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Original Article

Cardioprotective effects of creatine phosphate sodium in elderly breast cancer patients under epirubicin adjuvant chemotherapy

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Abstract: Purpose: To study the cardioprotective effects of Creatine Phosphate Sodium for injection in elderly breast cancer patients under Epirubicin adjuvant chemotherapy. Method: 130 breast cancer patients that received Epirubicin adjuvant chemotherapy were prospectively analyzed. They were randomly divided into the research group (n=65) in which the patients were administrated Creatine Phosphate Sodium, and the control group (n=65) in which the patients received standard chemotherapy. Echocardiographic indices, C reactive protein and cTnt, during chemotherapy were compared between groups. Results: After chemotherapy, CK-MB, LDH-1 and HBDB in the research group were significantly lower than those in the control group (P<0.001) and LAS, EF, E peaks and A peaks of research group were significantly higher than those in the control group (P<0.001). After chemotherapy, the incidence of electrocardiogram abnormality in the research group was significantly lower than that in the control group. Ater 2 rounds of chemotherapy, C reactive protein levels in the research group was significantly lower than control group (P<0.001). The cTnt of the two groups increased gradually. After 1 round of chemotherapy, cTnt of the research group was significantly lower than control group (P<0.001). Conclusion: Creatine Phosphate Sodium can effectively protect the heart of elderly breast cancer patients under Epirubicin Adjuvant Chemotherapy. It is expected to become the key to improving the efficacy of chemotherapy for breast cancer.

Keywords: Creatine phosphate sodium for injection, breast cancer, epirubicin, chemotherapy, cardioprotection

Introduction

Breast cancer is one of common malignant tumors in women, and the morbidity accounts for 7%~10% in various malignant tumors [1]. According to statistics, there are more than 1.35 million new breast cancer patients every year, and the incidence is still increasing annually [2]. At present, in some densely populated countries, breast cancer has become number one killer of women and poor health, and the mortality rate has exceeded 30% [3, 4]. Due to the increasing risk, breast cancer has been the focus of disease research. At present, treatment methods for breast cancer are mainly surgery combined with chemotherapy. As a new type of anthracycline drug, Epirubicin is a widely used broad spectrum anti-tumor drug for treating breast cancer during chemotherapy [5]. However, Epirubicin has great toxicity to the heart, and the dose dependant effect is also great, so the clinical value of Epirubicin is limited [6]. As a high energy phosphate compound in human tissue, Creatine Phosphate Sodium can provide phosphate groups for ADP through action of creatine kinase (CK) [7]. Then Adenosine Tri Phosphate (ATP) is formed in the body to supplement the aerobic oxidation capacity for cells. Besides, Creatine Phosphate Sodium stabilizes the electrophysiological state of muscle fibers and ischemic cardiomyocytes by inhibiting phospholipid membranes [8, 9].

In recent years, studies have shown that Creatine Phosphate Sodium can protect myocardial tissue by improving cell energy metabolism in the patient's body, and it has been widely used in cardiovascular diseases such as heart

failure [10-12]. Studies have also shown that Creatine Phosphate Sodium can effectively improve doxorubicin (Dox)-induced cardiomyocytes injury [13]. At present, there are few studies about application of Creatine Phosphate Sodium on breast cancer chemotherapy.

Therefore, retrospective analysis was carried out on 137 breast cancer patients that received Epirubicin adjuvant chemotherapy in our hospital, to verify the application value of Creatine Phosphate Sodium further, and to provide reference and guidance for clinical diagnosis and treatment on breast cancer.

Materials and methods

General data

We included 130 patients with breast cancer who underwent doxorubicin chemotherapy in our hospital. The patients were divided into the research group (n=65) who were administrated the sodium creatine phosphate during chemotherapy, and control group (n=65) who received standard chemotherapy only. This study has been approved by the Ethics Committee of our hospital, and all the above subjects have signed informed consent.

Inclusion criteria

Clinical symptoms conformed to the conditions of diagnostic criteria for breast cancer [14]; breast cancer was diagnosed after biopsy in our hospital; after diagnosis, tumor resection and follow-up chemotherapy were carried out in our hospital; patients agreed to cooperate with medical staff in hospital; ages of patients were more than 50 years old; medical records were complete.

Exclusion criteria: Patients combined with multiple tumors; serious cardiovascular and cerebrovascular diseases; severe liver and kidney insufficiency; mental illness; surgical contraindications; recent chemoradiotherapy history; drug allergy; patients who cannot take care themselves; transferred patients.

