

Effect of carvedilol on echocardiographic ejection fraction and fraction shortening in doxorubicin treated females with breast cancer

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الخلاصة

يعتبر النظام العلاجي المعتمد على الدوكسوروبوسين من أكثر العلاجات استخداماً لعلاج سرطان الثدي والذي قد يتسبب بتسمم القلب.

هدف الدراسة هو لتوضيح إمكانية تأثير عقار الكارفيديلول على الجزء المقذوف والاختصار الجزئي في فحص صدى القلب لدى النساء المصابات بسرطان الثدي اللواتي يستخدمن عقار الدوكسوروبوسين.

شاركت 16 امرأة تعاني من سرطان الثدي في هذه الدراسة. وزعت المريضات عشوائياً إلى مجموعتين، كل مجموعة تحوي على 8 مريضات. تضمنت المجموعة الأولى مريضات تم علاجهن بعقار الدوكسوروبوسين لست دورات مفصولة بواحد وعشرين يوماً، أما المجموعة الثانية فقد احتوت على مريضات تم علاجهن بعقار الدوكسوروبوسين + الكارفيديلول 3,125 ملغم عن طريق الفم، مرتان يومياً لمدة 5 أيام بعد كل جرعة من الدوكسوروبوسين لست دورات. تم قياس الجزء المقذوف والاختصار الجزئي عن طريق إجراء فحص صدى القلب لكل مريض قبل (وقت صفر) وبعد 3 أيام من وقت الجرعة الثانية والرابعة والسادسة. تم الحصول على النتائج التالية:

1- سبب النظام العلاجي المعتمد على الدوكسوروبوسين نقصان معنوي عالي في الجزء المقذوف والاختصار الجزئي في فحص صدى القلب بعد الجرعة الثانية والرابعة والسادسة مقارنة مع القراءات الأولية. $P < 0.01$

2- سبب استخدام الكارفيديلول مع الدوكسوروبوسين زيادة معنوية عالية في الجزء المقذوف والاختصار الجزئي في فحص صدى القلب مقارنة مع استخدام الدوكسوروبوسين فقط. $P < 0.01$ ، من هذه الدراسة، يمكن أن نستنتج بان عقار الكارفيديلول يسبب زيادة معنوية عالية في الجزء المقذوف والاختصار الجزئي لدى المريضات المصابات بسرطان الثدي اللواتي يستخدمن نظام علاجي المعتمد على الدوكسوروبوسين.

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Abstract

Background : Doxorubicin based regimen is the most common treatment of breast cancer which is highly complicated by cardiotoxicity.

Aim : To clarify the possible effects of carvedilol on echocardiographic ejection fraction and fraction shortening in doxorubicin based regimen in females with breast cancer.

Patients and Methods : A total of 16 females with breast cancer were included in this study. The patients were randomized into 2 groups , 8 patients each. Group I included patients were treated with doxorubicin based regimen for 6 cycles with 21 day apart. Group II included patients were received doxorubicin based regimen with carvedilol 3.125 mg , orally , twice daily for 5 days , for 6 cycles. Echocardiography was done to measure ejection fraction and fraction shortening at zero time and 3 days after 2nd , 4th and 6th cycles.

Results: Treatment with CAF regimen caused highly significant decrease in echocardiographic ejection fraction and fraction shortening after 2nd , 4th and 6th cycles in comparison to baseline readings ($P < 0.01$). Combined CAF + Carvedilol 3.125 mg orally twice daily for 5 days caused highly significant increment in echocardiographic ejection fraction and fraction shortening compared with that of CAF regimen group ($P < 0.01$).

Conclusion: Carvedilol causes significant increase in echocardiographic ejection fraction and fraction shortening in doxorubicin treated patients.

