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Original Research Article

Effects of Vitamin D On Cisplatin Induced Heart and Lung Toxicity in Albino Rat

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ABSTRACT

Background: While Cisplatin (CP) is a powerful DNA alkylating agent used to treat many malignancies, its clinical use is linked to a number of negative side effects. It has been proposed that vitamin D can shield biological systems against harm caused by CP. The current study's objective was to look into how vitamin D protects the rat heart and lung against cisplatin-induced damage.

Material and methods: Thirty adult male Albino rats; 180–220 g body weight were allocated into 3 groups; Group I (n=10) receiving saline, Group II (n=10); rats receiving CP (single dose of 6.5 mg/kg intraperitoneal) and Group III (n=10); receiving CP and 50 ng/kg/day alfacalcidol.

Results: Alterations included a significant increase in malondialdehyde (MDA) level in the CP group compared with the other groups (p value for comparing between control and each other group, statistically significant at $p \leq 0.05$). Histopathologically, CP induced severe changes were observed. However, the CP-induced disturbances significantly improved by treatment with Vitamin D.

Conclusion: According to this study, CP treatment significantly harmed rats' hearts and lungs; however, treatment with vitamin D significantly lessened these harms.

Keywords: Cisplatin, Immunohistochemical, Vitamin D, Malondialdehyde, Oxidative stress.

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INTRODUCTION

The widely used chemotherapy drug cisplatin (CP) is effective against a wide range of solid tumours, including small cell lung cancer, testicular, ovarian, head and neck, gastric, esophageal, and urinary bladder cancer [1-3]. It is a chelating anticancer that primarily causes cisplatin-DNA crosslinks, which result in cytotoxic lesions in malignancies, to provide its anticancer activity [4].

Nevertheless, despite its effectiveness, serious side effects severely restrict its usage in

clinical oncology. These include cardiotoxicity, ototoxicity, nephrotoxicity, neurotoxicity, and bone marrow suppression [5]. Additionally, oxidative stress, which damages the lungs and several other tissues and organs, is one of the negative effects. During cisplatin chemotherapy, interstitial inflammation, fibrosis, structural lung damage, and other severe consequences were described [6,7].

The enhanced lipid peroxidation brought on by free oxygen radicals and the decline in antioxidant properties are the causes of these unfavorable effects of cisplatin-induced lung damage [8].

A growing body of research suggests that administering antioxidants may be useful in reducing the damage caused by cisplatin [9,10]. Although vitamin D is a protein linked to bone metabolism, a variety of other functions have recently been discovered. The active form of vitamin D, 1,25(OH)2D3 (1,25 dihydroxy vitamin D3), and vitamin D in general play significant roles in human metabolism [11]. Anti-inflammatory and anti-apoptotic effects of vitamin D therapy reduce the ischemia reperfusion damage that results from myocardial infarction [12]. Increased oxidative stress and the apoptotic process are linked to vitamin D deficiency [13]. Since there are few data, its application in preventing CP side effects has also been considered, but more research is needed. One of the key objectives is to reduce the hazardous effects of CP by developing novel agents [14].The purpose of the current investigation was to determine if vitamin D therapy may offer histopathological analysis-based protection against oxidative lung and heart damage brought on by CP.

Aim of the work: The purpose of this study is to look into the role of vitamin D in preventing lung and heart damage brought on by cisplatin.

MATERIALS AND METHODS

Materials: Chemicals: Cisplatin (Cis) was used in a 1 mg/ml intravenous infusion (Cisplatin Mylan Pharma 1 mg/ml solution à diluer pour perfusion). Alfacalcidol (ALF; a vitamin D3 analogue) (One-Alpha 2 micrograms/ml oral drops).

Experimental Animals: thirty laboratory adult male albino rats, each of 180-220 gm average weight will be obtained from the Animal house center, Faculty of Medicine, Alexandria University. The animals will be allowed to acclimatize for two weeks before experiment. The animals will be maintained under standard laboratory conditions of temperature, humidity and 12 hours light/dark cycle. First injection of cisplatin is considered as day 0.