Methods

All patients received radical breast cancer surgery in our hospital, and all surgeries were completed by senior doctors in hour hospital. Chemotherapy regimens of thr control group were as follows: postoperative chemotherapy with Epirubicin and Docetaxel was used (SFDA approval number of Docetaxel was H20093-092, and SFDA approval number of Epirubicin was H19990280. Both materials were purchased from Zhejiang HaiZheng Pharmaceutical Co. Ltd.). The first chemotherapy treatment was within 2 weeks after surgery (with 75 mg/m^2 of Docetaxel and 70 mg/m^2 of Epirubicin). Subsequent chemotherapy was carried out 21 days after the last chemotherapy (with Docetaxel 75 mg/m^2 and Epirubicin 60 mg/m^2). The chemotherapy time was 1 day, and the total chemotherapy treatment was 6 cycles. For the research group, additional Creatine Phosphate Sodium injection was used (Creatine Phosphate Sodium for injection was purchased from Haikou Qili pharmaceutical Co. Ltd, with SFDA approval number H20053430). One gram of Creatine Phosphate Sodium for injection was used each time, and it was dissolved in water for injection, 0.9% of Sodium Chloride injection and 5% of Glucose injection. After being dissolved, intravenous drip was given within 30 to 45 minutes, and intravenous injection was given 2 hours after each cycle of chemotherapy. Electrocardiogram examinations were carried out one day before chemotherapy and after all cycles of chemotherapy, and ultrasonic diagnostic instrument was used to detect heart related indexes. Two ml of venous blood was extracted before chemotherapy and 24 hours after the chemotherapy respectively, to detect C reactive protein and cardiac troponin T (cTnt).

Outcome measures

Clinical data of the two groups were as follows: Creatine phosphokinase-isoenzyme-MB (CK-MB), hydroxybutyrate dehydrogenase (HBDB) and lactate dehydrogenase (LDH-1) before and after treatment. ECG indices before and after treatment were detected as follows: ST-T, Q-T interval, T wave, QRS complex and with premature beat. Electrocardiograph CardiMax FX-8322R (Fukuda Denshi, Japan) was used to measure left ventricular diastolic diameter (LVD), Left atrial systolic diameter (LAS), left ventricular fraction shortening (FS%), left ventricular ejection fraction (EF%), E and A peaks

Table 1. Comparison of clinical data [n (%)]

	Research group (n=65)	Control group (n=65)	t or X^2	P
Age	59.15±6.74	58.24±7.05	0.752	0.453
Course of disease (d)	14.67±7.24	15.83±7.52	0.896	0.372
Body weight (KG)	61.37±10.54	62.33±11.21	0.503	0.616
LVD (mm)	49.24±5.27	50.24±5.68	1.041	0.300
LAS (mm)	33.24±4.05	33.56±4.62	0.420	0.675
FS (%)	42.16±4.68	43.69±5.10	1.782	0.077
EF (%)	72.69±3.57	72.87±4.03	0.270	0.788
E peak (cm/s)	86.67±8.06	87.14±8.54	0.323	0.748
A peak (cm/s)	75.26±5.86	76.01±5.99	0.722	0.472
cTnt	0.28±0.14	0.26±0.16	0.758	0.450
CRP	91.82±10.33	89.74±11.21	1.100	0.273
Operation time (h)	2.14±0.26	2.20±0.31	1.196	0.234
Intraoperative blood loss (mL)	421.51±51.54	435.84±52.33	1.573	0.118
Gender			0.151	0.698
Male	62 (95.38)	61 (93.85)		
Female	3 (4.62)	4 (6.15)		
Combined disease			0.290	0.590
Hypertension	27 (41.54)	24 (3.92)		
Diabetes	38 (58.46)	41 (63.08)		
Smoking			0.493	0.482
Yes	36 (55.38)	32 (49.23)		
No	29 (44.62)	33 (50.77)		
Movement			0.173	0.677
Yes	14 (21.54)	16 (24.62)		
No	51 (78.46)	49 (75.38)		
Living Environment			0.182	0.670
Town	52 (80.00)	50 (76.92)		
Rural	13 (20.00)	15 (23.08)		
Pathological staging			0.352	0.553
I~II	49 (75.38)	46 (70.00)		
III~IV	16 (24.63)	19 (29.23)		

(cm/s). C reactive protein and Cardiac troponin T (cTnt) were detected during chemotherapy as well.

