THE EFFECTS OF CHRONIC ADMINISTRATION OF CISPLATIN ON OXIDATIVE STRESS IN THE ISOLATED RAT HEART

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EFEKTI HRONIČNE PRIMENE CISPLATINE NA OKSIDACIONI STRES IZOLOVANOG SRCA PACOVA

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ABSTRACT

Taken into consideration that molecular and cellular mechanisms involved in cardiotoxicity are still not clear the aim of this study was to compare the production of oxidative stress parameters in the isolated rat heart between animals chronically treated with cisplatin and saline. The hearts of male Wistar albino rats (n = 24, 12 per group, age 8 weeks, body mass 250±50 g) were excised and perfused according to the Langendorff technique at gradually increased coronary perfusion pressures (40-120 cmH_2O). We followed the production of superoxide anion radicals, hydrogen peroxide, and nitrites and also index of lipid peroxidation during the changes of coronary perfusion pressure (CPP) (from 40 to 120 cm H_2O) in coronary venous effluent. Modifications CPP were performed in order to determined if oxidative stress is involved in coronary endothelium response in conditions of hypoxia (lower than 60 cm H_2O) and hyperoxia (higher than 80 cm H_2O).

Based on the results of this research we can conclude that with enhancement of CPP the values of oxidative stress statistically increased. However, this increment is more prominent in control group as a result of preserved endothelium and its more powerful response to hyperoxia. On the other hand, damaged endothelium of cisplatin-treated animals had weaker response to hyperoxia, and also lower antioxidant capacity.

Keywords: *cisplatin, change of coronary perfusion pressure, isolated rat heart, oxidative stress*

SAŽETAK

Uzimajući u obzir činjenicu da molekulski i ćelijski mehanizmi nastanka kardiotoksičnosti nisu u potpunosti poznati cilj ovog istraživanja bio je da se uporedi nastajanje i oslobađanje parametara oksidacionog stresa kod izolovanog srca pacova između grupa tretiranih cisplatinom i fiziološkim rastvorom. Srca Wistar albino pacova (n = 24, 12 po grupi, starosti 8 nedelja, telesne mase 250±50 g) su izolovana i perfundovana po Langendorff tehnici pri rastućem koronarnom perfuzionom pritisku. Praćena je produkcija superoksid anjon radikala, vodonik-peroksida, nitrita i indeksa lipidne peroksidacije pri promeni koronarnog perfuzionog pritiska (CPP) (od 40 do 120 cm H_2O). Promena CPP je sprovedena sa ciljem da se utvrdi da li je oksidacioni stress uključen u odgovor koronarnog endotela u uslovima hipoksije (pritisci niži od 60 cm H_2O) i hiperoksije (pritisci viši od 80 cm H_2O).

Na osnovu rezultata ove studije možemo zaključiti da sa porastom vrednosti CPP vrednosti oksidacionog stresa statistički značajno rastu. Međutim ovo povećanje je izraženije u kontrolnoj grupi usled bolje očuvanosti endotela i njegovog jačeg odgovora na hiperoksiju. Sa druge strane endotel kod životinja tretiranih cisplatinom je oštećen i ima lošiju sposobnost da odgovori na hiperoksiju kao i smanjen antioksidacioni kapacitet.

Ključne reči: *cisplatina, promena koronarnog perfuzionog pritiska, izolovano srce pacova, oksidacioni stress*

ABBREVIATIONS

CK - creatine kinaze
CPP - coronary perfusion pressure
cTnI - Cardiac Troponin I
GSH - glutathione
H_2O_2 - hydrogen peroxide
NADPH - nicotinamide adenine dinucleotide phosphate hydrogen
NO - nitric oxide
NO_2^- - nitrites
Nrf2 - nuclear factor erythroid 2-related factor 2
$O_2^{\cdot-}$ - superoxide anion radical
ROS - Reactive oxygen species
SOD - superoxide dismutase
TBARS - thiobarbituric acid reactive substances