Experiment design: Male albino rats were randomly separated into three equal groups/ ten each, the control group, group I, receiving saline (the vehicle) orally, once daily for 21 days. Group II, CP group, receiving cisplatin (single dose of 6.5 mg/kg intraperitoneal) on day 0, 7, 14 and will be sacrificed on day 21. [15,16] Group III, receiving cisplatin (single dose of 6.5 mg/kg intraperitoneal) on day 0, 7, 14 and 50 ng/kg/day alfacalcidol orally by orogastric tube starting 5 days before first dose of cisplatin till day 21. They will be sacrificed on day 21. [15,16]

Estimation of MDA: At the end of the 21 day period, the animals were then sacrified, the heart and lung tissues were removed. Malondialdehyde (MDA) levels in the heart and lung tissue homogenate were measured. The measured outcomes were presented as MDA nmol/g tissue. (Biochemistry lab, El Mowasah, Faculty of Medicine, Alexandria University)

Histopathological and immunohistochemical investigations: Heart and both lungs were harvested and immediately fixed in 10% neutral buffered formalin. Sections were then dehydrated by ascending grades of ethanol (70%, 90% and 100%). Xylene was used as a clearing agent then both soft and hard paraffin were consecutively used for embedding. Five –micron-thick sections were obtained, dewaxed in xylene then rehydrated using descending grades of ethanol (100%, 90% and 70%). Sections from both heart and lung were stained by Harris Hematoxylin & Eosin (H&E) and Masson Trichrome stain. Sections from the lung were subjected to immunohistochemical staining for p53 (Clone DO-7, ready to use, mouse monoclonal antibody, DAKO, USA) and

myeloperoxidase (clone IR511, ready to use, rabbit, polyclonal antibody, DAKO, USA), performed by DAKO Autostainer. All sections were examined under light microscope (Olympus CX23).

Statistical analysis of the data: Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. Chi-square test was applied to investigate the association between the categorical variables. Alternatively, Fisher's Exact or Monte Carlo correction test was applied when more than 20% of the cells have expected count less than 5. For continuous data, they were tested for normality by the Shapiro-Wilk test. Quantitative data were expressed as range (minimum and maximum), mean, standard deviation and median. ANOVA was used for comparing the three studied groups and followed by Post Hoc test (Tukey) for pairwise comparison. Significance of the obtained results was judged at the 5% level.

RESULTS

MDA Measurement: The changes in the MDA are shown in table 1. The MDA concentrations in the tissues were used as an index of lipid peroxidation. The MDA levels in the lung and heart tissue were significantly higher in the cisplatin-treated group when compared to control group. On the other hand, it was observed that the MDA levels in lung and heart tissue significantly decreased in cisplatin and alphacalcidol-treated rats compared to the cisplatin group. These data was consistent with the histopathological and immunohistochemical findings.

Histological and immunohistochemical findings:

In the lungs, interstitial inflammation was scored as follows: absent (score 0), mild (score 1), moderate (score 2), severe (score 3). Fibrosis was assessed by trichrome stain and was scored as follows: absent (score 0), mild (score 1), moderate (score 2), dense (score 3). Fibrocellular lesions were given a score of 3 whenever encountered.

In the heart, the severity of interstitial inflammation and fibrosis was assessed and scored as follows: Absent oedema (score 0), mild to moderate interstitial oedema (score 1), moderate to severe interstitial oedema (score 2), absent interstitial inflammation (score 0), mild to moderate chronic inflammation (score 1), moderate to severe chronic inflammation (score 2). Trichrome stain was used to assess interstitial fibrosis as follows: No fibrosis (score 0), mild (score 1), moderate (score 2), marked (score 3).

Lung: The control group showed preservation of the lung architecture without detectable fibrosis or inflammation. Immunostaining for both p53 and myeloperoxidase was negative. Group II showed an overall preservation of the pulmonary architecture with interstitial inflammation and fibrosis. Few lymphoid aggregates, alveolar damage and granulomata were noted. Inflammation ranged from score 2 in 6/10 rats (60%) and score 3 in 4/10 rats (40%). Trichrome stain revealed interstitial fibrosis in all rats with a score of 1 in 3/10 rats (30%). Score 2 in 5/10 rats (50%) and score 3 in 2/10 rats (20%). Immunostaining for p53 ranged from 0.9% to 6% with a mean of 3.14 ± 1.60. Immunostaining for myeloperoxidase ranged from 2.5% to 21% with a mean of 9.92 ± 5.50. Group III showed a notable improvement with patchy inflammation that scored 1 in 5/10 rats (50%), 2 in 4/10 rats (40%) and 3 in 1/10 rats (10%). Trichrome staining showed patchy fibrosis that scored 1 in 7/10 rats (70%) and 2 in 3/10 rats (30%). Immunostaining for p53 ranged from 0% to 0.4% with a mean of 0.27 ± 0.15. Immunostaining for myeloperoxidase ranged from 1.07% to 3.33% with a mean of 2.42 ± 0.83. (Figures 1-3), (Table 1,2).

