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Evaluation of the changes in Tei-index (myocardial performance index) in Doppler echocardiography before and after treating with anthracycline combinations in children with malignancy

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Abstract

Background: Cardiomyopathy usually causes a cardiac dysfunction resistant to treatment due to anthracycline. This study aimed to evaluate the changes in Tei-Index (myocardial performance index) in patients with malignancies treated with anthracycline.

Material and Methods: This case-control study was done on 15 children who were treated with low-dose anthracycline (1-199mg/kg) called group A and 15 children who were treated with high dose (>200mg/kg) anthracycline called group B after acquiring consent from their parents. Children with no abnormality in Echo-Doppler results were included in this study. The patients' age range between 1- 17 years with a mean age of 6.57 years. Another group of healthy children were assigned to group C as a control group who had not received chemotherapy. The first echo was performed right before the treatment and the second one, two weeks after completing chemotherapy. Data were analyzed by the SPSS statistical software.

Results: Changes in mean Tei-index in group A were 0.36 ± 0.04 before treatment and 0.43 ± 0.11 after treatment. Changes in mean Tei-index in group B were 0.37 ± 0.04 before treatment and 0.45 ± 0.06 after treatment. There was no significant difference between the two groups using the independent T-test. (p-value= 0.57). No significant correlation between the changes in mean ejection fraction (EF) and treatment was found in the three groups (p-value=0.45).

Conclusion: This study showed a change in the Tei-index (MPI) in patients receiving anthracycline; regardless of the dosage, they got in their regimen. Given the use of anthracycline, any abnormal cardiac finding can alert the physicians to the possibility of cardiomyopathy, hence scheduling routine follow-ups are necessary.

Keywords: Doppler echocardiography, Malignancy, Tei-index

Introduction

Acute lymphoblastic leukemia (ALL) (1) The major types of cancer in children (younger than 15 years old) and adolescents (aged 15 to 19 years old) are different from those in adults, which are typically epithelial in origin. An estimate of 429,000 new cases of childhood cancers occurs worldwide each year. Globally, the reported incidence rates of these cancers are 141 per million person-years (children) and 185 per million person-years (adolescents) (1–3).

The anthracyclines are a potent class of chemotherapy agents used widely in the treatment of childhood cancers. Following their introduction to clinical practice in the early 1960s, the increased international collaboration among clinical trial centers has advanced the survival outcomes of these patients. According to the survivorship statistics in the United States in 2016, an overall 5-year survival rate for all childhood cancers has risen from 58% for those diagnosed between 1975 and 1977 to 83% for children diagnosed between 2005 and 2011(4). Similarly, in

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Australia, the 5-year survival rates of all childhood cancers have gone up from 72% for those diagnosed between 1983 and 1992 to 84% for children diagnosed between 2003 and 2012(5). Anthracycline chemotherapy (used to treat >50% of children with cancer) has contributed to the steady improvements in survival observed over the past several decades.

Cardiomyopathy progressing to congestive heart failure is an unfortunate complication of anthracyclines (6,7). Childhood cancer survivors are at a 5 to 15-folds of higher risk of anthracycline-related cardiotoxicity compared with age-matched controls without anthracycline exposure (8–13). The outcome is poor, such that the 5-year survival rates are <50% after a diagnosis of congestive heart failure(14,15). Cardiomyopathy risk increases with anthracycline use (16,17).

The Tei-Index (myocardial performance index) or MPI is a useful and non-invasive Doppler ultrasound index that combines the systolic and diastolic function of the ventricles, which is calculated as follows:)Isovolemic relaxation time pulse +Isovolemic contraction time (÷ Ejection time (ICT+IRT)/ET

The Tei-Index indicates ventricular function and its change indicates a move towards heart problems and diseases (18). The myocardial performance index is the same as the Tei-index, which is also measured by Doppler ultrasound.

By using Tei-Index, it is possible to specifically diagnose and detect subclinical cases of myocardial dysfunction early. Since the first changes in the heart and cardiotoxicity are not seen in routine echocardiography and ECG; Doppler echocardiography and Tei-Index are used instead (19). This study aimed to evaluate the changes in Tei-Index in malignancies treated with anthracyclines.

