

Original Research Article

Protective effect of carvedilol against anthracycline-induced cardiomyopathy on patients with breast cancer and lymphoma

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ABSTRACT

Background: Anthracycline antibiotics are potent antineoplastic agents. Unfortunately, despite its broad effectiveness, anthracycline therapy is associated with irreversible dilated cardiomyopathy. Toxic effect may occur at any stage of anthracycline treatment. When it takes place, medical therapy is mostly insufficient. Therefore, prevention of cardiomyopathy has great clinical importance. This study aimed at evaluating the protective effect of carvedilol against anthracycline-induced cardiomyopathy on patients with breast cancer and lymphoma.

Methods: In a randomized clinical trial, 66 patients with breast cancer or lymphoma selected for chemotherapy in Tabriz city hospital. These patients randomized in three groups; the first group (control) received placebo; the second group (A) received carvedilol 6.25mg/d and the third group (B) received carvedilol 12.5mg/d for 4months. Conventional echocardiography and tissue Doppler study were employed for evaluating the patients on the baseline and at the end of survey.

Results: At the end of 4 months of follow-up, 1 (4.5%) patient in group B, 2 (9.1%) patients in group A and 4 (18.2%) patients of the control group had died. Clinical systolic dysfunction was encountered in 5 (27.8%), 5 (25%) and 1 (4.8%) patients in the control, A and B groups, respectively. A distinctive clinical diastolic dysfunction was encountered in 5 (27.8%), 3 (15%) and 3 (14.3%) patients in the control, A and B groups, respectively. Carvedilol with a dose of 6.25mg/d prohibited the diastolic dysfunction at the end of study without a significant effect on the prevention of diastolic dysfunction. Carvedilol with a dose of 12.5mg/d effectively prevented both the systolic and diastolic dysfunctions at the end of study.

Conclusions: The current study showed that prophylactic administration of carvedilol with a dose of 12.5 mg/d might significantly prevent the systolic and diastolic dysfunction of the left ventricle in patients receiving chemotherapy with anthracycline.

Keywords: Anthracycline, Carvedilol, Cardiomyopathy

INTRODUCTION

Anthracycline antibiotics is one of the effective medicine against cancer and despite this benefit, they have some irreversible cardiomyopathy side effect with distribution of 5-20% and then medicine treatment has no effect on its improvement and has the mortality of more than 50%.

So, preventing cardiomyopathy has clinical importance. Acute poisoning is just like myocardia and may cause congestive heart failure. Dilatory cardiomyopathy is considered with some signs and symptoms like fatigue, activity shortness of breath, orthopnea, bradycardia and pulmonary edema. In Echocardiography, firstly the diastolic dysfunction disorder and then systolic

dysfunction disorder can be observed specially with the movement of left ventricular septal.¹

Early recognition of cardiotoxicity is so important in preventing cardiomyopathy. Lack of 10% of left ventricular ejection fraction (EF) with dose of 200 mg/m² of body surface of Doxorubicin has specificity of 72% and sensitivity of 90% in cardiotoxicity diagnosis.² The mechanism of cardiotoxicity includes Apoptosis, free radicals of oxygen, mitochondria dysfunction disorder and activation of metalloproteinase matrix. Carvedilol in addition to effect on Beta 1, 2 and Alfa had some antioxidant property that has been confirmed in several studies on animal on very limited on human.³

The aim of this study was to investigate the effect of prescribing prophylactic carvedilol on incidence of cardiomyopathy resulted from anthracyclines.

METHODS

In this randomized clinical trial study, 66 people were selected who were treated under anthracycline program by recognition of lymphoma and breast cancer and has been referred to Tabriz city hospital from June 2012 to June 2013 and followed up for 4months. The candidate patients for chemotherapy were randomly divided into three groups each with 22 cases. The first, second and third group took Placebo, 6.25 and 12.5mg/day of carvedilol, respectively. This prescription started 24hours before chemotherapy and lasted for 4months. Both patients and the person presenting medicine or placebo were blinded. The patients in this study, were under echocardiography and tissue Doppler by Vingmed System® CV 75.

The function of left ventricular was measured during diastole and systole before chemotherapy and during acute phase and in case of clinical signs and during acute phase in fourth months and in order to exact computation of EF, Anoles speed of Mitral valve was used.

The above information was compared before and after chemotherapy. The total amount of medicine used in breast cancer was 360mg doxorubicin and/or 600mg

epirubicin. The total amount of medicine used in non-Hodgkin Lymphoma was 400mg doxorubicin and in Hodgkin lymphoma it was 300mg.

The patients with the history of chemotherapy, radiotherapy, congestive heart Failure disorder or congestive and limited fixed cardiomyopathy, coronary artery disease, medium to severe disorder of mitral valve and aortic in primary echocardiography, branch block, thyroid dysfunction disorder and prohibition of prescription of carvedilol and simultaneous serious disease and patients using ACEI, ARB, diuretic and beta blocker, age <12years old and poor-view patients to echo were excluded from study.