Statistical analysis showed a significant difference among the three groups in both inflammation and fibrosis score ($p<0.001$, Monte Carlo significant test). Both inflammation and fibrosis scores were significantly different between group I and each of groups II and III ($p<0.001$, Monte Carlo significant test). However, only the inflammation score was significantly lower in group III than group II ($p<0.037$, Monte Carlo significant test), while the fibrosis score in group III was not significantly better than group II ($p=0.248$, Monte Carlo significant test). Statistical analysis also

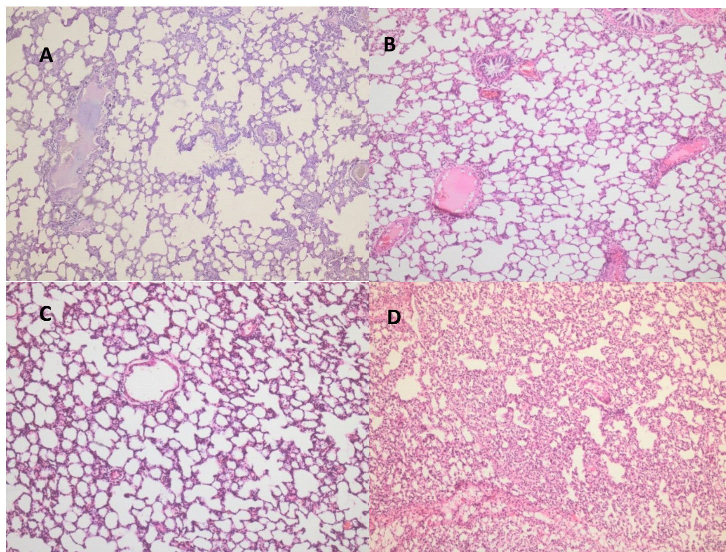

Fig. 1: Inflammation score in lung. A; score 0 in group I. B: score 1 in group III. C: score 2 in group III. D: score 3 in group II (H&E x100)

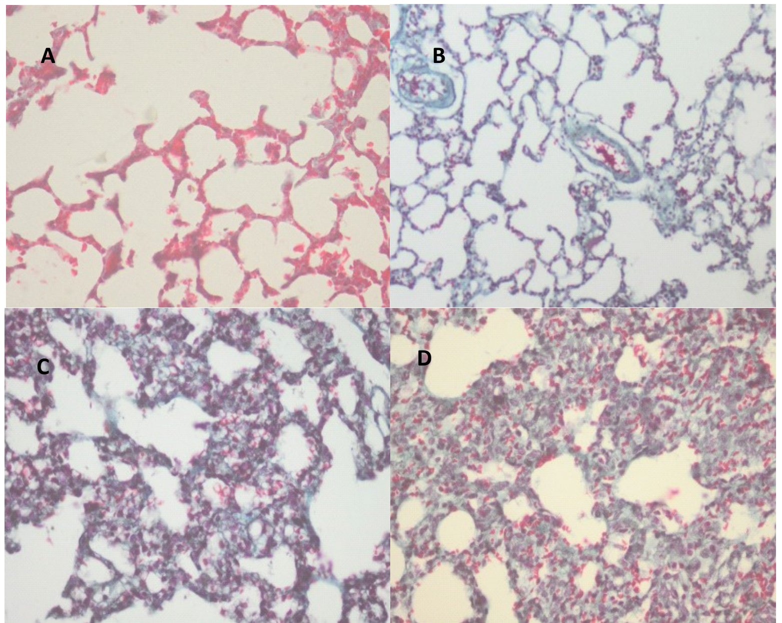

Fig. 2: Fibrosis score in lung. A; score 0 in group I. B: score 1 in group III. C: score 2 in group III. D: score 3 in group II (Trichrome x400)

