhythmia requiring treatment	3	3	0
Heart failure treated	2	2	0
Hypotension requiredEnalapril dose reduction / treatment	3	2	1
Hyperkalemia	Nil	Nil	Nil
Abnormal RFT	Nil	Nil	Nil
Abnormal LFT	Nil	Nil	Nil

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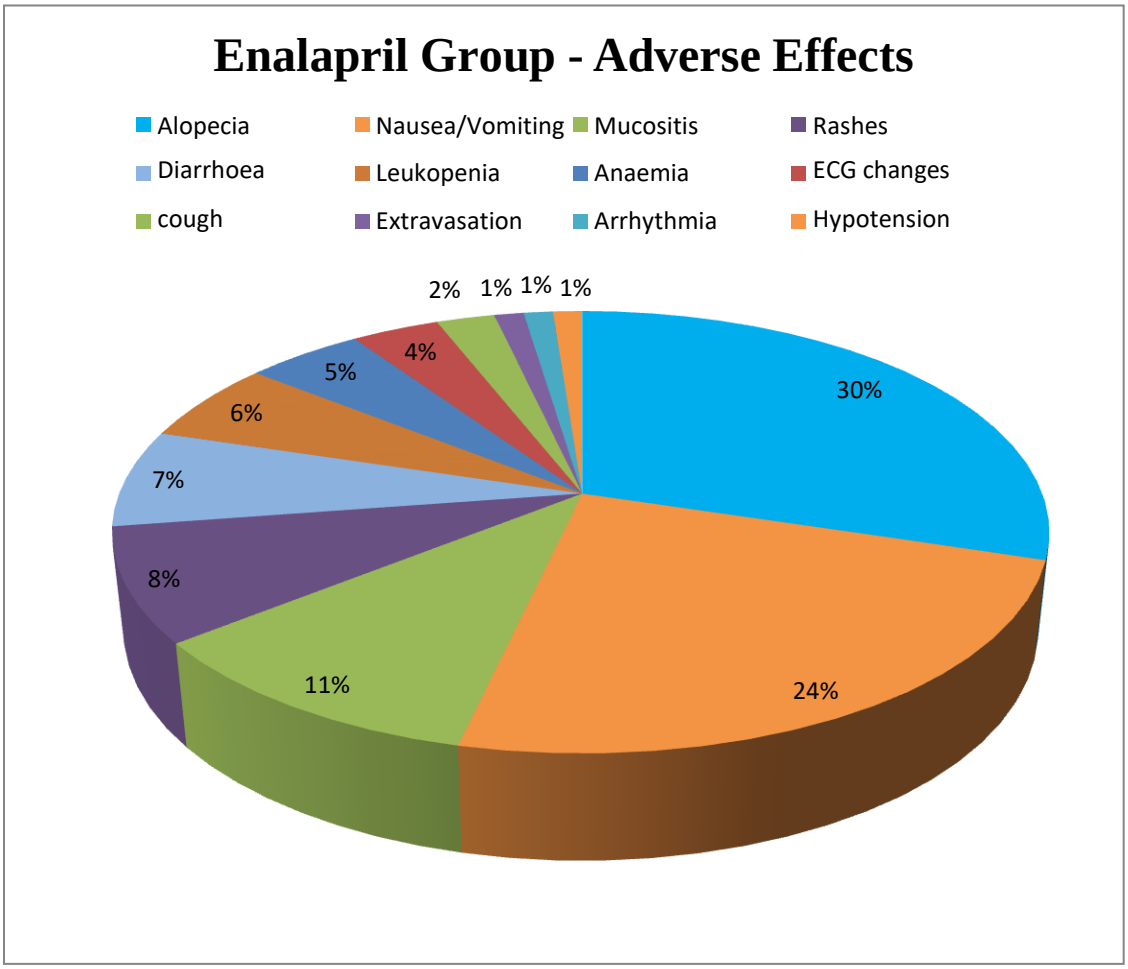
Table 12: Cardiac events in patients with persistent Troponin I elevation

Cardiac events		Control Group	Enalaprilgroup
No of patients		7 (23.3%)	7 (23.3%)
Patients with H/O Mediastinal irradiation		4(13.3%)	3(10%)
LVEF <50% & FS <25%	End of CT	3 (42.8%)	2 (28.5 %)
	End of study	5 (71.4%)	0 (0%)
> 10 % reduction in LVEF & FS		7 (100%)	1 (14.3%)
ECG changes (Nonspecific)		5 (71.4%)	2 (28.5 %)
Arrhythmia requiring treatment		3 (42.8%)	0 (0%)
Heart failure treated		2 (28.6%)	0 (0%)
Hypotension required treatment		2 (28.6 %)	1 (14.3%)