Statistical method

SPSS 24.0 statistical software was used (from Shanghai YuChuang Network Technology Co. Ltd) to analyze the data. Counting data were expressed in the form of (rate), such as changes in electrocardiogram, and Chi-square test was used for comparison between groups. Measurement data were expressed in the form of (mean ± standard deviation), such as C reactive protein and cTnt, and independent t test was used for comparison between groups. Repeated measures ANOVA was used for comparison at multiple time points. The difference was statistically significant if P<0.05.

Results

Comparison of general data

There was no significant difference in age, course of disease, weight, heart ultrasound detection related indicators, operation time, intraoperative blood loss, sexual distinction, smoking, exercise habits and pathological stage, etc. between the two groups (P>0.050) (**Table 1**).

Comparison of myocardial enzymes levels

By comparing the indexes of change in myocardial enzymes before and after chemotherapy, there was no significant difference in CK-MB, LDH-1 and HBDB between two groups (P>0.050); after chemotherapy, the three indexes of the two groups were both significantly lower than the indexes before chemotherapy (P< 0.001), but CK-MB, LDH-1 and HBDB of the research group were significantly lower than control group (P<0.001) (**Table 2**).

Comparison of echocardiography indicators

Before chemotherapy, there was no significant difference in echocardiography indices between two groups (P>0.050). After chemotherapy, echocardiography indices of both groups decreased significantly (P<0.001), but there were no significant differences between research group and control group in LVD, FS (P>0.050). LAS, EF, the peak value of E and the peak value of A of the research group were sig-

Table 2. Comparison of myocardial enzyme changes before and after treatment

		Research group (n=65)	Control group (n=65)	t	P
Before chemotherapy	CK-MB	76.15±1.52	76.24±2.01	0.256	0.798
	LDH-1	187.62±23.65	194.34±25.63	1.554	0.123
	HBDB	321.75±35.65	318.25±36.14	0.008	0.994
After chemotherapy	CK-MB	36.67±1.84*	65.63±3.84*	54.832	<0.001
	LDH-1	54.69±11.57*	105.76±26.20*	14.383	<0.001
	HBDB	109.67±21.55*	182.61±31.64*	15.360	<0.001

Remarks: *Comparison of myocardial enzyme indicators with same group before treatment. P<0.001.

Table 3. Comparison of various indicators of cardiac ultrasound before and after chemotherapy

		Research group (n=65)	Control group (n=65)	t	P
Before chemotherapy	LVD (mm)	49.24±5.27	50.24±5.68	1.041	0.300
	LAS (mm)	48.04±5.65	49.35±6.03	1.278	0.204
	FS (%)	42.16±4.68	43.69±5.10	1.782	0.077
	EF (%)	72.69±3.57	72.87±4.03	0.270	0.788
	E peak (cm/s)	86.67±8.06	87.14±8.54	0.323	0.748
	A peak (cm/s)	75.26±5.86	76.01±5.99	0.722	0.472
After chemotherapy	LVD (mm)	41.62±3.54*	41.63±3.22*	0.017	0.987
	LAS (mm)	26.84±2.14*	25.14±2.30*	4.363	<0.001
	FS (%)	34.62±2.81*	35.07±3.04*	0.876	0.383
	EF (%)	64.67±2.96*	59.64±4.85*	7.137	<0.001
	E peak (cm/s)	76.68±6.04*	70.59±6.57*	5.502	<0.001
	A peak (cm/s)	67.66±5.84*	62.15±6.21*	5.211	<0.001

Remarks: *Comparison of UCG with same group before chemotherapy. P<0.001.

Table 4. Comparison of ECG indicators before and after chemotherapy [n (%)]

		Research group (n=65)	Control group (n=65)	X^2	P
Before chemotherapy	ST-T change	7 (10.77)	7 (10.77)	0.000	1.000
	Q-T interval extension	6 (9.23)	7 (10.77)	0.085	0.770
	T wave low or inverted	10 (15.38)	8 (12.31)	0.258	0.612
	QRS low voltage	8 (12.31)	9 (13.85)	0.068	0.795
	Premature beat	5 (7.69)	4 (6.15)	0.119	0.730
Total		36 (55.38)	35 (53.85)	0.031	0.860
After chemotherapy	ST-T change	2 (3.08)	4 (6.15)	0.699	0.403
	Q-T interval extension	1 (1.54)	4 (6.15)	1.872	0.171
	T wave low or inverted	3 (4.62)	3 (4.62)	0.000	1.000
	QRS low voltage	3 (4.62)	7 (10.77)	1.733	0.188
	Premature beat	2 (3.08)	3 (4.62)	0.208	0.648
Total		11 (16.92)	21 (32.31)	4.145	0.042

Remarks: *Comparison of ECG with same group before chemotherapy. P<0.001.

nificantly higher than control group (P<0.001) (**Table 3**).