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INTRODUCTION

Platinum chemotherapeutic agents are the principal therapeutics in the treatment of various cancers, including ovarian, testicular, and bladder cancer. Cis-diamminedichloroplatinum(II) (cisplatin), as the parent compound, is one of the most-used and the most effective platinum-derived agents in treatment of malignancies. Cisplatin binds to DNA, forming inter and intra-strand cross-links, resulting in defective DNA templates, arrest of DNA synthesis in rapidly dividing cancer cells (1). However, its therapeutic use is limited by cellular resistance and severe side-effects in normal tissues (2-4). In the literature the most commonly mentioned side-effects are nephrotoxicity, ototoxicity and peripheral neuropathy (5-7). Although not often cardiotoxicity is very serious and difficult side effect associated with cisplatin use. Acute vascular events were recorded during the drug administration, and may be associated with an increased long-term cardiovascular risk (8, 9). According to literature data cardiovascular events associated with cisplatin treatment are electrocardiographic changes, arrhythmias, myocarditis, cardiomyopathy and congestive heart failure (10). Toxic effects of cisplatin may be due to inhibition of protein synthesis, DNA damage, peroxidation of the cell membrane, mitochondrial dysfunction (11).

The mechanism of antitumor effects of cisplatin is almost fully known, but molecular and cellular mechanisms involved in cardiotoxicity are still not clear. Some experimental and clinical studies support the opinion that an increase of biomarkers of oxidative stress is involved in cisplatin's cardiotoxicity (12). It's well known that toxicity in numerous tissues and organ system such as liver, kidney, ear, and cardiovascular and nervous systems, induced by drugs is mediated with oxidative stress. There are a lot of evidences that oxidative stress had important role in acute kidney injury induced by cisplatin usage. Reactive oxygen species (ROS) directly act on cell components, including lipids, proteins and DNA, destroying their structure (13, 14).

The aim of this study was to compare the production of oxidative stress parameters in the isolated rat heart in animals chronically treated with cisplatin. On this way, we wanted to assess the influence of this antitumor drug on ROS generation and potential oxidative damages. Modifications of coronary perfusion pressure were performed in order to determined if oxidative stress is involved in coronary endothelium response in conditions of hypoxia (lower than 60 cm H_2O) and hyperoxia (higher than 80 cm H_2O).

MATERIAL AND METHODS

Experimental protocol

This was chronic experimental study, conducted on male Wistar albino rats, (body weight 250±50g) aged 8 weeks. The animals were divided into two groups (12 animals per group): experimental and control. Experimental group was treated with cisplatin for 4 weeks (4mg/kg body weight, once a week, intra-peritonealy). Control group was treated with saline for 4 weeks, once week, intra-peritonealy. After the four weeks of experimental protocol, the animals were anasthetized with ketamine (10mg/kg) and xylazine (5mg/kg) and then euthanized via cervical dislocation (Schedule 1 of the Animals/Scientific Procedures, Act 1986, UK).

All research procedures were carried out in accordance with European Directive for welfare of Laboratory animals N^0 86/609 EEC and principles of Good Laboratory Practice (GLP), and approved by Ethical committee of the Faculty of Medical Science.

Isolated rat heart preparation

Following a quick thoracotomy and rapid cardiac arrest by superfusion with ice-cold isotonic saline, the hearts were promptly excised and attached to the Langendorff apparatus via aortic cannulation and then were retrogradely perfused under a constant perfusion pressure of 70 cmH_2O with complex Krebs-Henseleit solution. The composition of the Krebs-Henseleit buffer (perfusion medium) was as follows (in mmol/l): NaCl (118); KCl (4.7); $CaCl_2 \times 2H_2O$ (2.5); $MgSO_4 \times 7H_2O$ (1.7); $NaHCO_3$ (25); KH_2PO_4 (1.2); glucose (5.5). It was equilibrated with gas mixture (5% CO_2-95% O_2) at 37°C, (pH 7.4).