The price of carvedilol and the cost of echocardiography and tissue doppler has been paid by the research grant and written consent was taken from the patients. Collected data were analyzed as Mean ±SD, frequency and percent in SPSS program version 16. p<0.05 was statistically considered meaningful.

RESULTS

The frequency of mortality rate in control group was 18.2%, in 6.25mg carvedilol group was 9.1% and in 12.5mg carvedilol group was 4.5% and not meaningfully different. The average age of control group was 27/15±50/43 (74-19) years old, the 6.25mg carvedilol group was (76-17) 16/14±70/45years old, and 12.5mg carvedilol group was 00/11±52/52 (68-33) and there is no statistically meaningful difference between three groups. There is no statistically meaningful difference between 3 groups in term of gender and the type of cancer. The average of aggregation dose of Adriamycin in control group was 12/23±34/394mg/m², in 6.25mg carvedilol group was 43/12±45/378mg/m² and in 12.5mg Carvedilol group was 45/12±23/387mg/m² and there was no statistically meaningful difference between three groups.

The average aggregation dose of Epirubicin in control group was 34/12±12/556mg/m², in 6.25mg carvedilol group was 23/14±25/576 and in 12.5mg carvedilol group was 17/17±54/576mg/m² and there was no statistically meaningful difference between three groups.

Table 1: Echocardiography and basic tissue doppler in patients of three groups.

Groups Variables	Control	Carvedilol 6.25mg	Carvedilol 12.5mg	P-value
LVEF (%)	58/3±56/62	60/5±35/07	61/7±00/06	0/38
Diameter of LVDD (mm)	4/0±13/61	4/0±17/39	3/0±93/34	0/23
Diameter of LVSD (mm)	3/0±00/35	2/0±92/44	2/0±73/29	0/07
E wave speed (cm/s)	68/14±5/67	75/13±15/71	67/5±38/04	0/09
E/a ratio	0/0±99/45	1/0±03/21	0/0±83/17	0/09
Maxillary systolic velocity of mitral valve (cm/s)	17/2±56/38	17/2±25/77	17/2±33/92	0/94
EI/EA	3/1±53/02	3/0±37/97	3/0±69/66	0/52
Spreading speed (cm/s)	58/8±72/17	65/10±90/78	66/12±38/09	0/05

There was no statistically meaningful difference of frequency of pure systole cardiomyopathy and diastole cardiomyopathy between 3 groups. The percent of frequency of systole cardiomyopathy after chemotherapy in control group was 27.8% and in experiment (carvedilol acceptors) was 14.7% and it was not statistically meaningful. The percent of frequency of pure diastole cardiomyopathy after chemotherapy in control group was 27.8% and in experiment group was 14.6% and not statistically meaningful.

According to results of echocardiography and basic tissue Doppler (before chemotherapy), left ventricular ejection fraction ($p=0.375$), end-diastolic diameter of left ventricular ($p=0.226$), the end-systolic diameter of left ventricular ($p=0.069$), speed of wave E ($p=0.086$), E/A ratio ($p=0.087$), the peak systole speed of Mitral valve ($p=0.939$), Ei/Ea ratio ($p=0.518$) and Spreading speed ($p=0.053$) had no statistically meaningful difference among three groups (Table 1).

After 4 months of chemotherapy, based on results of echocardiography and doppler, it is recognized that in

control group the average changes of the peak systolic speed of mitral valve ($p=0.135$) and Ei/Ea ratio ($p=0.245$) after chemotherapy was not statistically meaningful compared to the basic amounts. The average end-diastolic diameter of left ventricular ($p=0.012$) and the end-systolic diameter of left ventricular ($p=0.003$) after chemotherapy meaningfully increased compared to basic amounts. The average left ventricular ejection fraction ($p<0.001$), the speed of wave E ($p=0.048$), E/A ratio ($p=0.023$) and speed development ($p=0.048$) after chemotherapy meaningfully decreased compared to basic amounts.

In carvedilol groups the average changes of end-systolic diameter of left ventricular ($p=0.104$), the speed of wave E ($p=0.068$), E/A ratio ($p=0.632$), the peak systolic speed of Mitral valve ($p=0.149$), Ei/Ea ratio ($p=0.493$), posterior and anterior movement of Mitral valve ($p=0.462$) and Spreading speed ($p=0.220$) after chemotherapy was not statistically meaningful compared to basic amounts. The average ejection fraction and end-diastolic diameter of left ventricular after chemotherapy meaningfully decreased compared to basic amounts (Table 2).

Table 2: Echocardiography and basic tissue Doppler in patients of three groups 4 month after Chemotherapy.

