RESEARCH ARTICLE

# Single or Divided Administration of Cisplatin Can Induce Inflammation and Oxidative Stress in Male Sprague-Dawley Rats

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## Abstract

**BACKGROUND:** Cisplatin is one of the most potent chemotherapy drugs to treat various types of cancer, however the use of cisplatin has some the adverse effect, such as the increase of oxidative stress and inflammation by malondialdehyde (MDA) and nuclear factor kappa B (NF-κB) activation. Since the dosing of cisplatin is critical, we observed the effect of single and multiple doses of cisplatin injection on rats' inflammation and oxidative stress level.

**METHODS:** Total of 27 male Sprague-Dawley rats were divided into 9 sub-groups, each consisted of 3 rats. The baseline sub-group received no treatments; Group 1 (sub-group 1.1, 1.2, 1.3, and 1.4) were administered one single dose of 5 mg/kg BW/intravenously (i.v) of cisplatin; and Group 2 (sub-group 2.1, 2.2, 2.3, and 2.4) were given 0.2 mg/kg BW/i.v of cisplatin twice a week for two months. Rats were observed for their body weight, NF-κB, and MDA level based on the assigned group.

**RESULTS:** Body weight loss was observed in the 1st week after treatment for Group 1, and 7th week for Group 2. Group 1 and Group 2 showed increasing level of NF-κB and MDA since the 1st observation, which was the 1st week and 5th week, respectively. NF-κB and MDA and levels were also significantly increasing in both groups for every week of observation ($p<0.05$).

**CONCLUSION:** Cisplatin injection either in single or divided dose can induce inflammation and oxidative stress thus decrease the body weight. However, dividing cisplatin in smaller dose can delay the inflammation effect on subjects.

**KEYWORDS:** cisplatin dose, MDA, NF-κB, body weight, inflammation, oxidative stress

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## Introduction

Cancer is a leading cause of death worldwide, nearly one in six deaths in 2020, and the cases keep increasing.(1,2) Cisplatin or cis-diamminedichloroplatum (CDDP), is one of the most potent chemotherapy drugs for various types of cancer.(3) Cisplatin consists of one platinum atom in the middle, two chlorine atoms and two ammonia atoms in the group as a ligand.(4,5) After administration of single dose 4-10 mg/kg body weight (BW)/intra-peritoneally (i.p.) of cisplatin, the drug will be excreted through urine 43-50% in the first 24 hours, and the rest in 72 hours. The highest concentration of cisplatin was found in the mitochondria (37%), then in the cytosol (27%), in the nucleus (22%) and in the microsome (14%).(6) Cisplatin can prevent the replication of deoxyribonucleic acid (DNA), affect the synthesis of ribonucleic acid (RNA) and protein, also stimulate apoptosis of tumor cells.(7,8) The tumor cells death was induced by disruption of vital organelle balance such as the endoplasmic reticulum (ER) and mitochondria. (9) A study using DU145 and A549 cell lines showed that administration of cisplatin can cause mitochondrial disruption and inhibition of DNA transcription caused by reactive oxygen species (ROS), so that as an anti-cancer drug, dose determination is important because of its

cytotoxic effect.(10) Cisplatin can induce oxidative stress, which in turn triggers the release of Fas-Fas ligand binding in the kidney causing the death of renal tubular cells, on the other hand, ROS cause amplification of Fas-L and causes cancer cell.(11,12) Previous data showed that 8 mg/kgBW/i.p. cisplatin could increase malondialdehyde (MDA) (13), and 4-HNE increase after cisplatin administration, while administration of curcumin (14) or vitamin C could reduce MDA and 4-HNE levels (15).