Perfusion of the isolated rat heart

After 30 minutes period of stabilization at constant CPP of 70 cm H_2O experimental protocol was conducted. The experimental protocol implied changing of perfusion pressure from 40 cm to 120 cm. The isolated hearts were stabilized at each perfusion pressure and then the samples of coronary venous effluent were collected for biochemical analyses. The recorded values during the first measure at each perfusion pressure (40, 60, 80, 100 and 120 cm H_2O) were marked as values of control conditions, while the second measure of parameters at each coronary perfusion pressure were marked as experimental conditions.

Biochemical assays

Index of lipid peroxidation (Thiobarbituric Acid Reactive Substances – TBARS)

The degree of lipid peroxidation in coronary venous effluent was estimated by measuring of thiobarbituric acid reactive substances (TBARS) using 1 % thiobarbituric acid (TBA) in 0.05 sodium hydroxide (NaOH) incubated with coronary effluent at 100 °C for 15 minutes and read at 530 nm. Krebs-Hensenleit solution was used as a blank probe (15).

Nitrite determination

Nitric oxide was assessed as nitrite and quantified by the spectrophometric method using the *Griess*-reagent. 0.5 ml of perfusate was precipitated with 200 µl of 30%

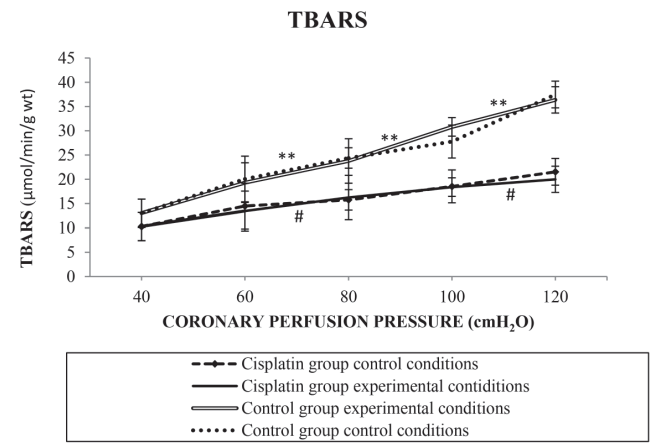

Figure 1 The effects of chronic adiministration of cisplatin and saline on index of lipid peroxidation in coronary venous effluent throughout changing the coronary perfusion pressure
All values are expressed as mean ± SD. Wilcoxon signed rank test were used in statistical analysis, *p* values less than 0.05 (marked with * or # depending on groups) were considered to be statistically significant and *p* values less than 0.01 (marked with ** or ## depending on groups) were considered to be statistically high significant.

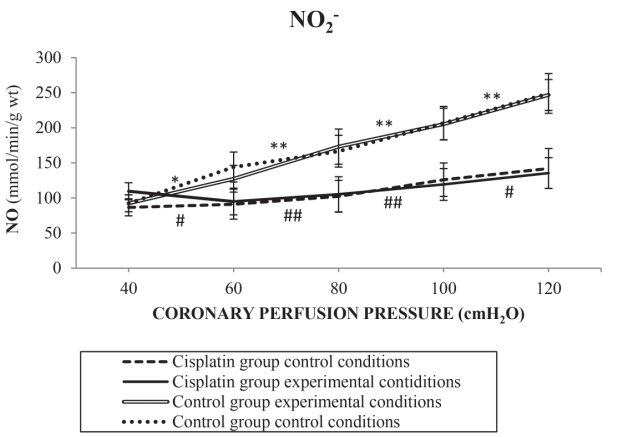

Figure 2 The effects of chronic adiministration of cisplatin and saline on production of nitrites in coronary venous effluent throughout changing the coronary perfusion pressure
All values are expressed as mean ± SD. Wilcoxon signed rank test were used in statistical analysis, *p* values less than 0.05 (marked with * or # depending on groups) were considered to be statistically significant and *p* values less than 0.01 (marked with ** or ## depending on groups) were considered to be statistically high significant.

sulfosalicylic acid, vortexed for 30 min and centrifuged at 3000 x g. Equal volumes of the supernatant and Griess's reagent, containing 1% sulfanilamide in 5% phosphoric acid/0.1% napthalene ethylenediamine-dihydrochloride was added and incubated for 10 min in the dark and read at 543 nmol/l. The nitrite levels were calculated by using sodium nitrite as a standard (16).