Groups Variables	Control	Carvedilol 6.25mg	Carvedilol 12.5mg	P-value
LVEF (%)	53/3±94/80	53/7±15/76	56/6±81/20	0
Diameter of LVDD (mm)	4/0±56/57	4/0±50/46	4/0±09/37	0/01
Diameter of LVSD (mm)	3/0±24/44	3/0±00/55	2/0±85/35	0
E wave speed (cm/s)	63/10±1/71	71/12±35/68	66/5±43/03	0/04
E/a ratio	0/0±86/33	1/0±00/38	0/0±81/17	0/02
Maxillary systolic velocity of mitral valve (cm/s)	16/1±61/50	17/3±05/24	15/4±38/34	0/14
EI/EA	3/0±88/78	3/0±51/80	3/0±79/66	0/25
Spreading speed (cm/s)	52/8±17/83	62/9±95/58	64/9±90/80	0/04

DISCUSSION

In this paper, carvedilol was prescribed in 6.25 and 12.5 mg/day for four months. However, in the end of study, the percent of frequency of pure systolic and diastolic cardiomyopathy after chemotherapy in carvedilol group was less than control group (27.8% versus 14.6%) but the difference was not statistically meaningful.

On the other hand, the investigation by 2-dimensional echocardiography and color doppler showed that prescription of carvedilol in 6.25mg/day has a protective effect toward diastolic disorder and with 12.5mg/day has a protective effect toward both diastolic and systolic disorder.

Matusi et al in a study on animals (rat) showed that carvedilol prescription may have a preventing effect toward cardiomyopathy of doxorubicin.⁴ In another study on animals by Santos et al, it was shown that prescription

of prophylactic carvedilol can prevent mitochondrial cardiomyopathy of doxorubicin.⁵ Spallarossa et al showed in an animal study that prescription of prophylactic carvedilol can prevent cardiomyopathy of doxorubicin.⁶ Cruz et al in a study on Hamster showed that prescription of carvedilol in 1 mg/day for each kg/day can improve heart function.⁷

As we can see, above investigations has confirmed the protective effect of carvedilol in animal models. Only in 2 studies the effect of carvedilol on treatment or prevention of cardiomyopathy caused by chemotherapy has been considered.

Kalay et al in a study in turkey studied 50 patients with lymphoma or breast cancer randomly in two carvedilol groups (12.5mg/day) and placebo. In this study, Echocardiography and Transmitral pulsed Doppler was used before chemotherapy and in the end of 6th month of study in order to determine the systolic and diastolic

function of left ventricular. It has to be noted both groups were matched before chemotherapy. In the end of six months, no meaningful difference was observed in experimental group as left ventricular ejection fraction and diastolic and systolic diameters. Whereas in control group, in the end of six months left ventricular ejection fraction meaningfully decreased and systolic and diastolic diameters increased. In study of Doppler results only the speed of wave E (E-velocity) in experiment group meaningfully decreased. Whereas in control group in addition to the E-velocity, E/A ratio decreased, too. In the other hand, it was shown in this study that carvedilol with mentioned dose has a protective effect toward systolic and diastolic disorder of left ventricular caused by Anthracyclines.⁸

As it was mentioned before, the protective effect toward both systolic and diastolic disorder was observed in 12.5mg daily and in 6.25mg only the diastolic function of left ventricular was protected. It has to be considered that based on MOCHA guideline the proposed dose of carvedilol in patients with heart disorders is 12.5 to 50mg.⁵

There isn't a full agreement about a proper dose of carvedilol in chronic artery patients. Especially that the protective effect of this medicine has not been widely investigated on cardiomyopathy caused by chemotherapy yet and more research is needed.⁸

Low sample size and lack of long-term effects of anthracycline in heart diseases are two main limitation in Kalay et al study and also in our study. However, this study has two advantages: evaluation of tissue Doppler parameters in addition to using popular echocardiography for patients and using two different doses of carvedilol and compare them.

According to the results of present study, the prescription of carvedilol with dose of 12.5milligram per day can have protective effect toward systolic and diastolic disorder of left ventricular. Although the percent of frequency of clinical cardiomyopathy in studied groups has no meaningful difference. It has to be considered that the most important reason for no meaningful difference is low sample size despite the obvious difference between groups.⁸

In present study, for four month observing patients, the mortality rate in control group, carvedilol group with dose of 6.25mg/day and 12.5mg/day were 16, 8 and 4 per 100000, respectively. In Kalay et al study, the mortality rate in control and experimental group was reported 16 and 4 per 100000, respectively which is not statistically meaningful. It also concluded that although this difference is not statistically meaningful but considerable.⁸

On the other hand, Mukai et al in Japan investigated the effect of prescription of carvedilol with initial dose of

2mg/day and increase to 10-20mg/day in 5 patients with cardiomyopathy from anthracycline. It is shown in this paper that the prescription of carvedilol can improve the symptoms of patients, ventricular function and diastolic and systolic diameters.⁹ This is in contrast with the papers that found out the cardiomyopathy from anthracycline is irreversible.¹⁰

CONCLUSION

The prescription of carvedilol with two doses of 6.25 and 12.5mg/day may decrease the findings of echocardiography and tissue doppler for diastolic and systolic disorder. Therefore, according to the possible effect of carvedilol in preventing myopathy of chemotherapy, so, it seems that further studies with more samples clarifies more detailed results.

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Ethical approval: The study was approved by the institutional ethics committee

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