Key words : Carvedilol , Doxorubicin , Cardiotoxicity , Ejection fraction , Fraction Shortening

Introduction

Breast cancer is originating from breast tissues, most commonly from inner lining of milk ducts or the lobules. Cancers originating from ducts are known as ductal carcinomas ; those originating from lobules are known as lobular carcinomas⁽¹⁾. Anthracyclines are potent antineoplastic agents used extensively to treat a range of cancers, including leukemias, lymphomas, sarcomas, and carcinomas⁽²⁾. In large clinical trials, approximately one in four patients experienced congestive heart failure when the cumulative dose of doxorubicin exceeded 500 mg/m², nearly 50% had cardiac events when doxorubicin dose above 600 mg/m², and nearly all patients had cardiotoxicity when doxorubicin dose above 800 mg/m². The incidence of clinical cardiac failure increases precipitously when the dose above 550 mg/m² with the majority developing cardiomyopathy within the first year of completion of treatment.

It had been suggested that cardiomyopathy not only develops at a much lower cumulative dose than previously thought, but it may also manifest even years after treatment, especially in pediatric oncology survivors⁽³⁾. Many mechanisms of DIC have been proposed and studied. Nevertheless, the iron-mediated formation of ROS and promotion of myocardial oxidative stress remain by far the most frequently proposed mechanism⁽⁴⁾. As the anthracycline-induced cardiotoxicity is largely irreversible, it is crucial to detect the myocardial injury at its earliest possible stage. Among the first approaches employed for sensitive and reliable detection of anthracycline cardiotoxicity was an endocardial biopsy. However, its invasive nature hinders and in fact nearly prevents its routine use in seriously sick oncologic patients. Actual recommendations for cardiac monitoring of anthracycline-treated patients are mostly based on the non-invasive examination of the left ventricular (LV) systolic function, since its decline is a well-known hallmark of anthracycline cardiotoxicity^(5, 6,7,8,9). Both echocardiography and radio-ventriculography are employed, but a relatively low sensitivity of these approaches does not allow to cover the early phases of myocardial injury so that only more pronounced and distinct cardiotoxicity can be revealed^(6,7).

Carvedilol is a nonselective β -blocker with additional vasodilating and antioxidative properties. The drug is used for the treatment of hypertension and stable angina pectoris, and was the first β -blocker to be approved for the treatment of congestive heart failure (CHF) in adults⁽¹⁰⁾.

Patients and methods

The study approved by college scientific committee and informed consent was taken from patients.

The study sample included female patients who attended the oncology unit in al-Sadar medical city in Al-Najaf governorate from 1st day of April to the 30th day of December 2010 with histopathological evidence of breast cancer. 16 patients were enrolled in this study. Exclusion criteria were Patients with past-medical history of myocardial infarction, diabetes mellitus, Cardiac and renal failure. Patients were divided randomly into:

Group 1 : Patients were treated with Doxorubicin based regimen for 6 cycles with 21 days apart.

Group 2 : Patients were treated with Doxorubicin based regimen + Carvedilol 3.125 mg administered orally twice daily for 5 days, for each cycle for 6 cycles with 21 days apart.

Carvedilol: It was given as a tablet in a dose of 3.125mg twice daily , orally for 5 days , for each cycle. (Hexal Germany Batch NO. 9Y9587).

Methods: The weights of the patients are measured by using well calibrated digital weight and height scale measuring device model 1986 , made by Jookad company , Japan.

Body Surface Area (BSA): is in square meter (m^2) as an index of body surface area calculated according to monogram of Dubois ⁽¹¹⁾.

Body Mass Index (BMI): is calculated by the following equation: $BMI = \text{Weight (kg)} / \text{Height (M}^2)$ ⁽¹²⁾.

Echocardiography(ECHO): Each individual included in this study (control and patients groups), underwent echocardiography , at zero time and 3 days after 2nd , 4th and 6th cycles. Study was performed by a protocol determined by using Kretz technique type and model 530D with 2-4 MHZ transducer made in Australia in 1996 for measuring left ventricular ejection fraction and fraction shortening.

Left Ventricular Ejection Fraction (LVEF): It employs the percent of left ventricle volume instead of the percent change of left ventricle dimension , it is calculated as the percent ratio of the difference between end diastolic and end systolic volumes to the end diastolic volume ⁽¹³⁾.

Fraction Shortening (FS): This parameter reflects the relative change of left ventricular internal dimension throughout the cardiac cycle ,it is measured as the ratio of the difference between end diastolic and end systolic internal diameters to the end diastolic internal diameter. This ratio is multiplied by 100 to obtain the percent of Fraction shortening. It is the most commonly applied M-Mode derived measure of left ventricular systolic function ⁽¹³⁾.