Nuclear factor kappa B (NF-κB) activation from its binding form, inhibitor of kappa B (IκB) can increase cancer cell proliferation, inhibit apoptosis and induce neovascularization process so that cancer metastases occur.(16,17) Cisplatin phosphorylate and degrade IκB, translocate it into the nucleus to regulate gene expression. (18) Inhibitors of IκB phosphorylation will decrease NF-κB activation and increase tumor cell sensitivity to cisplatin. (19) The administration of single dose 7 mg/kg BW/i.p. of cisplatin in Wistar rats increase the expression of MAPK/p38 and NF-κB/p65 in testicular tissue compared to the control group and the group receiving curcumin.(20) Research using oral squamous cell carcinoma showed that administration of flavonoids two hours before administration of cisplatin inhibited protein kinase B (Akt) and IκB kinase subunit beta (IKK-β) which in turn suppressed NF-κB. In previous studies it was said that NF-κB causes resistance to cisplatin.(21-24)

Cisplatin injection commonly administered in a single dose in every treatment cycle.(15) A study on adult male albino rats showed that single dose administration of 5 mg/kg BW cisplatin affected some hepato-cardiotoxicity biomarkers of rats compared to the control animals.(25) However, rats that were administered the low doses of 0.2 mg/kg BW cisplatin, twice weekly for two months, also showed hepatotoxicity signs.(26) Since knowing the dosing of cisplatin is critical (15), it is important to ensure the required duration and doses of cisplatin administration that can cause inflammation and oxidative stress. Whether cisplatin administration in higher dose as a one single dose or smaller dose given twice a week for two months that will show effect faster should be evaluated. Hence, in this study we observed the effect of cisplatin injection when given in single and divided doses on NF-κB and MDA level.

## Methods

### Study Design and Animal Treatment

This was an experimental animal study performed at the Anatomical Pathology Laboratory of the Faculty of Medicine, Universitas Sebelas Maret, Surakarta, and the Inter-University Center Universitas Gadjah Mada, Yogyakarta, in July 2021. Total 27 of male Sprague-Dawley rats aged ~8 weeks and weighed 150-200 grams were included in this study. Rats were divided into 9 sub-groups, each sub-group consisted of 3 rats.

The baseline sub-group received no treatments; the Group 1 sub-groups (sub-group 1.1, 1.2, 1.3, and 1.4) were