Comparison of ECG abnormalities

There was no significant difference in ECG abnormalities between the two groups before chemotherapy (P>0.050). After chemotherapy, ECG abnormalities in both groups were significantly lower than before chemotherapy (P< 0.001). After chemotherapy, ECG abnormalities of the research group was 16.44%, and it was significantly lower than 32.81% of control group, and P=0.042 (**Table 4**).

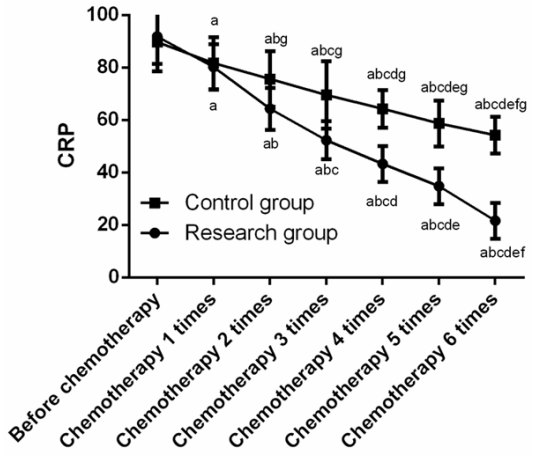

Figure 1. Change of C Reactive Protein during Chemotherapy. a-results compared with C reactive protein of same group before chemotherapy, P<0.001; b-results compared with C reactive protein of same group after 1 round of chemotherapy, P<0.001; c-results compared with C reactive protein of same group after 2 rounds of chemotherapy, P<0.001; d-results compared with C reactive protein of same group after 3 rounds of chemotherapy, P<0.001; d-results compared with C reactive protein of same group after 4 rounds of chemotherapy, P<0.001; e-results compared with C reactive protein of same group after 5 rounds of chemotherapy, P<0.001; f-results compared with C reactive protein of research group at the same time point, P<0.001.

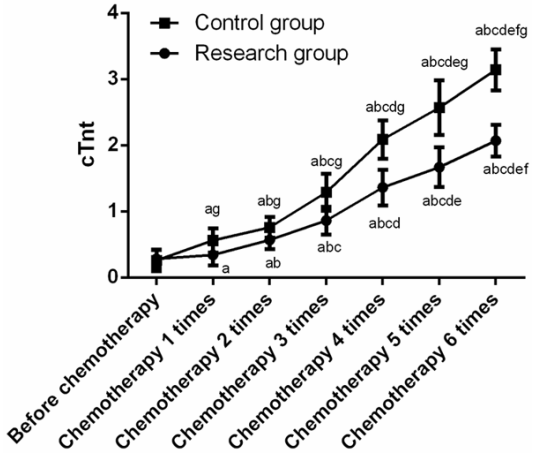

Figure 2. Change of cTnt during Chemotherapy. a-results compared with cTnt of same group before chemotherapy, P<0.001; b-results compared with cTnt of same group after 1 round of chemotherapy, P<0.001; c-results compared with cTnt of same group after 2 rounds of chemotherapy, P<0.001; d-results compared with cTnt of same group after 3 rounds of chemotherapy, P<0.001; d-results compared with cTnt of same group after 4 rounds of chemotherapy, P<0.001; e-results compared with cTnt of same group after 5 rounds of chemotherapy, P<0.001; f-results compared with cTnt of research group at the same time point, P<0.001.

Comparison of C reactive protein levels

Before chemotherapy and after one treatment of chemotherapy, there was no significant difference in C reactive protein between the two groups (P>0.050). After the second treatment of chemotherapy, C reactive protein of the research group was significantly lower than control group (P<0.001). In both groups, C reactive protein was the highest before chemotherapy, and it decreased after 1 treatment of chemotherapy, and it reached the lowest value after 6 treatments of chemotherapy (P< 0.001) (**Figure 1**).