Statistical Analysis: Data were translated into a computerized database structure. An expert statistical advice was sought for. Statistical analysis were computer assisted using SPSS version 15. The data are expressed as mean \pm SEM unless otherwise stated. Statistical analysis was carried out using Paired T-TEST. Significance differences was set at $\alpha = 0.05$. P value less than the 0.05 level of significance was considered statistically significant.

Results

Table 1 : Anthropometric data for patents included in this study.

Anthropometric data	Mean \pm SD
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Age (year)	38.53± 3.88
Sex	All are females
Weight (kg)	72.43±6.51
Height (cm)	157.92±4.69
*BSA (m ²)	1.71±0.06
**BMI (kg/m ²)	29.21±4.41

*Body Surface Area .

**Body Mass Index.

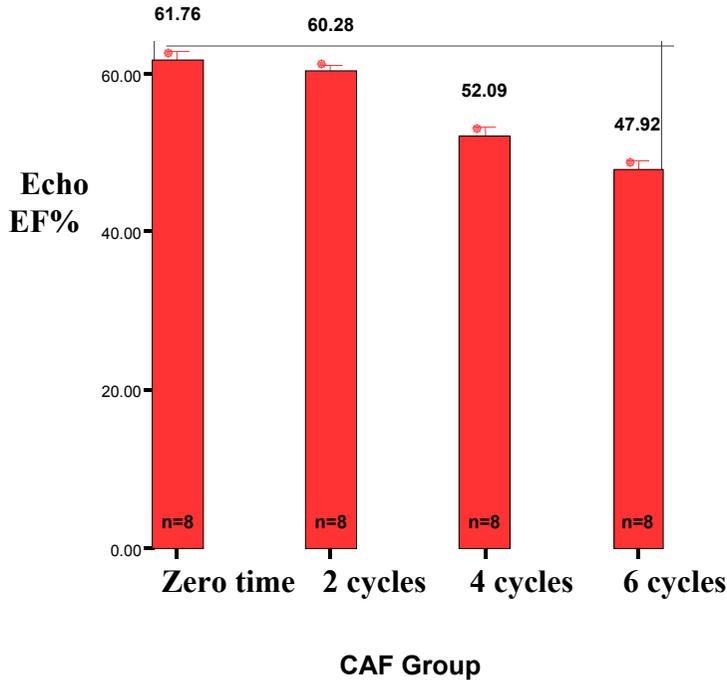


Figure 1:Mean of changes in echocardiographic ejection fraction (%) after 2 , 4 and 6 cycles compared with baseline value among patients treated with CAF regimen.

In comparison to baseline level, there was a significant reduction in echocardiographic ejection fraction (%) after 2, 4 and 6 cycles in CAF regimen group (p< 0.01).

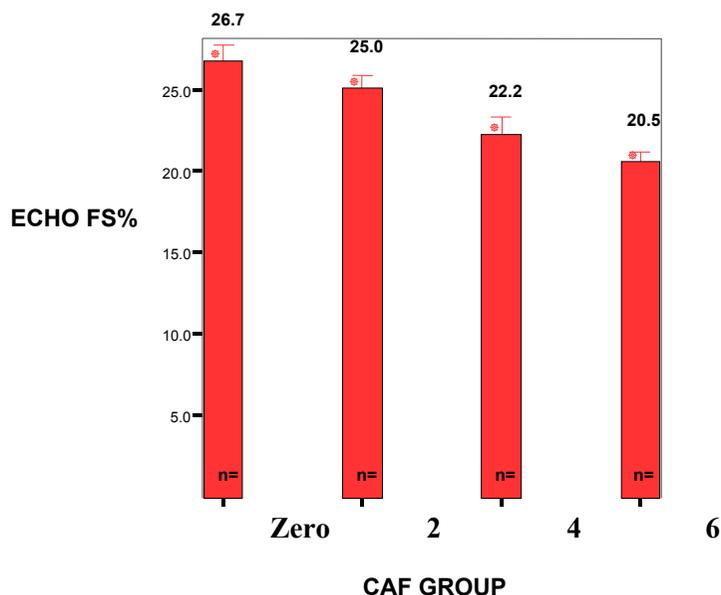


Figure 2 : Mean of changes in echocardiographic fraction shortening (%) after 2 , 4 and 6 cycles compared with baseline value among patients treated with CAF regimen. There was a significant reduction in echocardiographic fraction shortening (%) after 2, 4 and 6 cycles in CAF regimen group ($p < 0.01$).

