

A study of effect of carvedilol on serum creatine kinase- MB and troponin I levels in doxorubicin treated females with breast cancer

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الخلاصة:

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

الهدف: هدف الدراسة هو لتوضيح إمكانية تأثير عقار الكارفيديلول على أنزيم CK-MB وبروتين Troponin I لدى النساء المصابات بسرطان الثدي اللواتي يستخدمن عقار الدوكسوروبوسين.

المرضى وطريقة العمل: شاركت ١٦ امرأة تعاني من سرطان الثدي في هذه الدراسة. وزعت المريضات عشوائيا إلى مجموعتين، كل مجموعة تحوي على ٨ مريضات. تضمنت المجموعة الأولى مريضات تم علاجهن بعقار الدوكسوروبوسين لست دورات مفصولة بواحد وعشرين يوما، أما المجموعة الثانية فقد احتوت على مريضات تم علاجهن بعقاري الدوكسوروبوسين + الكارفيديلول ٣,١٢٥ ملغم عن طريق الفم ، مرتان يوميا لمدة ٥ أيام بعد كل جرة من الدوكسوروبوسين لست دورات. تم قياس مستوى أنزيم CK-MB وبروتين Troponin I في مصل الدم لكل مريضة قبل (وقت الصفر) وبعد ٣ أيام من وقت الجرعة الثانية والرابعة والسادسة.

النتائج: تم الحصول على النتائج التالية:

١- سبب النظام العلاجي المعتمد على الدوكسوروبوسين زيادة معنوية عالية في مستوى أنزيم CK-MB وبروتين Troponin I بعد الجرعة الثانية والرابعة والسادسة مقارنة مع القراءات الأولية. $P < 0.01$

٢- سبب استخدام الكارفيديلول مع الدوكسوروبوسين نقصان معنوي عالي في مستوى أنزيم CK-MB وبروتين Troponin I مقارنة مع استخدام الدوكسوروبوسين فقط. $P < 0.01$

الاستنتاج: من هذه الدراسة ، يمكن أن نستنتج بان عقار الكارفيديلول يسبب نقصان معنوي عالي في مستوى أنزيم CK-MB وبروتين Troponin I لدى المريضات المصابات بسرطان الثدي اللواتي يستخدمن نظام علاجي المعتمد على الدوكسوروبوسين.

Summary:

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 serum CK-MB and Troponin I 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. Serum CK-MB and Troponin I were measured at zero time and 3 days after 2nd, 4th and 6th cycles in both groups.

Results: The following results were obtained:

1- Treatment with doxorubicin based regimen caused highly significant elevation in serum CK-MB and Troponin levels after 2nd, 4th and 6th cycles in comparison to baseline readings ($P < 0.01$).

2- Combined CAF + Carvedilol 3.125 mg orally twice daily for 5 days caused highly significant decrement in serum CK-MB and Troponin I levels compared with that of doxorubicin based regimen group ($P < 0.01$).

Conclusion: From the present study, we can conclude that Carvedilol causes highly significant decrease in serum CK-MB and Troponin I levels in doxorubicin treated patients.

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⁾. Creatine kinase and CK-MB isoenzyme Cytoplasmic CK is a dimer, composed of M and/or B subunits, which associate forming CK-MM, CK-MB and CK-BB isoenzymes⁽⁵⁾. Serum CK-MB is considerably more specific for myocardial damage than is serum total CK, which may be elevated in many conditions where skeletal muscle is damaged⁽⁶⁾. It appears evident that in approximately one third of patients treated with potentially cardiotoxic chemotherapy, the increase in troponin concentrations in the blood underlines the occurrence of irreversible Myocardial cell injury⁽⁷⁾. It is important to note that the increase of troponin concentrations was detected at different intervals after chemotherapy administration in the various studies, indicating that it may be necessary to collect several blood samples to demonstrate the possible increase of the marker⁽⁸⁾. 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⁽⁹⁾.

Patients and methods:

The study sample included female patients who attended the oncology unit in al-Sadar medical city in Al-Najaf Al-Ashraf governorate from 1st day of April to the 30th day of December 2010 with histopathological evidence of breast cancer. 16 patients were included in this study. Exclusion criteria were Patients with past-medical history of MI, DM, Cardiac and renal failure. Patients were divided randomly into 2 groups:

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. It was manufactured by 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 ⁽¹⁰⁾.

Body Mass Index (BMI): is calculated by the following equation: $BMI = \text{Weight (kg)} / \text{Height (M}^2\text{)}$ ⁽¹¹⁾.

2.4 Collection of blood samples:

1 ml of blood was collected at zero time and 3 days after 2nd, 4th and 6th cycles for estimation of CK-MB and Troponin I.

Each blood sample was left for 15 minutes and centrifuged at 2500 rpm for 15 minutes, then serum was collected and frozen in the clinical immunology unit in al-Sadar medical city, in Al-Najaf Al-Ashraf Governorate.

Measurement of CK MB:

Source : DRG Creatine Kinase (MB- Isoform) (EIA).

Measurement of Troponin I:

Source : DRG Troponin I Elisa (cTn I) (EIA-2952).

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

Anthropometric data	Mean± SD
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.