Superoxide determination

The level of superoxide anion radical ($O_2^{\cdot-}$) was measured using Nitro Blue Tetrazolium (NBT) reaction in TRIS-buffer with coronary venous effluent and read at 530 nm. Krebs-Hensenleit solution was used as a blank probe (17).

Hydrogen peroxide determination

The level of hydrogen peroxide (H_2O_2) was measured using phenol red oxidation with H_2O_2 from coronary venous effluent in the presence of horse-radish peroxidase and read at 610 nm (18).

Substances

All substances necessary for the preparation of Krebs-Henseleit buffer as well as Cisplatin were purchased from the company Sigma-Aldrich GmbH, Germany. For treatment of control group and dissolution of cisplatin was used saline (0.9% NaCl, Hemofarhospital Logica) comercially purchased.

Statistical Analysis

All values are expressed as mean ± SD. Wilcoxon signed rank test and Mann Whitney test were used in statistical analysis, *p* values less than 0.05 were considered to be statistically significant and *p* values less than 0.01 were considered to be statistically high significant. Wilcoxon signed rank test (for difference between related samples) was used for analyzed the difference between biochemical parameter at different coronary perfusion pressure. The Mann Whitney test was used for analyzed the difference between biochemical parameter in different groups at same coronary perfusion pressure. The statistical analysis was performed using SPSS 19.0 for Windows.

RESULTS

The effects of chronic adiministration of cisplatin and saline on TBARS values in coronary venous effluent throughout changing the coronary perfusion pressure

In a group treated with cisplatin with increase of CPP TBARS values increased, but that changes were statistically significant between 60 cm and 80 cm and also between 100 cm and 120 cm. On the other hand, in control group that increase was greater and statistically high significant (Figure 1). Comparing the effects between the groups it can be observed statistically high significant difference at higher CPP (from 80 to 120 cm, Table 1).

The effects of chronic adiministration of cisplatin and saline on production of nitrites in coronary venous effluent throughout changing the coronary perfusion pressure

In the both tested groups comparing the effects of changing CPP at production of nitrites there are statistically high significant differences (Figure 2). Also there were statistically high significant differences in production of nitrites at all examined CPP except at 40 cm between groups (Table 1).

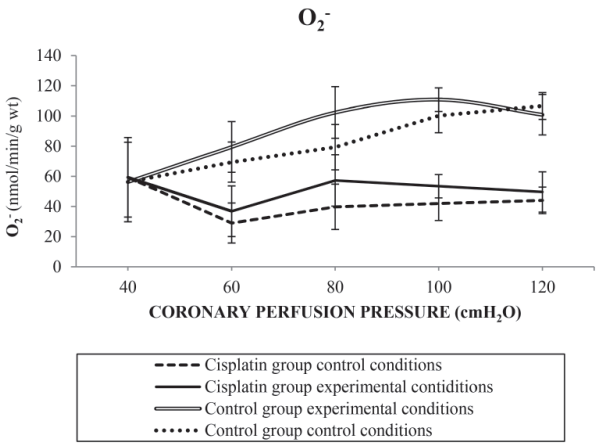

Figure 3 The effects of chronic adiministration of cisplatin and saline on production of superoxide anion radical in coronary venous effluent throughout changing the coronary perfusion pressure
All values are expressed as mean ± SD.