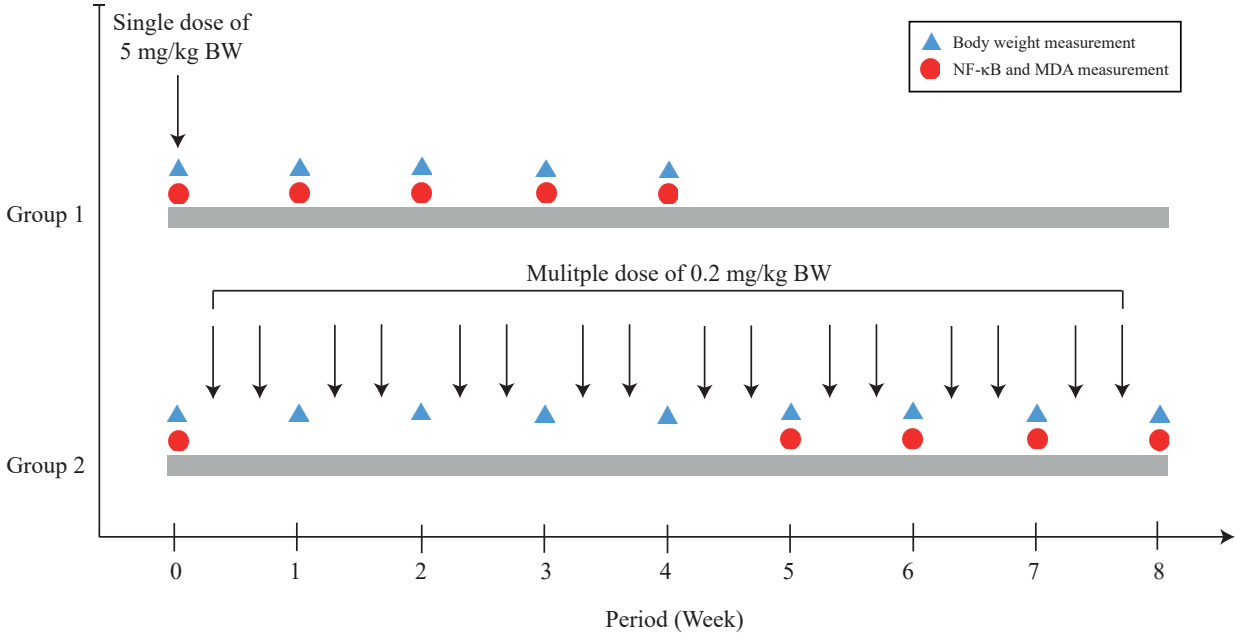


**Figure 1. Study timeframe.**

administered one single dose of 5 mg/kg BW/intravenously (i.v) of cisplatin; and the Group 2 sub-groups (sub-group 2.1, 2.2, 2.3, and 2.4) were given 0.2 mg/kg BW/i.v of cisplatin twice a week for two months. The dose determination for the single dose and the multiple dose of cisplatin was based on previous studies.(25,26)

Rats' body weight, NF-κB level, and MDA level were all measured at the baseline (before the administration of cisplatin). Then for Group 1, rats' body weight, NF-κB level, and MDA level were also measured at the week 1-4. For Group 2, the body weight was measured at week 1-8, while the NF-κB and MDA level were measured on week 5-8. Detail timeframe of the study was shown in Figure 1. At the end of each observation, rats were sacrificed after the blood sample was taken, based on the sub-group. All the protocols have been approved by the Health Research Ethics Committe of Dr. Moewardi General Hospital, Surakarta (No. 805/IX/HREC/2021).

### NF-κB Examination

The marker of inflammation, NF-κB, was examined using the Fine test (Catalog No. ER1186, Wuhan Fine Biotech, Wuhan, China). The basic principle of NF-κB examination was sandwich enzyme-linked immune-sorbent assay (ELISA). Antibody was pre-coated onto 96-well plates and the biotin conjugated antibody was used as detection antibodies. The standards, samples and biotin conjugated detection antibody were added to the wells, then HRP-Streptavidin was added. The 3,3',5,5'-Tetramethylbenzidine (TMB) substrates were used to visualize HRP enzymatic reaction. The optical density was proportional to the target amount of sample captured in plate at 450 nm absorbance in a microplate reader, and the concentration of target was calculated, with the sensitivity of <0.094 ng/mL.(27)

### MDA Examination

MDA, as an oxidative stress marker, was examined using thiobarbituric acid reactive substances (TBAR) assay kit OxiselectTM (Catalog No. STA-330, Cell Biolabs, San Diego, CA USA). The unknown MDA in samples or standards were reacted with thiobarbituric acid at 95°C. After incubation, the samples and standards were read either spectrophotometrically or fluorometrically. The MDA content in unknown samples was determined by comparing with the predetermined MDA standard curve.(28)

### Statistical Analysis

To find whether the data was normally distributed or not, we ran a Saphiro Wilks test. Meanwhile, to compare differences between the results, we run an Analysis of Variance (ANOVA) Unpaired T-Test with significance of $p<0.05$. ta were analyzed with SPSS ver. 26 (IBM Corporation, Armonk, NY, USA).

## Results

Body weight of rats in Group 1 increased after the single dose administration of cisplatin, but started decreasing after the 1st week until the 4th week. Meanwhile, the body weight of rats in Group 2 kept increasing since the low dose of cisplatin was given until the 7th week. And after the 7th week, body weight lost occurred (Table 1, Figure 2). This indicated that the low dose administration of cisplatin was able to delay the rats' body weight loss until the 8th week.

Table 2 and Figure 3 showed NF-κB and MDA level of the study rats at each observation. Group 1 and Group 2 showed increasing level of NF-κB and MDA since the 1st observation, which was the 1st week after cisplatin administration for Group 1 and 5th week for Group 2, when compared to the baseline sub-group.

NF-κB level of Group 1 in the 1st week was slightly similar if compared to the NF-κB level of Group 2 in the 5th week. This indicated that the administration of the low dose of cisplatin took longer time to reach the similar inflammation effect. Meanwhile, for the MDA level of Group 1 in the 4th week was similar with the MDA level of Group 2 in the 8th week, even though showed larger differences in the earlier weeks.