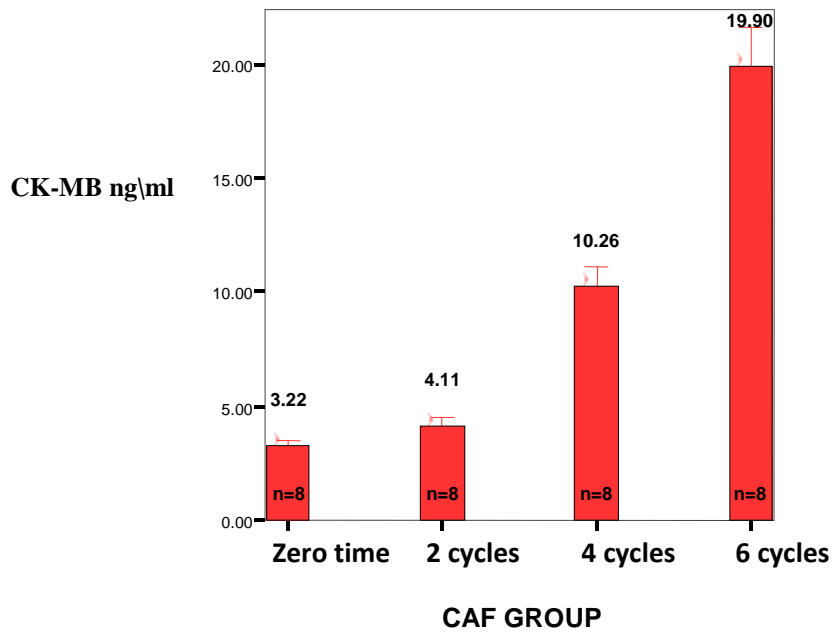


Figure 1: Mean of changes in serum CK-MB level after 2, 4 and 6 cycles compared with baseline value among patients treated with doxorubicin based regimen. In comparison to baseline level, there was high significant increment in serum CK-MB level (ng/ml) after 2, 4 and 6 cycles in doxorubicin based regimen group ($p < 0.01$).

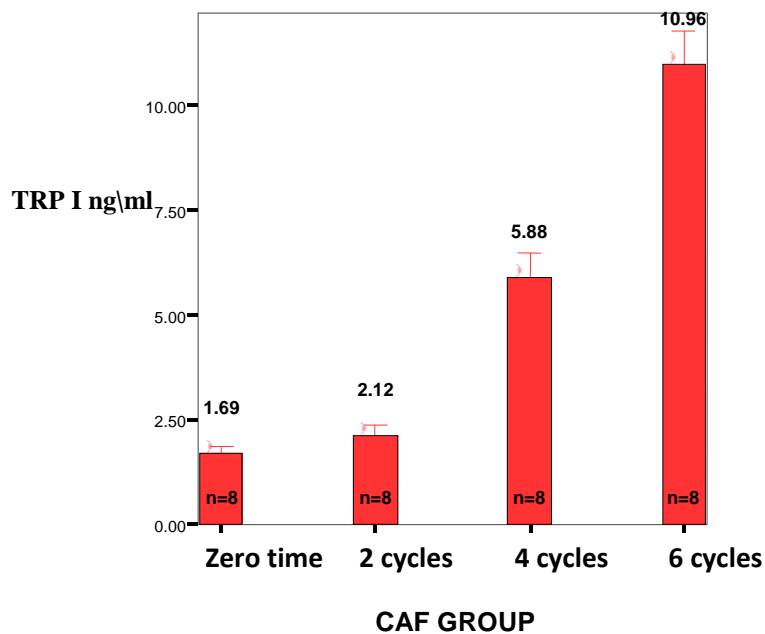


Figure 2: Mean of changes in serum TRP I level after 2, 4 and 6 cycles compared with baseline value among patients treated with CAF regimen. In comparison to baseline level, there was high significant increment in serum TRP I level (ng/ml) after 2, 4 and 6 cycles in CAF regimen group ($p < 0.01$).

Table (2): Comparison between effect of CAF and CAF + Carvedilol (3.125 mg) on serum CK-MB and Troponin I levels after 6th cycle.

parameter	CAF	CAF+ Carvedilol 3.125mg	P value
CK-MB	19.90 ± 0.83	12.08 ± 0.47	P < 0.01
TRP I	10.96 ± 0.40	6.06 ± 0.13	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⁽¹²⁾. Mitochondria have been identified as one of the targets in ADR-induced sub-cellular damage in heart tissues⁽¹³⁾. 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⁽¹⁴⁾. Doxorubicin caused highly significant increment in serum CK-MB level as compared with baseline measurement (P < 0.01). This result is consistent with result of⁽¹⁵⁾ and⁽¹⁶⁾. This increase in serum CK-MB level indicates an injury or damage to cardiac cells by doxorubicin which may be due to the inhibition of nucleic acid and protein synthesis⁽¹⁷⁾ and⁽¹⁸⁾ attributed the increase of CK-MB to the excessive production of free radicals and lipid peroxides that might have caused leakage of cytosolic enzymes and to cell membrane damage. Doxorubicin produced highly significant increase in serum TRP I level in comparison to the baseline readings (P < 0.01). This finding agree with⁽¹⁹⁾ and this is due to doxorubicin induced cardiac damage. Carvedilol produced highly significant decrement in serum CK-MB level as compared with doxorubicin treated group (P< 0.01). This result is consistent with that of⁽²⁰⁾. Carvedilol decreases the extent of cellular vacuolization in cardiac myocytes and prevents the decline in mitochondrial calcium super loading capacity and inhibition of the respiratory complexes of heart mitochondria caused by doxorubicin⁽²⁰⁾. Cardiac TRP I was decreased in highly significant manner by carvedilol in comparison to that in doxorubicin treated group.

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