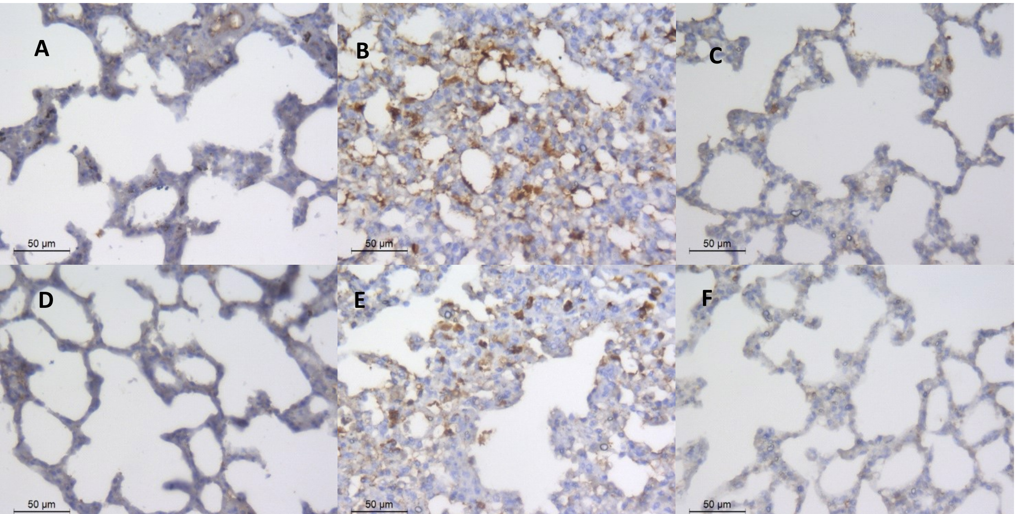

Fig. 3: Immunohistochemical staining in lung. A: p53 expression in group I. B: p53 expression in group II. C: p53 expression in group III. D: Myeloperoxidase expression in group I. E: Myeloperoxidase expression in group II. F: Myeloperoxidase expression in group III. (IHC x400).

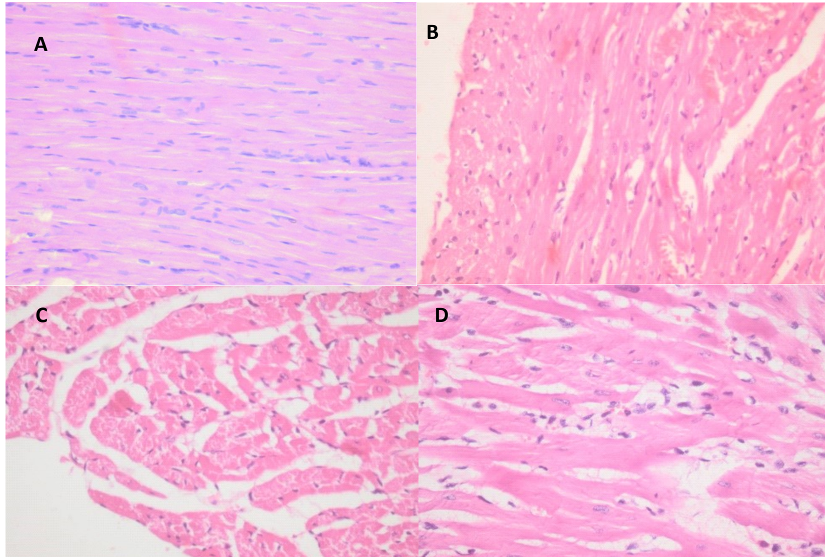

Fig. 4: Signs of heart injury. A; No oedema or inflammation in group I. B: Score 1 oedema and inflammation in group III. C: Score 2 oedema in group II with cytoplasmic fragmentation. D: Score 2 inflammation in group II (H&E x400).