Graph 2: Adverse Effects



The following adverse effects noted in enalapril treated group

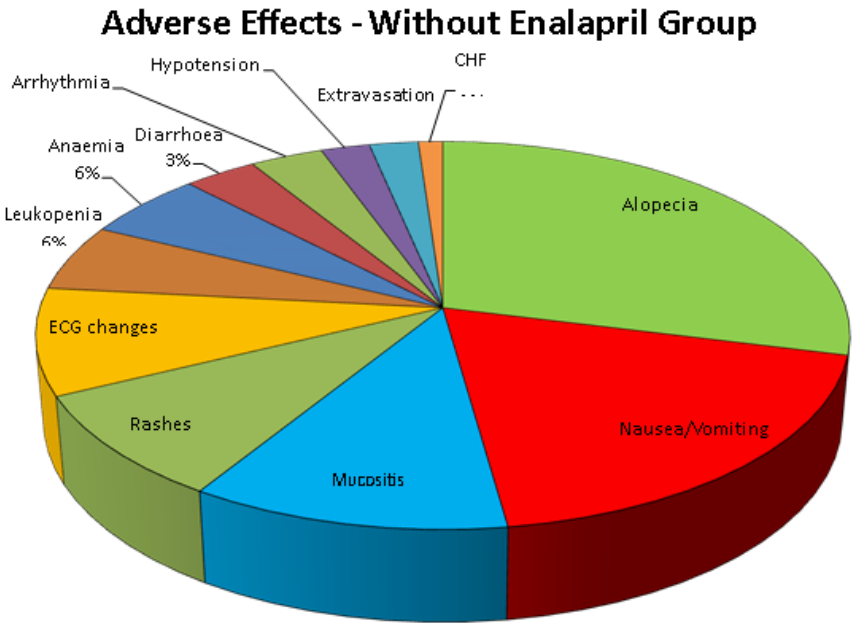
Alopecia (30%), Nausea & Vomiting (24%), Mucosal ulcer (11%),Skin Rashes (8%), Diarrheoa (7%), Leucopenia (6%), Anaemia (5%), ECG changes (4%), Cough (2%), Extravasations, Arrhythmia and Hypotension each 1%. These are shown in pie diagram.

The following adverse effects noted in Control Group

Alopecia (29%), Nausea & Vomiting (19%), Mucosal ulcer (11%), Skin Rashes (9%), Diarrhea (3%), Leucopenia (6%), Anaemia (5%), ECG changes (9%), Extravasations (2%), Arrhythmia (3%),

Hypotension (2%), Congestive Heart Failure (1%.). These are shown in pie diagram.

Graph 3: Adverse effects noted in control group



DISCUSSION

Breast cancer is the most common cancer among females in developed countries like USA and UK. It is the second most common cancer of females after cervical cancer in developing countries like India. From the last decade onwards the incidence of breast cancer in urban populations increased dramatically. [12]. It is mainly due to western life style, changes in the food habits, sedentary life style, obesity, smoking habit and alcohol intake. Surgery is the primary modality of treatment in early breast cancers. For advanced stages adjuvant therapies like radiotherapy, chemotherapy and hormonal therapy are commonly used to prevent the metastasis and to prolong the disease-free interval. Among chemotherapy anthracyclines-based combination chemotherapy is commonly used to treat breast cancer because it is highly efficacious in reducing the tumor burden [13]. Doxorubicin is an antitumor antibiotic with wide spectrum of activity over the many neoplastic disorders including carcinoma of breast. Since 1970 its introduction as a cancer chemotherapeutic agent, it is one of the main components of various chemotherapeutic regimen in most of the solid cancers, hematological neoplasm's, lymphomas, sarcomas and carcinomas including breast cancer [14]. Drug induced cardiotoxicity is a rapidly evolving condition because of number of cancer survivors has been increased. Doxorubicin induced cardiotoxicity is mainly due to dose dependent cumulative toxicity via free radical injury and oxidative stress to the cardiac myocytes. Doxorubicin can cause acute reversible cardiotoxicity and delayed irreversible cardiomyopathy years after doxorubicin therapy. Prevalence of doxorubicin induced cardiotoxicity is not known [15].

Worldwide, the overall incidence of this cardiotoxicity is underestimated because of its delayed presentation. The onset of asymptomatic & subclinical cardiotoxicity not only negatively impacts the cardiac outcome of breast cancer patients and also limits their therapeutic opportunities seriously [16].

Early prediction of cardiotoxicity by identifying high risk groups by measurement of cardiac biomarker like Troponin I soon after doxorubicin therapy, patients with elevated Troponin I are the greatest risk of development of cardiotoxicity in future eventhough asymptomatic at early stages. So it is mandatory to evaluate cardiac function of the patients undergoing doxorubicin therapy by means of serial measurement of left ventricular ejection fraction and fractional shortening by echocardiogram before, during and after doxorubicin therapy periodically and early intervention will prevent or delay the development of chronic cardiotoxicity [17]. By prophylactic administration of Enalapril, an Angiotensin Converting Enzyme Inhibitor in high risk groups minimize the cardiovascular morbidity and mortality in different clinical settings including doxorubicin induced cardiotoxicity by inhibiting Angiotensin II