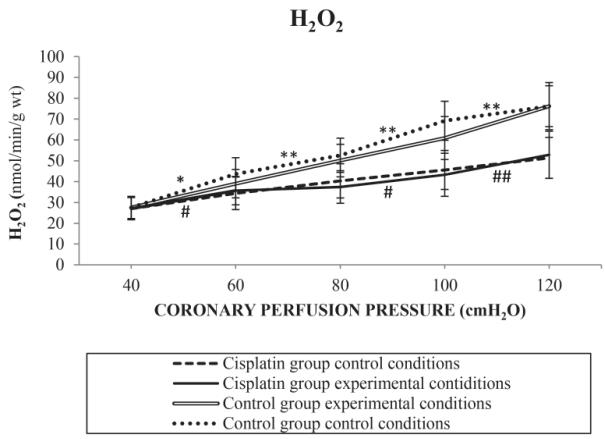

Figure 4 The effects of chronic adiministration of cisplatin and saline on production of hydrogen peroxide in coronary venous effluent throughout changing the coronary perfusion pressure
All values are expressed as mean ± SD. Wilcoxon signed rank test were used in statistical analysis, *p* values less than 0.05 (marked with * or # depending on groups) were considered to be statistically significant and *p* values less than 0.01 (marked with ** or ## depending on groups) were considered to be statistically high significant.

The effects of chronic adiministration of cisplatin and saline on production of superoxide anion radical in coronary venous effluent throughout changing the coronary perfusion pressure

There were no statistically significant changes in production of superoxide anion radical during the CPP changes in both groups (Figure 3). Also there was no statistically significant difference in production of superoxide anion radical between groups at same CPP values (Table 1).

The effects of chronic adiministration of cisplatin and saline on production of hydrogen peroxide in coronary venous effluent throughout changing the coronary perfusion pressure

In a group chronically treated with cisplatin statistically significant changes in production of hydrogen peroxide were existed. With an increase of CPP the production of hydrogen peroxide rised. On the other hand, in control group, statistically high significant changes in production of hydrogen peroxide were recorded with increase of CPP (Figure 4). Comparing the effects of changing of coronary perfusion pressure in these groups, we can notice that there were statistically high significant differences in production of hydrogen peroxide at higher CPP (from 80 to 120 cm, Table 1).

DISCUSSION

Previously was mentioned that cisplatin usage is associated with a numerous side effects, whereby one of the most commonly and detail characterized is nephrotoxicity. Cisplatin activates glucose-6-phosphate dehydrogenase and hemoxinase, which increase free radical production and decrease the production of antioxidative enzymes. It increases concentrations of calcium into cells, which leads to activation of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase and stimulating of ROS production. There are evidence that cisplatin-treated animals have increased levels of superoxide anion radical (O_2^-), hydrogen peroxide (H_2O_2) (19). Free radicals, formed in this way, induced the damaging of lipid components in cell membrane by peroxidation and mitochondrial dysfunction (20, 21). Beside the increment of ROS production, the achievement of reactive nitrogen species was observed in

Table 1. Comparison of oxidative stress between cisplatin and control groups at different coronary perfusion pressure

Control group vs. Cisplatin group					
	40 CPP	**60 CPP**	**80 CPP**	**100 CPP**	**120 CPP**
Index of lipid peroxidation	> 0.05	0.020	0.004	0.001	0.000
Nitric oxide	> 0.05	0.000	0.000	0.000	0.000
Superoxide anion radical	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
Hydrogen peroxide	> 0.05	> 0.05	0.001	0.000	0.000

Mann Whitney test were used in statistical analysis, p values less than 0.05 were considered to be statistically significant and p values less than 0.01 were considered to be statistically high significant.

cisplatin-induced nephrotoxicity. Concentration of nitric oxide and peroxynitrite in kidney were increased in animals treated with cisplatin. Peroxynitrite, which is generated by the reaction of nitric oxide (NO) with superoxide, is a strong oxidant that can damage subcellular organelles, membranes. Peroxynitrite induced changing of protein structure and function, lipid peroxidation, chemical cleavage of DNA and reduction in cellular defenses by oxidation of thiol pools. Aforementioned claims can serve as evidence that peroxynitrites are involved in cisplatin-induced nephrotoxicity. On the other hand it is still controversial if nitric oxide had toxic role in kidney injury (22, 23).