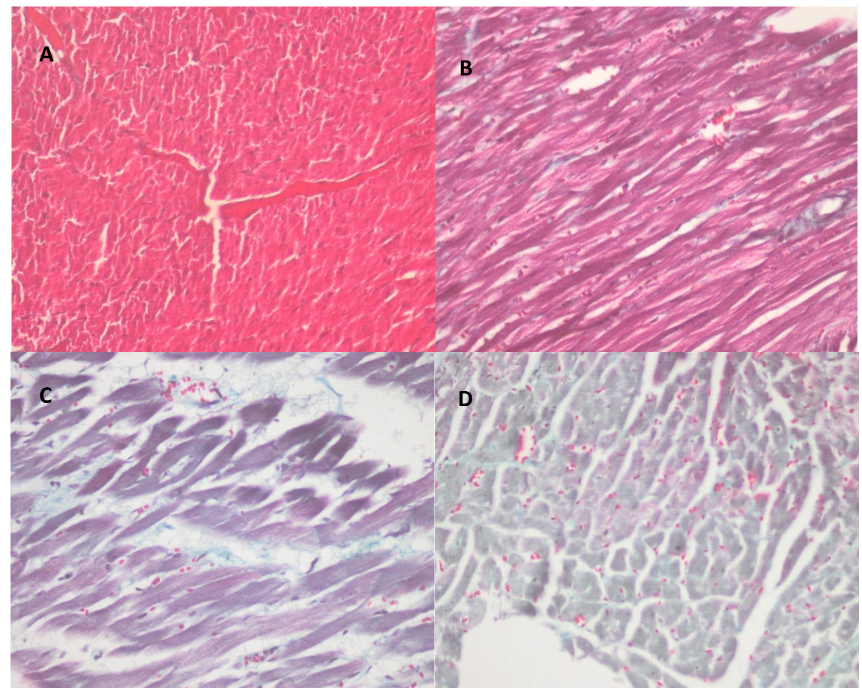

Fig. 5: Fibrosis score in heart. A: score 0 in group I. B: score 1 in group III. C: score 2 in group II. D: score 3 in group II (Trichrome x400)

showed a significant difference among the three groups in the percentage of staining for both p53 and myeloperoxidase (p<0.001, One way ANOVA test). The percentage of staining for both p53 and myeloperoxidase was significantly different between group II and each of groups I and III (p<0.001, Post Hoc test (Tukey)). However, the percentage of p53 and myeloperoxidase immunostaining was not significantly different between group I and group III (p=0.798 and p=0.231 respectively, Post Hoc test (Tukey)).(Table 1,2).

Heart: In the control group (group 1), the cardiomyocytes showed normal morphology with no detectable oedema, inflammation or signs of injury. Trichrome stain showed no interstitial fibrosis. Group II (Cisplatin) showed signs of injury including increased eosinophilia, cytoplasmic fragmentation with membrane disruption, myofiber atrophy as well as nuclear pyknosis and karyolysis. The interstitial oedema was score 1 in 3/10 rats (30%) and score 2 in 7/10 rats (70%). The interstitial chronic inflammatory infiltrate was score 1 in 3/10 rats (30%) and score 2 in 7/10 rats (70%).

Table 1: Comparison between the three studied groups according to different parameter.

	Control (n = 10)	Cisplatin (n = 10)	Alphacalcidol (n = 10)	F (p)	Sig. bet. groups.
p53 (%)					$p_1<0.001^*$,
Mean ± SD.	0 ± 0	3.14 ± 1.60	0.27 ± 0.15	35.452^*	$p_2=0.798$,
Median (Min. – Max.)	0 (0 – 0)	2.73 (0.90 – 6.0)	0.35 (0 – 0.40)	($<0.001^*$)	$p_3<0.001^*$
Myeloperoxidase (%)					$p_1<0.001^*$,
Mean ± SD.	0 ± 0	9.92 ± 5.50	2.42 ± 0.83	25.883^*	$p_2=0.231$,
Median (Min. – Max.)	0 (0 – 0)	8.29 (2.5 – 21)	2.79 (1.07 – 3.33)	($<0.001^*$)	$p_3<0.001^*$
MDA Heart in Tissue homogenate (nmol/g)					$p_1<0.001^*$,
Mean ± SD.	86.4 ± 9.2	306 ± 73.3	145 ± 22.2	65.087^*	$p_2=0.019^*$,
Median (Min. – Max.)	89 (70 – 97)	276 (229 – 442)	139 (110 – 180)	($<0.001^*$)	$p_3<0.001^*$
MDA Lung in Tissue homogenate (nmol/g)					$p_1<0.001^*$,
Mean ± SD.	68.4 ± 9.16	235 ± 43.9	107 ± 30.2	78.312^*	$p_2=0.025^*$,
Median (Min. – Max.)	68 (56 – 88)	236 (174 – 301)	112 (53 – 155)	($<0.001^*$)	$p_3<0.001^*$