mediated oxidative stress to the cardiomyocyte, cardiacremodeling and cardiac hypertrophy .With this background the present study was undertaken to find out the effect of doxorubicin on cardiovascular system and to evaluate the cardio protective effect of enalapril on doxorubicin induced cardiotoxicity in a tertiary care center in south Indian population [18]. This study was undertaken in 60 female patients who were diagnosed as breast cancer, irrespective of the size and stage of the cancer were recruited and allocated into 30 in each group as per the protocol. Baseline investigations like complete haemogram, blood sugar, blood urea, serum Creatinine, serum Bilirubin, serum electrolytes were done. Cardiac function was assessed by ECG, plasma troponin I level. Patients with LVEF >50% & FS >25% were included for the study. Both the groups received six cycles of chemotherapy containing doxorubicin, cyclophosphamide & 5- Fluorouracil. In the present study the mean age of participants in enalapril and withoutenalapril group respectively were 53.3±9.5 & 52.1±9.8 years [19]. Majority of patients belonged to post-menopausal age group between 50 – 65 years in both the groups. In the present study TnI measured at baseline, 24hrs after first dose of doxorubicin and at the end of chemotherapy schedule (6^{th} cycle) used to predict early myocardial injury. 26.7% & 30% of subjects in both the groups were showed elevated TnI after 24 hrs. 23.3% of the participantsin both the groups showed persistent elevation of TnI at the end of chemotherapy schedule were considered as high-risk patients [20].

After the completion of six cycles of chemotherapy first group consists of 30 patients were started Enalapril 5mg/day orally at bedtime and the dose gradually increased up to 10 mg per day continuously for 6 months. Remaining 30 patients did not receive enalapril and both group of patients were observed for 9 months. Doxorubicin induced subclinical and clinical cardiotoxicity was monitored by ECG, Ejection fraction & Fractional shortening by echocardiogram at 6^{th} and end of the study (9^{th} month) in all these participants. Left ventricular function was monitored by serial measurement of LVEF & FS by echocardiogram. In this study both these parameters were monitored at baseline, end of chemotherapy schedule, 6^{th} & 9^{th} month of the study. When compare LVEF & FS between these two groups, mean LVEF & FS were gradually decreased in control group at the end ofdoxorubicin schedule, 6^{th} month & 9^{th} month of the study from the baseline value which is statistically significant ($p < 0.001$) [21]. In enalapril treated group mean LVEF & FS were gradually increased at the 6^{th} month and 9^{th} month of the study from the mean LVEF & FS at the end of chemotherapy cycle which is statistically significant ($p < 0.001$) [22]. At the end of the study mean LVEF is attained the baseline value in enalapril treated patients. In control group both LVEF & FS was gradually reduced to 7.8% & 9.2%; 9.2% & 12.2%; 11.4% & 14.1% respectively at the end of chemotherapy,6^{th} & 9^{th} month of the study from the baseline value. But in enalapril treated group both LVEF & FS was gradually increased to 5.9% & 6.3% at 6^{th} month, 8.5%&9.6% at 9^{th} month respectively compared to the values at the end of chemotherapy (6^{th} cycle) . Both LVEF & FS reaches the baseline value at the end of 9^{th} month [23]. Asymptomatic, subclinical cardiotoxicity , is defined as more than 10% reduction in LVEF & FS from the baseline value and those LVEF & FS values are >50% & >25% respectively. The patients with subclinical toxicity are more prone to develop congestive cardiac failure and cardiomyopathy in future [24]. In this study 36.1% patient & 3.3% patients in control and enalapril treated groups showed sub clinical cardiotoxicity by means of more than 10% decrease in both LVEF & FS from the baseline value [25]. At the end of 9^{th} month 20% of patients in control group showed both LVEF & FS less than 50% & 25%. But in enalapril treated group all the 30 patient's L↑EF & FS were above the normal value. ECG changes like sinus tachycardia, prolonged PR interval, T wave inversion were seen in 10% & 26% of patients in enalapril treated and control groups respectively [26]. All these changes were reverting to normal in both these groups. Arrhythmias developed in 10% of patients in control group and were treated successfully [27]. Symptomatic heart failure occurred in 2 persons (6.6%) in control group and was treated. No one developed arrhythmia & CHF in enalapril treated group. Hypotension was developed in one patient in each group, enalapril dose was reduced from 10mg to 5mgin enalapril treated patient and also treated with IV fluids [28-30].

CONCLUSION

Cancer and the resultant cardiotoxicity from both conventional and contemporary therapy substantially affect an increasing number of survivors. The optimal strategy for preventing and managing chemotherapy-induced cardiotoxicity remains unknown. We would contend that the routine use of neurohormonal antagonists for primary cardioprotection in this population is not currently justified, given only marginal benefits and associated adverse events, particularly with long-term use. Their use for secondary prevention in patients with subclinical cardiotoxicity should be individualized and carefully considered. On the other hand, dexrazoxane provides effective primary cardioprotection against anthracycline-induced cardiotoxicity, and its use beyond the current FDA-approved indications should be

investigated further. Longitudinal studies are needed to determine the prognostic value of subclinical markers of treatment-related cardiovascular injury on the long-term risk of CVD.

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