Table (2): Comparison between effect of CAF and CAF + Carvedilol (3.125 mg) on different parameters after 6th cycle.

parameter	CAF	CAF+ Carvedilol 3.125mg	P value
Echo EF%	47.92 ± 0.56	51.37 ± 0.74	P < 0.01
Echo FS%	20.53 ± 0.37	22.61 ± 0.62	P < 0.01

The data expressed as mean ± SEM

Discussion

Adriamycin is one of the most frequently used chemotherapeutic drugs in the treatment of cancer. However, the clinical usefulness of doxorubicin is limited by a dose-related cardiac toxicity. Acute doxorubicin induced cardiotoxicity alters the organization of the cardiomyocytes and induces apoptosis, which is a potentially modifiable and preventable form of myocardial tissue loss⁽¹⁴⁾. Mitochondria have been identified as one of the targets in ADR-induced sub-cellular damage in heart tissues⁽¹⁵⁾.

Doxorubicin is an anthracycline, which is widely used for the treatment of various cancers. The clinical use of doxorubicin is limited by acute and chronic cardiotoxicity, which often leads to progressive heart failure with impaired contractility, arrhythmias, or sudden death ⁽¹⁶⁾. Doxorubicin caused highly significant reduction in echocardiographic ejection fraction after 6 treatment cycles in comparison to baseline values ($P < 0.01$). This finding is in agreement with that revealed by ⁽¹⁷⁾. The mechanism beyond this effect is thought to include heightened oxidative stress status leading to apoptosis of endothelial cells and cardiomyocytes ⁽¹⁸⁾. In present study, there was highly significant decline in echocardiographic fraction shortening by doxorubicin compared with baseline readings ($P < 0.01$). This finding is in consistency with ⁽¹⁹⁾ and it may be attributed to the same mechanism. Carvedilol produced highly significant increment in echocardiographic ejection fraction in comparison to that of doxorubicin treated group ($P < 0.01$). This is in consistency with ⁽²⁰⁾. This effect may be due to pleotropic effect of carvedilol. In present study, carvedilol improved echocardiographic fraction shortening in highly significant way as compared with doxorubicin treated group ($P < 0.01$). This result agree with ⁽²¹⁾. The mechanisms underlying this cardioprotective effect are not fully understood. However, several reports suggest that cardioprotection may be afforded through the potent antioxidant activity of carvedilol, which is not shared by all β -adrenergic antagonists ^(22,23,24). Carvedilol has been shown to scavenge oxygen free radicals ⁽²⁵⁾ and to inhibit lipid peroxidation in biological systems ^(22,23). Moreover, the antioxidant Protection of carvedilol occurs through a chain-breaking mechanism in post-ischemic rat hearts ⁽²³⁾. The capacity of carvedilol to inhibit lipid peroxidation is much greater than that of other β -adrenergic blocking agents, such as propranolol ⁽²²⁾. A distinctive characteristic of carvedilol is its Potent antioxidant properties that are not shared by other h-adrenergic receptor antagonists ⁽²²⁾. This antioxidant activity of carvedilol is attributed to its ability to chelate free iron **(26)**, which is widely implicated in enhancing the free radical-mediated toxicity caused by doxorubicin. Carvedilol is superior to atenolol, a β -adrenergic receptor antagonist without antioxidant properties, in diminishing DOX induced negative impact on systolic blood pressure and left ventricular fractional shortening as well on increased lipid peroxidation ⁽²⁷⁾, which could either be explained by a direct effect on cardiac tissue or to vascular effects of the drug. More recently, the balance tilted for a predominant effect on the cardiac tissue as ⁽²⁸⁾ showed that carvedilol

diminishes both the cardiac mitochondrial toxicity and histopathology caused by doxorubicin.

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