SD: **Standard deviation** *: Statistically significant at $p \leq 0.05$

F: **F for One way ANOVA test**, Pairwise comparison between each 2 groups was done using **Post Hoc Test (Tukey)**

p: p value for comparing between the three studied groups

p_1: p value for comparing between **Control** and **Cisplatin**

p_2: p value for comparing between **Control** and **Alpha calcidol**

p_3: p value for comparing between **Cisplatin** and **Alpha calcidol**

Table 2: Comparison between the three studied groups according to heart and lung injury.

	Control (n = 10)	Cisplatin (n = 10)	Alphacalcidol (n = 10)	χ^2 (p)	Sig. bet. groups.
Heart injury					
Interstitial oedema					
No	10 (100%)	0 (0%)	0 (0%)	33.558^*	$^{MC}p_1<0.001^*$,
Mild to moderate	0 (0%)	3 (30%)	8 (80%)	$^{MC}p<0.001^*$	$^{MC}p_2<0.001^*$,
Moderate to severe	0 (0%)	7 (70%)	2 (20%)		$^{FE}p_3=0.070$
Inflammation					
No	10 (100%)	0 (0%)	0 (0%)	30.477^*	$^{MC}p_1<0.001^*$,
Mild to moderate	0 (0%)	3 (30%)	6 (60%)	$^{MC}p<0.001^*$	$^{MC}p_2<0.001^*$,
Moderate to severe	0 (0%)	7 (70%)	4 (40%)		$^{FE}p_3=0.370$
Fibrosis					
No	10 (100%)	0 (0%)	0 (0%)		
Mild	0 (0%)	3 (30%)	6 (60%)	29.668^*	$^{MC}p_1<0.001^*$,
Moderate	0 (0%)	3 (30%)	2 (20%)	$^{MC}p<0.001^*$	$^{MC}p_2<0.001^*$,
Severe	0 (0%)	4 (40%)	2 (20%)		$^{MC}p_3=0.512$
Lung injury					
Inflammation					
No	10 (100%)	0 (0%)	0 (0%)	34.791^*	$^{MC}p_1<0.001^*$,
Mild	0 (0%)	0 (0%)	5 (50%)	$^{MC}p<0.001^*$	$^{MC}p_2<0.001^*$,
Moderate	0 (0%)	6 (60%)	4 (40%)		$^{MC}p_3=0.037^*$
Severe	0 (0%)	4 (40%)	1 (10%)		
Fibrosis					
No	10 (100%)	0 (0%)	0 (0%)	31.971^*	$^{MC}p_1<0.001^*$,
Mild	0 (0%)	3 (30%)	7 (70%)	$^{MC}p<0.001^*$	$^{MC}p_2<0.001^*$,
Moderate	0 (0%)	5 (50%)	3 (30%)		$^{MC}p_3=0.248$
Severe	0 (0%)	2 (20%)	0 (0%)		

χ^2 : **Chi square test** FE: **Fisher Exact** MC: **Monte Carlo**

p: p value for comparing between the three studied groups

p_1: p value for comparing between **Control** and **Cisplatin**

p_2: p value for comparing between **Control** and **Alphacalcidol**

p_3: p value for comparing between **Cisplatin** and **Alphacalcidol**

*: Statistically significant at $p \leq 0.05$

The interstitial fibrosis was score 1 in 3/10 rats (30%), score 2 in 3/10 rats (30%) and score 3 in 4/10 rats (40%). Group III (Alphacalcidol) showed an overall mild histological improvement with more focal membrane disruption and nuclear changes. However, atrophy and increased eosinophilia were still noted. The interstitial oedema was score 1 in 8/10 rats (80%) and score 2 in 2/10 rats (20%). The interstitial inflammation was score 1 in 6/10 rats (60%) and score 2 in 4/10 rats (40%). The interstitial fibrosis was score 1 in 6/10 rats (60%), score 2 in 2/10 (20%) rats and score 3 in 2/10 rats (20%). (Figures 4 and 5), (Table 2).