Comparison of cTnt levels

There was no significant difference in cTnt between the two groups before chemotherapy (P>0.050). After one treatmente of chemotherapy, cTnt of the research group was significantly lower than control group (P<0.001). In both groups, the cTnt value was the lowest before chemotherapy, and it increased after one treatment of chemotherapy, and it reached the highest value after 6 treatments of chemotherapy (P<0.001) (**Figure 2**).

Discussion

Breast cancer is one of the malignant tumors with highest incidence in clinic especially in women. As an antitumor drug, Epirubicin has been widely used in clinic [15]. With extensive use of Epirubicin, cardiotoxicity injury in patients of anthracyclines has become a hot research in clinic [16]. During chemotherapy, Epirubicin can damage the myocardial function of patients by necrosis of myocardial cells and destroying normal muscle segment structure [17]. Studies have also shown that Epirubicin can increase the process of oxidative stress in patients and disturb calcium transport, and the balance of mitochondrial redox function will be eventually destroyed [18]. Myocardial injury usually begins one week after treatment, therefore, how to effectively solve the toxic effects of Epirubicin during chemotherapy is one of the keys to curing patients [19]. Creatine Phosphate Sodium is a compound that provides exogenous energy for cardiomyocytes, and its main function is to provide energy for cell

metabolism [20]. Creatine Phosphate Sodium has the characteristics of safety, high efficiency and less side effects. Creatine Phosphate Sodium can provide energy for adenosine triphosphate after methylation in liver with guanidine acetic acid formed by glycine and arginine. At present, it is mainly used in treatment of heart failure and heart surgery [20]. At present, in the process of breast cancer chemotherapy, there is little research literature for reference. Through experimental analysis, the purpose of this study is to prove that Creatine Phosphate Sodium has protective effects for myocardial function during chemotherapy with Epirubicin on breast cancer.

After chemotherapy, the results of this experiment showed that CK-MB, LDH-1 and HBDB of the research group were significantly lower than control group, and it indicated that Creatine Phosphate Sodium can significantly improve cardiac enzymes function of breast cancer patients. The electrocardiogram results of the two groups showed that all indexes in the research group were significantly better than control group, and it further proved the protective effect of Creatine Phosphate Sodium on damaged myocardium. The main reason may be that Creatine Phosphate Sodium has a strong ability for myocardial cells to maintain high energy phosphoric acid state. Meanwhile, Creatine Phosphate Sodium can also inhibit synthetic ability of PRPP, so that the synthesis of adenine nucleotide is increased [21]. During Epirubicin chemotherapy, cardiotoxicity invades, while Creatine Phosphate Sodium protects fibrous membranes through inhibiting the action of phospholipase [22], so the toxic effect of Epirubicin was resisted. The resistance effect of Creatine Phosphate Sodium on free radical peroxidation damage can also form a protective barrier for the internal environment of myocardial tissue, and it prevents secondary damage from oxidative stress response of Epirubicin. CTnt is a serum marker for detecting myocardial injury in clinic [23]. C reactive protein is the most representative inflammatory factor [24]. By detecting changes of patients during chemotherapy, it is known that cTnt and C reactive protein of the two groups had significant differences before the second chemotherapy treatment. cTnt and C reactive protein of the two groups increased during the chemotherapy process, but the rising degree of the research group was significantly lower than control group. It indicated that the protective effect of Creatine Phosphate Sodium on myocardial injury is very significant. The results are consistent with the research results of Wang [13], and it corroborated the results of this experiment. At present, the clinical use of Creatine Phosphate Sodium is still limited to treatment of heart diseases. This study has proved the application value of Creatine Phosphate Sodium in the process of Epirubicin chemotherapy for breast cancer, and it may be a key point of cancer therapy in the future. However, due to the limited experimental conditions, there are still some inadequacies of this experiment. For example, the cardinal number of research objectives was small, and it was unable to carry out statistical analysis of big data. Besides, subjects were relatively few, and age span was small, and grouping was not elaborate. We cannot eliminate the possible differences in application of Creatine Phosphate Sodium in breast cancer patients with different courses of disease, different stages and different ages. We will follow up subjects for a longer period of time, and we will constantly improve our experiments to obtain the best results.

In conclusion, Creatine Phosphate Sodium can effectively protect against myocardial function of elderly breast cancer patients during Epirubicin chemotherapy, and it is expected to become the key to improve chemotherapy efficacy for breast cancer.

Disclosure of conflict of interest

None.

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