Materials and Methods

This case-control study was performed in Ali Ibn Abi-Taleb Hospital in Zahedan in 2016 on children with various malignancies who were candidates for anthracycline chemotherapy. This was performed after approval by the ethics committee of Zahedan University of Medical Sciences with the code IR.ZAUMS.REC.1391.2515.

This was done in three groups. Due to the regulations established at Ali Ibn Abi-Taleb Hospital, the sample size of 15 patients in each group was considered. Group A included 15 children who were treated with low-dose anthracycline (1-199mg/kg). Group B was 15 children who were treated with high dose (>200mg/kg) anthracycline.

The control group (group C) included 30 patients admitted to Ali Ibn Abi-Taleb Hospital in Zahedan with the same age, sex, and weight who did not have malignancy and heart problems. They did not receive any medication. After obtaining informed consent from patients and their parents, all patients underwent a Doppler echo and entered the study if the echo was normal. Patients with a history of heart problems or abnormal echocardiography were excluded from the study. Then patients' information including age, sex, weight, and the prescribed dose of anthracycline were recorded in information forms. Patients underwent Doppler echo two weeks after the end of chemotherapy, and their Tei-Index and Ejection Fraction (EF) were evaluated. Figure 1 shows that the Tei-index was calculated as (ICT + IRT) / ET. The time interval between the end and the onset of the mitral or tricuspid inflow was denoted by “a,” and the left or right ventricular ejection time was represented by “b”. Mean values were obtained by averaging five beats (20). SPSS version 17 was used for statistical analysis and the significance level of the tests was considered less than 0.05.Quantitative data were analyzed using statistical analysis of variance and qualitative variables using the chi-square test.

Results

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In this study, 60 children participated in 3 groups: 15 in group A, 15 in group B, and 30 in group C. Results showed that 34(56.6%) of patients were boys and 26 (43.4) were girls whose age ranged from 1-17 years old with a mean age of 6.57 years old.

The levels of the Tei-index in groups A and B were measured before chemotherapy and compared with the control group. The results were as follows:

1- Group A: the mean MPI index was 0.36±0.04, the minimum value was 0.28 and the maximum was 0.42.

2- Group B : the mean MPI index was 0.37±0.04, the minimum value was 0.30 and the maximum was 0.45

3- Group C: the mean MPI index was 0.35±0.03, the minimum value was 0.30 and the maximum was 0.42.

Therefore, the MPI index was normal in three groups at the beginning of the study and before starting chemotherapy with no significant difference (p=0.46). Figure 2 shows the initial numerical changes in the MPI index before chemotherapy.

Then the Tei-index levels in groups A and B were measured after chemotherapy and compared with the control group. the results were as follows:

1- group A: The mean MPI index was 0.43±0.11, the minimum value was 0.32, and the maximum was 0.75.

2- group B: the mean MPI index was 0.45±0.06, the minimum value was 0.35, and the maximum was 0.59

Table I shows the MPI changes in patients before and after Anthracycline treatment.

There was no significant difference between the two groups using an independent T-test (p-value=0.57). Therefore, there was no correlation between the post-treatment level of the Tei-index and the use of anthracyclines in either group. Figure 3 shows the initial numerical changes in the MPI index after chemotherapy. The Left Ventricular EF in groups A and B were measured before chemotherapy and compared with the control group, with the following results: In group A, the mean EF changes were 64%±4%, the minimum value was 60% and the maximum was 75%.

In group B, the mean EF changes were 65%±4%, the minimum value was 60% and the maximum was 75%. In the control group mean of EF changes was 64%±3%, the minimum value was 60% and the maximum was 69%. There was no significant difference between groups B and C using the independent T-test. (p-value=0.45). Therefore, there was no significant correlation between the mean changes of EF in groups A and B compared to group C, regardless of the dose the patients got.

Left Ventricular EF in groups A and B was measured after chemotherapy and compared with the control group, the results were as follows:

1- In group A, the mean of EF changes was 63%±5%, the minimum value was 58% and the maximum was 77%.

2- In group B, the mean of EF changes was 65%±5%, the minimum value was 55% and the maximum was 88%.

3- In group C, the mean of EF changes was 63%±5%, the minimum value was 58% and the maximum was 77%.