Statistical analysis showed a significant difference among the three groups in oedema, inflammation, and fibrosis scores ($p<0.001$, Monte Carlo significant test). Oedema, inflammation, and fibrosis scores were significantly different between group I and each of groups II and III ($p<0.001$, Monte Carlo significant test). However, oedema, inflammation and fibrosis scores were not significantly better in group III than group II ($p=0.07$, $p=0.370$ and $p=0.512$, Fischer Exact significant test, Fischer Exact significant test, and Monte Carlo significant test respectively).

DISCUSSION

Cells have been shielded against the toxicity caused by cisplatin using a variety of techniques. The course of oxidative damage brought on by cisplatin may be influenced by the development of therapies to stop the production of free radicals. The majority of antioxidants are usable for this purpose. In this work, the biochemical and histological effects of vitamin D on cisplatin-induced lung and heart damage in rats were examined. The lung and heart tissues of the CP treated group had considerably higher levels of MDA, according to the results of the biochemical testing. These results are consistent with those of Afsar et al. [17], who stated that MDA and H_2O_2 levels rose in the context of lung injury caused by cisplatin. Previous studies showed that oxidative stress may be assessed using a number of markers, including MDA [18].

Oxidative stress is caused by free oxygen radicals, which oxidises the lipids in cell membranes. These subsequently create hazardous byproducts (such MDA), which exacerbate cell damage [19].

According to several researchers, there is a connection between MDA and difficulties brought on by cisplatin. [20,21] Reduced antioxidant synthesis in tissues that have been exposed to cisplatin as a result of increased ROS activity may be one explanation for the increase in MDA concentration. As a result, there may be an increase in the generation of MDA.

In noncancerous organs (such as the kidney, liver, testicles, brain, and lung), therapeutic use of cisplatin results in oxidative stress and DNA damage [22]. In the pathophysiology of cisplatin-induced oxidative damage, tissue damage may be related to a reduction in antioxidant defence mechanisms [23].

In the present investigation, interstitial inflammation and fibrosis were brought on by CP therapy in lung tissue. Alveolar destruction, a few lymphoid masses, and granulomata were also observed. According to these findings, which are in line with those of Leo et al.[24], cisplatin treatment causes structural lung damage that is accompanied by interstitial inflammation, fibrosis, and obliterative bronchiolitis. Cytotoxic medications have been linked to lung fibrosis and inflammation in clinical studies [25]. Several lung illnesses are treated with antioxidants. According to prior studies, antioxidant-based products could lessen the negative effects of anticancer medications while also increasing their efficiency [26].

Significant cardiac degenerative alterations were also found, including increased eosinophilia, cytoplasmic fragmentation with membrane rupture, myofiber atrophy, nuclear pyknosis, and karyolysis. The CP-induced cardiac damage has been labelled as degeneration, cardiomyocyte necrosis, fibrous tissue reaction, degenerative alterations, vacuolated cytoplasm, and engorgement of blood vessels in previous research [27,28]. Additionally, CP can promote the production of thromboxanes and platelet aggregation, which accelerates thrombogenesis. Patients with metastatic disease and those with known risk factors are also at an increased risk for thromboembolic events [29].

An earlier investigation demonstrated that CP can cause blatant cardiotoxicity by inducing mitochondria-mediated apoptosis [30]. As a consequence of CP metabolism, ROS is one among the primary factors in secondary cardiac lesions brought on by chemotherapy. The early event that initiates apoptosis is ROS production, which may result in lipid peroxidation and cardiomyocyte membrane degradation and ultimately cause cardiomy-ocyte apoptosis or necrosis [31].

Cardiomyocytes subjected to CP treatment had a significant increase in ROS and superoxide anion buildup, indicating that oxidative stress is intimately linked to its harmful effects [32].

Particular focus is placed on the production of ROS and their harmful effects on myocardial tissue due to the dearth of antioxidant enzymes in cardiac tissue [33].

According to Swamy et al., the production of ROS damages the myocardium and makes cell walls more permeable. Therefore, it has been hypothesised in the past that employing free radical scavengers will lessen cardiotoxicity and shield the heart from oxidative stress [34].

The goal of the current investigation was to determine whether using antioxidant products, specifically vitamin D, could shield rats from or avoid CP-induced cardiotoxicity and pulmonary toxicity. In the current investigation, elevated MDA levels in the CP-managed group guarantee the formation of lipid peroxidation.