The week-to-week comparation of NF-κB and MDA mean differences were shown in Table 3 and Table 4, respectively. The NF-κB level showed significant

**Table 1. Mean±SD body weight of rats.**

| Observation Period | Body Weight Change (g) | |
|---|---|---|
| | Group 1 | Group 2 |
| Baseline | 175.00±2.65 | 177.33±2.52 |
| 1st week | 180.56±5.68 | 181.78±5.74 |
| 2nd week | 180.50±4.54 | 184.50±4.74 |
| 3rd week | 180.00±5.62 | 186.50±5.34 |
| 4th week | 176.75±5.80 | 189.87±3.94 |
| 5th week | N/A | 192.53±3.62 |
| 6th week | N/A | 193.80±2.98 |
| 7th week | N/A | 194.00±3.27 |
| 8th week | N/A | 181.78±5.74 |

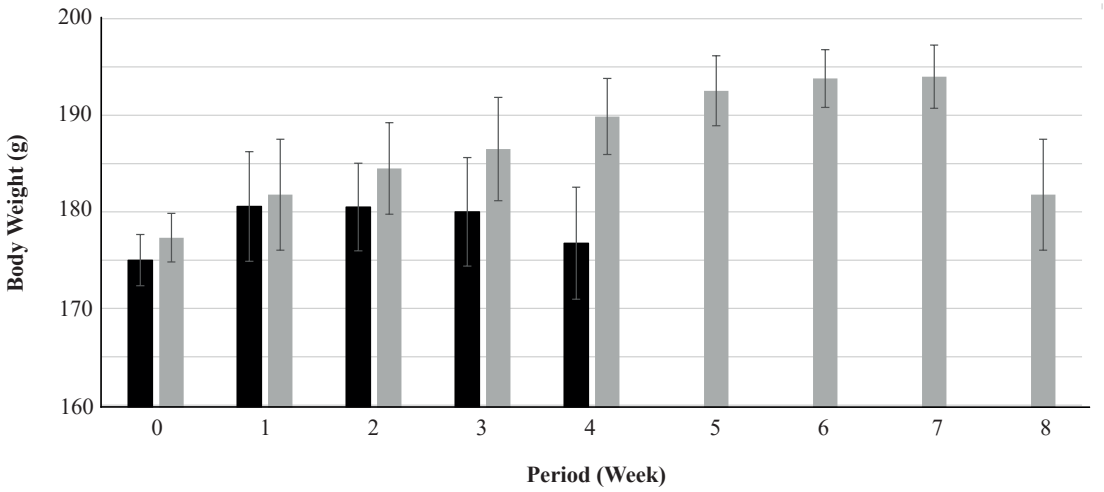


**Figure 2. Rats' body weight during the observation period.** Black bar: group 1; Grey bar: group 2.

differences in almost every observation for Group 1 and Group 2 ($p$<0.005) except for 3rd and 4th observations in both group ($p$=0.064).

Meanwhile, for the MDA level, there was a significant difference in Group 1 between the 1st and 4th observations ($p$=0.008), between the 2nd and 4th observations ($p$=0.003) and also between the 3rd and 4th observations ($p$=0.012). While in Group 2, the MDA level was significantly different in every observation, which was shown by $p$<0.05.

## Discussion

Our data showed that the rats received single dose of cisplatin experienced weight loss since the first week after injection, while the divided dose group started losing weight after 7 weeks (Table 1). Previous study finds significant difference in body weight loss in the rats group received 5 mg i.p. cisplatin compared to the control group ($p$<0.005). (29) Another study shows that cisplatin administration significantly decreases the rats' body weight compared to the control group.(30) Administration of cisplatin increases the production of ROS (peroxiredoxin III/PRX III and manganese superoxide dismutase/MnSOD) in muscle mitochondria, stimulates the production of proinflammatory cytokines thereby triggering the destructive metabolism of skeletal muscle causing muscle wasting and cachexia. (31,32) Giving cisplatin in divided smaller dose can alleviate this weight loss effect, hence delaying the rats' body weight loss duration.