There was no significant difference between the three groups using the independent T-test. (p-value=0.26). Therefore, there was no significant correlation between the mean EF changes after the treatment in neither of the two groups compared to the control group.

Table II shows the mean of EF changes in patients before and after Anthracycline treatment.

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Table I: The MPI changes in patients before and after Anthracycline treatment

Groups	Before treatment	After treatment	P_{value}
A	0.36±0.04	0.43±0.11	0.042
B	0.37±0.04	0.45±0.06	0.00

Table II: The mean of EF changes in patients before and after Anthracycline treatment

Groups	Before treatment	After treatment	V_{alue}
A	%64±4	%63±5	0.388
B	%65±4	%65±5	0.645

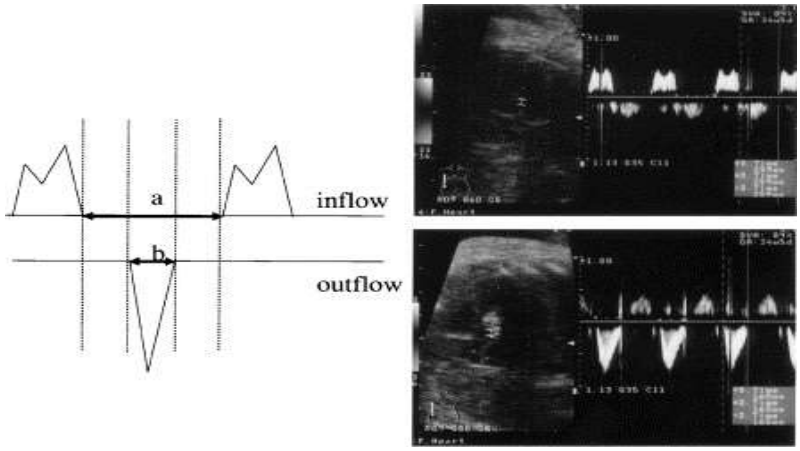

Figure 1: Tei-index is calculated by the formula (ICT+IRT)/ET

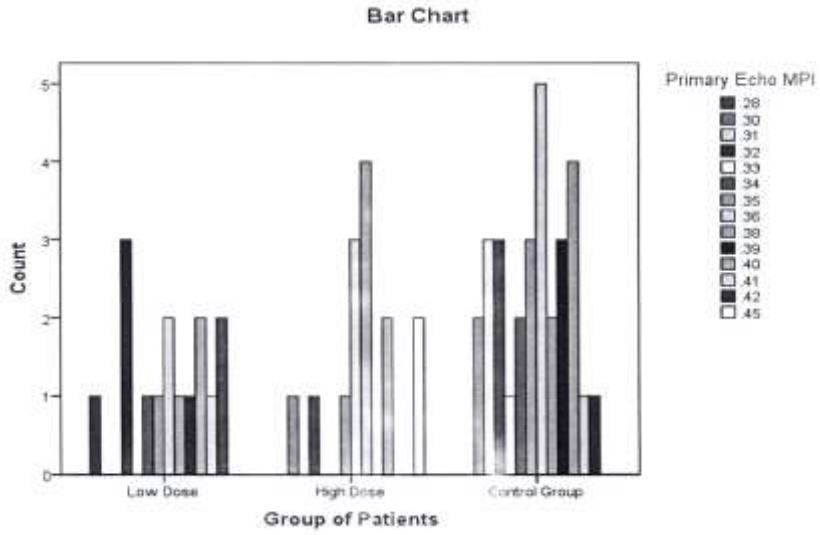

Figure 2: The initial numerical changes in the MPI index before chemotherapy

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Discussion

The anthracyclines are a potent class of chemotherapy agents used widely in the treatment of childhood cancers. Cardiac toxicity is one of the most important known side effects of anthracycline for which echocardiography is a widely used method to monitor heart function during and after anthracycline treatment(4).

This study aimed to evaluate the changes in Tei-Index in patients with malignancy treated with an anthracycline. The results of this study showed that the mean index in the groups receiving low dose and high dose of anthracycline compared to the control group in addition to their initial echo was increased. But the regimen dosage made no significant difference.