The fact that production of ROS is fundamental mechanism in nephrotoxicity, were rised attention of scientists to correlate production of ROS with occurrence of cardiotoxicity. There are a few papers which describe that concomitant use of antioxidants with cisplatin can reduce cardiotoxicity (24-26). Rosic and colleagues assessed the protective effects of N-acetylcysteine (NAC) on cisplatin-induced changes in myocardium (27). Results of their study showed that NAC coadministration with cisplatin mitigated cisplatin-induced disturbances of cardiodynamic and oxidative stress parameters, as well as morphological changes in myocardium and coronary blood vessels, by reduction of oxidative stress. As a results of increase production of ROS transcription and translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) into the nucleus occurred. Activation of this factor induces the expression of many genes involved in synthesis of different antioxidative enzymes and heme oxygenase-1, which are important to protect the cells against oxidative stress and inflammation. Increased production of ROS can lead to increment in the expression of nuclear factor kappa B and production of pro-inflammatory cytokines such as tumor necrosis factor-alpha, chemokines such as monocyte chemoattractant protein-1. All these factors induce apoptosis and consequently myocardial injury (28, 29).

Results of our study showed that in both groups increment of coronary perfusion pressure values causes increase in production of oxidative stress biomarkers (Figure 1-4). The values of superoxide anion radical enhanced with increase of CPP, but that changes between two different CPP were not statistically significant (Figure 3). Also when we compare the values of superoxide anion radical between control and cisplatin group we didn't get any statistically significant difference (Table 1). On the other hand, the values of all other examined biomarkers of oxidative stress have statistically significant increased with enhancement of CPP (Figure 1, 2, 4) in both groups. Likewise, there was statistically significant difference in these parameters between groups. Based on the results of this study (Table 1) we can observe that there is no difference in production of oxidative stress biomarkers in conditions of hypoxia between groups.

Two groups of authors showed that animals treated with saline had greater levels of reduced glutathione and superoxide dismutase in heart tissue, than animals treated with cisplatin. These results demonstrated that animals treated with cisplatin had lower antioxidant capacity than animals treated with saline. In accordance to this we can assume that in our study animals treated for 4 weeks with cisplatin had relieved capacity for struggle with free radicals. So despite the fact that in coronary effluent of control group levels of free radical were higher, antioxidant capacity of these isolated hearts is preserved, and damages induced by changes of CPP will be lower than in cisplatin group. Also these authors confirm that administration of single dose of cisplatin induced increase of markers of heart injury, such as: levels of LDH and creatine kinaze (CK), cardiac troponin I (cTnI) in serum, as well as cardiac CK-MB index and CK-MB activities (24, 30). El-Sawalhi and coworkers also compare the effects of administration of cisplatin and saline on antioxidant capacity. These researchers found that administration of cisplatin induced a significant decrease of catalase and gluthatione peroxidase activity in postmitochondrial and mitochondrial fractions of heart tissue (25). Cardiac tissue generally had very low level of antioxidant enzymes such as superoxide dismutase (SOD) and catalase. Additional decreased of SOD activity in cisplatin-treated group can be explained by losing of copper and zinc which are essential for activity of this enzyme (31). On the other hand cisplatin had a great affinity to sulfur contained into glutathione (GSH), so conjucation of GSH by cisplatin caused depletion of GSH and decrease of redox state. Also the reduction of GSH may be explained by decrease activity of glutathione reductase induced by direct attack of cisplatin (32, 33). El-Sawalhi with coworkers in their research also showed that treatment with cisplatin induced increase of NADPH oxidase activity (25). NADPH oxidase is a major source of endoplasmic reticulum stress, and it be reported that plays an essential role in cisplatin-mediated ROS generation. So NADPH could initiate oxidative stress at early stages of cardiotoxicity and together with other enzymes acts synergistically to augment of oxidative stress (34).

Based on the results of this research we can conclude that with enhancement of coronary perfusion pressure the values of oxidative stress statistically significant increase. However, this increment is more present in control group as a result of preserved endothelium and its more powerful response to hyperoxia. On the other hand damaged endothelium of cisplatin-treated animals had weaker response to hyperoxia, and also lower antioxidant capacity. Finding of present study help in understanding of connection between oxidative stress and cisplatin usage, and thus elucidate molecular interactions involved in its mechanisms of action.

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