Results of this study showed that the NF-κB level increased since the 1st week in Group 1 and in the 5th week in

**Table 2. Mean±SD NF-κB and MDA level of rats.**

| Group | Observation Period | NF-κB (ng/mL) | MDA (nmol/mL) |
|---|---|---|---|
| Baseline | 0th week | 602.59±6.55 | 4.51±0.16 |
| Group 1 | 1st week | 669.12±6.45 | 6.87±0.81 |
| | 2nd week | 717.13±5.47 | 10.27±0.51 |
| | 3rd week | 1556.70±55.91 | 11.95±0.12 |
| | 4th week | 2012.29±54.97 | 16.97±0.26 |
| Group 2 | 5th week | 644.22±6.98 | 4.97±0.16 |
| | 6th week | 690.43±4.43 | 9.01±0.25 |
| | 7th week | 1532.45±57.23 | 11.39±0.22 |
| | 8th week | 1984.43±52.88 | 16.95±0.16 |

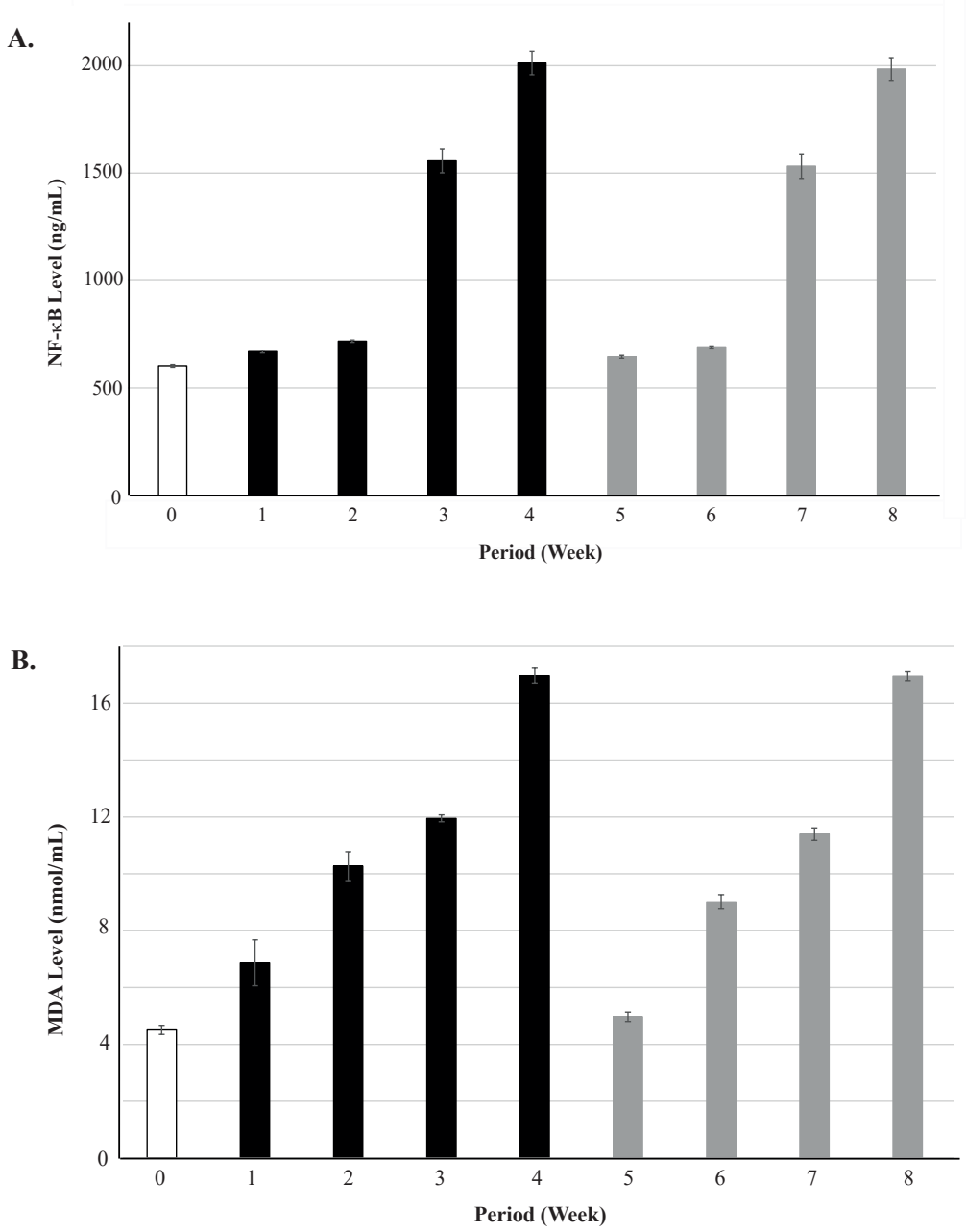


**Figure 3. Rats' NF-κB and MDA level during the observation period.** White bar: baseline sub-group; Black bar: group 1; White bar: group 2.

Group 2, compared to the baseline sub-group (Table 2 and Table 3). There is an increase in the expression of NF-κB/p65 in testicular tissue ten days after administration of single dose 7 mg/kg BW/i.p. of cisplatin.(20) Data from a study on oral squamous cell carcinoma line shows that 30 minutes after administration of cisplatin, p65 is translocated into the nucleus and results in the activation of NF-κB (23), through IκB phosphorylation and proinflammatory pathways (33). This activation leads to the secretion of tumor necrosis factor (TNF)-α and various interleukins (IL) such as IL-6, IL-1α and decrease the secretion of IL-10.(34,35) By giving single dose 7.5 mg/kg BW of cisplatin, not only increased NF-κB, and proinflammatory cytokines such as TNF-α, IL-6, but also increasing serum creatinine, blood urea nitrogen (BUN) as well as decreasing albumin and IL-10.(36) NF-κB plays a role in tumor cells growth and survival.