No significant correlation was found between the changes in the mean EF and treatment; in the three groups. In a study conducted by Rohde et al., the mean of Tei index was not accurate in predicting the systolic dysfunction at baseline. Some studies have shown that the Tei index has been confirmed to predict major cardiovascular events. Left venticular systolic dysfunction has been widely regarded as the most common complication of anthracycline-induced cardiac toxicity (21-24). A study by Rohde et al. showed that the Tei index had a sensitivity of 75%, specificity of 55%, a positive predictive value of 22%, and a negative predictive value of 93% (25). This was inconsistent with the result of the current study.

In another study by Eidem et al., out of 26 children receiving anthracycline compounds, a significant increase in Tei-Index occurred before any other changes in echocardiography (25), which was consistent with the results of the current study.

In another study by Eluria et al. On 831 children treated with anthracyclines, the results showed that the risk of heart failure increased over time and was completely dose-dependent(25). In a study by Nagy et al. It was shown that children less than one-year-old had a diastolic dysfunction in their tissue doppler ultrasound following anthracyclines (26). In Xu X–Y et al. study, the MPIs in right and left ventricles following Anthracycline use increased significantly in comparison with the control group (27).

A study by Bellman et al. Showed that the Tei index was altered in patients undergoing anthracycline chemotherapy regimens for malignancies or solid tumors. It is noteworthy that no changes were observed in the right ventricle in this study. Their results showed that low-dose anticyclone administration had a significant negative effect on left ventricle performance but did not affect right ventricle performance (28).

Some studies have shown that there was a wide range of individual susceptibility to chemotherapy-induced cardiotoxicities such as Adriamycin and anthracycline. Old age seemed to be a major predictor, significantly increasing the risk of future cardiac toxicity (29).

Some studies pointed to another possible effect of tetracycline on the left ventricle and right ventricle performance as a degree of cardiac toxicity which can be related to the ventricular afterload (30).

A study by Tamer et al. showed that an early subclinical diagnosis of anthracycline cardiac toxicity could not be achieved by echo alone. Long-term side effects of anthracycline chemotherapy may be measured as a reduction in left ventricle longitudinal and circumferential strain and strain rate (31).

The study by Zhang et al, showed that the t-index associated with serum hs-c TnT levels in anthracycline-treated patients was useful for monitoring the initial cardiac toxicity induced by anthracycline therapy. The findings of this study also showed that the age of patients was an important factor in anthracycline-induced cardiac toxicity. They also stated that the Tei index seemed to be a sensitive parameter that detects

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systolic heart disorders and can be a valuable tool for assessing anthracycline-induced cardiac toxicity (32). Their results were in line with this study.

Nuclear imaging of the heart has been recognized as a sensitive indicator and for many years has been an accurate method for detecting anthracycline-induced cardiac toxicity, but compared to the Tei-index, it raised some concerns over the risks of cumulative radiation (33,34).

Several studies have shown that the Tei index assessed the severity and prognosis of cardiopulmonary diseases, such as dilated cardiomyopathy, chronic heart failure, ischemic heart disease, congenital heart disease, valvular disease, amyloidosis, and pulmonary hypertension. But the study by Senju et al. showed that Tei-index is a good indicator of early subclinical myocardial damage induced by anthracycline, but it depended on the dose of the drug(35). The current results showed the same, but in this study, there was no significant difference between groups A and B. Some studies have reported that the Tei index was a combination of systolic and diastolic parameters; sensitive criteria for identifying the cardiac side effects caused by anthracycline. Tei index shows changes in myocardial function in most treated patients (i.e., in approximately 80% of cases), even at low and moderate doses of anthracycline (36).

The results of this study suggested that children receiving anthracycline should have their Tei-index monitored before and after the treatment to determine the side effects of this drug before the onset of clinical symptoms.

Conclusion

In patients receiving anthracyclines, early detection of any abnormal findings in the myocardium can help with determining a patient's progress towards heart failure and cardiomyopathy, or whether it is indicative of any progression. This study showed that the changes in Tei-index were one of the first findings in these patients, accounting for which nudges the physician towards the possibility of cardiomyopathy in the future.

Conflict of interest

The authors declare no conflict of interest.

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