The mitochondria's antioxidant defense system and the generation of ROS are effectively in balance. By boosting ROS generation and inhibiting the antioxidant defense system, treatment with CP upsets this equilibrium (oxidant-antioxidant ratio) [35]. By interacting with cell membrane lipids and proteins and subsequently damaging nucleic acids, the produced radicals can severely harm cardiac tissue, releasing free radicals and cardiac enzymes that are thought to be delicate markers of cardiac tissue lesions [36].

Additionally, due to the greater opening of the mitochondrial permeability transition pore caused by CP's production of ROS, it starts the dependent process of the mitochondria's apoptosis-causing mitochondrial release of cytochrome c into the cytosol [37].

Strong antioxidant vitamin D, which has been demonstrated to have positive benefits in several pathological diseases, is crucial for maintaining overall human health [38]. It is a lipid-soluble vitamin that also contains Vitamin D3 and Vitamin D2 (ergocalciferol) (cholecalciferol). The hormonally active form of cholecalciferol, 1, 25 (OH) 2 derivative, is produced during the metabolism of vitamin D. It engages in a variety of biological processes, including the regulation of calcium and phosphorus metabolism [39].

According to studies, 1, 25 (OH) 2 lowers oxidative stress, protects cells from oxidative damage brought on by free radicals, and lessens tissue and cell damage [39, 40].

Higher quantities of these lipophilic chemicals have been suggested to reduce the amount of peroxided lipids that build up in membranes [41]. The reduction of chronic inflammation, the suppression of oxidative stress, and the maintenance of mitochondrial respiratory function have all been suggested as additional crucial roles for vitamin D [38]. Additionally, a lack of vitamin D is linked to the pathophysiology of some diseases by causing greater cellular oxidative damage [42].

According to the prior data and the results of the current investigation, it was shown that giving vitamin D to animals receiving cisplatin reduced the MDA levels in their heart and lung tissues compared to the cisplatin alone group. A partial improvement in the histopathological status of lung and heart tissues of the alphacalcidol group compared to the CP group may explain that vitamin D improved the CP-induced increased lipid peroxidation. The declining of lipid peroxidation in these tissues appears to indicate that Vitamin D is a potent antioxidant that has a role in balancing mitochondrial activities, preventing oxidative stress, lipid peroxidation, and DNA damage [38].

Meanwhile, it was noted that VD, a lipophilic molecule that is present in cell membranes to prevent lipid peroxidation, has antioxidant capacity that plays a significant role in defending healthy cell membranes from oxidative damage caused by free radicals [41]. There have been

reports of Vitamin D's ameliorative, anti-oxidative, and anti-inflammatory effects on lead-induced toxicity model in rats [43].

Additionally, 1, 25 (OH) 2D3 has been investigated to mediate the increase of cell cycle regulators in vitro and in vivo [45]. Vitamin D was also demonstrated to have restorative and anti-apoptotic effects on diabetic rat testicular tissue [44].

The results of the current study show how important oxidative damage and inflammation are in the development of pulmonary-cardiotoxicity brought on by CP therapy. Our results further suggest that protecting against lung and heart damage in CP-treated rats may be achieved by supplementing with vitamin D simultaneously as an antioxidant and an anti-inflammatory agent. Vitamin D is an ideal option for clinical medication development due to its amazing ability to mitigate the pulmonary-cardiotoxicity brought on by CP treatment.

CONCLUSION

The results of the current investigation unequivocally show that vitamin D reduces the histopathological and oxidative damage to the lungs and heart brought on by CP. In light of this, vitamin D may be able to protect against the heart and lung damage caused by CP. Clinical research is therefore necessary to confirm these protective benefits.

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Compliance with ethical standards

Conflicts of Interests:

Sally Mahmoud Mohamed Hussein omar, Marwa Mohamed Abd El Aziz Ahmed, Ola Abd El-Samie Mohamed Khalil, and Marwa Mahmoud Mady declare that we have no conflict of interest.

Ethical approval the present study was approved by the Ethical guidelines of Alexandria University on laboratory animals and the national institute for the care and use of laboratory animals. Further the Alexandria Faculty of Medicine ethical committee approval was obtained.

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