(30) NF-κB target gene is involved in the development of inflammation, causes the production of proinflammatory cytokines, chemokines, adhesion molecules and regulates proliferation, apoptosis, morphogenesis and cell differentiation.(37) Administering cisplatin in dividing dose seems to delay the NF-κB level increasing.

**Table 3. Repeated ANOVA test for NF-κB level in Group 1 and Group 2.**

| Group | Observation Period (Week) | | 2nd | 3rd | 4th |
|---|---|---|---|---|---|
| **Group 1** | **1st** | Sig | 0.001* | 0.006* | 0.004* |
| | | Mean difference | -48.18 | -887.577 | -1343.163 |
| | | 95% CI lower bound | -54.339 | -1198.816 | -576.337 |
| | | 95% CI upper bound | -42.021 | -1698.877 | -987.45 |
| | **2nd** | Sig | N/A | 0.007* | 0.004* |
| | | Mean difference | N/A | -839.397 | -1294.983 |
| | | 95% CI lower bound | N/A | -1156.572 | -1647.903 |
| | | 95% CI upper bound | N/A | -522.221 | -942.064 |
| | **3rd** | Sig | N/A | N/A | 0.064 |
| | | Mean difference | N/A | N/A | -455.587 |
| | | 95% CI lower bound | N/A | N/A | -973.879 |
| | | 95% CI upper bound | N/A | N/A | 62.706 |
| **Group 2** | **1st** | Sig | 0.006* | 0.007* | 0.004* |
| | | Mean difference | -46.213 | -888.233 | -1340.213 |
| | | 95% CI lower bound | -62.545 | -1210.126 | -1698.644 |
| | | 95% CI upper bound | -29.882 | -566.341 | -981.782 |
| | **2nd** | Sig | N/A | 0.008* | 0.004* |
| | | Mean difference | N/A | -842.02 | -1294 |
| | | 95% CI lower bound | N/A | -1176.235 | -1640.247 |
| | | 95% CI upper bound | N/A | -507.805 | -947.753 |
| | **3rd** | Sig | N/A | N/A | 0.064 |
| | | Mean difference | N/A | N/A | -451.98 |
| | | 95% CI lower bound | N/A | N/A | -962.741 |
| | | 95% CI upper bound | N/A | N/A | 58.781 |

*Significant if $p<0.05$.

Our study also showed that the MDA level was increased in each week of observation for both groups (Table 2 and Table 4). Cisplatin induces ROS production caused by various mechanisms such as membrane lipid peroxidation, protein denaturation, DNA damage, inflammation, and apoptosis of normal cells.(26) Administration of single dose 7 mg/kg BW of cisplatin increased MDA levels 6 times and decreased glutathione (GSH) in kidney tissue when compared to the control group.(38)

In this study, MDA was increased 4 times at 4th week in Group 1 and at 8th week in Group 2. The increase in ROS is caused by cisplatin administration is not due to the response to nuclear DNA signaling damage, but to direct damage to mitochondria. Cisplatin binds to mitochondrial DNA as well as nuclear DNA, but because mitochondrial DNA does not have nucleotide excision repair (NER), damaged mitochondrial DNA cannot be removed. Non-functioning mitochondria are more resistant to cisplatin. (10) ROS formation is associated with various triggers for organ injury, ROS stimulates increased expression of membrane-bound Fas ligand (mFasL) and mFas in renal and renal epithelial cells causing DNA fragmentation during cell death, leading to acute kidney injury.(12) A study on rats using single dose 7 mg/kg BW i.p. of cisplatin showed seminiferous tubules damage, there is an increase in MDA and a decrease in GSH in testicular tissue, testicular damage and a decrease in body weight when compared to controls ($p=0.048$) for MDA and $p<0.001$ for GSH.(39) Giving cisplatin either in single or divided dose increases oxidative stress.

In this study, we did not have a control group and higher dose group that being observed fully until the 8th week. It is necessary to conduct further study with the comparable observation time between all groups.

**Table 4. Repeated ANOVA test for MDA level Group 1 and Group 2.**

| Group | Observation Period (Week) | | 2nd | 3rd | 4th |
|---|---|---|---|---|---|
| **Group 1** | **1st** | Sig | 0.056 | 0.06 | 0.008* |
| | | Mean difference | -3.4 | -5.08 | -10.097 |
| | | 95% CI lower bound | -7.012 | -10.657 | -14.124 |
| | | 95% CI upper bound | 0.212 | 0.497 | -6.069 |
| | **2nd** | Sig | N/A | 0.267 | 0.003* |
| | | Mean difference | N/A | -1.68 | -6.697 |
| | | 95% CI lower bound | N/A | -5.671 | -8.288 |
| | | 95% CI upper bound | N/A | 2.311 | -5.105 |
| | **3rd** | Sig | N/A | N/A | 0.012* |
| | | Mean difference | N/A | N/A | -5.017 |
| | | 95% CI lower bound | N/A | N/A | -7.417 |
| | | 95% CI upper bound | N/A | N/A | -2.617 |
| **Group 2** | **1st** | Sig | 0.001* | 0.002* | 0.001* |
| | | Mean difference | -46.213 | -888.233 | -1340.213 |
| | | 95% CI lower bound | -62.545 | -1211.126 | -1698.644 |
| | | 95% CI upper bound | -29.882 | -566.341 | -981.782 |
| | **2nd** | Sig | N/A | 0.034* | 0.004* |
| | | Mean difference | N/A | -842.02 | -1294 |
| | | 95% CI lower bound | N/A | -1176.235 | -1640.249 |
| | | 95% CI upper bound | N/A | -507.805 | -947.753 |
| | **3rd** | Sig | N/A | N/A | 0.009* |
| | | Mean difference | N/A | N/A | -451.98 |
| | | 95% CI lower bound | N/A | N/A | -962.741 |
| | | 95% CI upper bound | N/A | N/A | 58.781 |

*Significant if $p<0.05$.

## Conclusion

Cisplatin injection either in single or divided dose can induce inflammation and oxidative stress thus decrease the body weight. However, dividing cisplatin in smaller dose can delay the inflammation effect on subjects.

## Authors Contribution

BRAS, BP, BW, and VW were involved in concepting the study and data analysis. BRAS performed the data acquisition/collection, interpreted the study results, and created the figures and tables. BRAS, BP, BW, VW, and SOE took parts in preparing and giving critical revision of the manuscript.

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