EVALUATION OF THE POSSIBLE PROTECTIVE EFFECT OF METFORMIN IN CISPLATIN-INDUCED NEPHROTOXICITY IN ADULT MALE ALBINO RATS

By

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ABSTRACT

Backgrounds: Clinical use of cisplatin is limited by its nephrotoxicity as cisplatin-induced oxidative stress which leads ultimately to kidney dysfunction.

Objective: Evaluation of the nephron-protective effect of metformin against nephrotoxicity induced by cisplatin in adult albino rats.

Materials and Methods: Sixty adult male albino rats were divided randomly into 6 equal groups: Group 1 (control group) was injected with 1 ml isotonic saline solution intraperitoneally (I.P). Group 2 was injected with single dose of cisplatin I.P 3.5mg/kg. Group 3 was injected with single dose of cisplatin I.P 7.5 mg/kg. Group 4 was given an oral dose of metformin (350 mg/kg/day for 10 days). Group 5 was given 100 mg kg/day metformin for 3 days before cisplatin injection I.P at a dose of 7.5 mg/kg on day four, and metformin continued for 7 days after. Group 6 was given 350 mg kg/day metformin for 3 days before cisplatin injection I.P at a dose of 7.5 mg/kg on day four, and metformin continued for 7 days after. Body weight of each rat was recorded on day 1, 4, 7 and 10 and average weight for each group was calculated. At the end of specified duration (10 days), rats were sacrificed and both kidneys were excised, processed and stained with Hematoxylin and Eosin for histopathological study and with Periodic Acid-Schiff (PAS) and Mallory’s stain stains for histochemical study.

Results: Rats injected with high dose of cisplatin (7.5 mg/kg) showed more loss of average body weight and higher blood urea nitrogen (BUN) and serum creatinine (Cr) levels than those rats injected with 3.5 mg/kg cisplatin. Rat group injected with high dose of cisplatin (7.5 mg/kg) and given low dose metformin (100 mg/kg/day) showed less loss of average body weight and improved renal functions than rat group given high dose of cisplatin (7.5 mg/kg) and high dose of metformin (350 mg/kg/day). Histopathological examination with H&E and histochemical examination with PAS and Mallory’s stains revealed mild glomerular, tubular and interstitial changes in cisplatin low dose group compared to cisplatin high dose group which showed more renal damages. Group given metformin low dose + cisplatin high dose showed less renal damage than those given high dose of cisplatin+ high dose metformin.

Conclusion: Metformin has protective effects against cisplatin-induced nephrotoxicity in adult male albino rats.

Key words: Cisplatin, nephrotoxity, metformin.
INTRODUCTION
Cisplatin is an important chemotherapeutic agent useful in the treatment of several cancers. Several side effects of cisplatin have been reported, mainly nephrotoxicity and myelosuppression which limit its clinical use (Florea and Büsselberg, 2011). Inflammation, oxidative stress injury, and apoptosis probably explain part of Cisplatin nephrotoxicity, primarily in the proximal tubular epithelium (Chirino and Pedraza-Chaverri, 2009). Cisplatin or its metabolites may be absorbed by kidney tubular cells through organic cation transporters located on the baso-lateral side of the tubular cells, which will lead to subsequent tubular cell death including apoptosis and necrosis (Gabbiani et al., 2010). Reactive oxygen species production, depletion of antioxidant systems and stimulation of renal accumulation of lipid peroxidation products are the main mechanisms associated with cisplatin-induced nephrotoxicity (Peres and da Cunha, 2013). Cisplatin-induced nephrotoxicity is associated with structural and functional damage to the mitochondria (Zsuzsanna et al., 2012). Cisplatin also binds to DNA and disrupts DNA function (Dasari and Tchounwou, 2014).

Many researches were targeted to find a substance to ameliorate toxic effects of cisplatin on kidney through antagonizing mechanism of cisplatin action. Rutin which has an anti-oxidant and anti-inflammatory effect via decreasing the oxidative stress, and repairing the histopathological changes was tested. It showed minimal histopathological findings in the form of minimal interstitial congestion and minimal tubular injury, while glomeruli and the blood vessels appeared normal (Alhoshani et al., 2017). Garlic extract and metformin (MF), alone or in a combination, tried to ameliorate gentamycin induced tubular toxicity (Rafieian-Kopaei et al., 2013). Ceftriaxone which had anti-fibrotic potential acts as a nephron-protective agent and could be used as adjuvant therapy to improve cisplatin-induced nephrotoxicity, as Ceftriaxone given before cisplatin treatment improved renal function biomarkers and renal histoarchitecture (Abdel-Daim et al., 2017).

Metformin treatment was found to restore significantly diabetic nephropathy-induced oxidative stress mRNA levels in Streptozotocin diabetic nephropathy (Alhaider et al., 2011). Various studies had emphasized the anti-inflammatory and antioxidant role of metformin through multiple mechanisms. So, metformin can be an appropriate treatment option for many diseases, when inflammatory processes and oxidative stress play a role in their pathogenesis (Dehkordi et al., 2019). Metformin was found to protect against tubular injury by restoring the biochemical alterations. Moreover, metformin protected podocytes in diabetic nephropathy in rats (Kim et al., 2012).

( The present study aimed to investigate the proved protectivity of metformin in different doses of cisplatin-induced nephrotoxicity).

MATERIALS AND METHODS
Animals: This study was done on sixty adult male albino rats of local strain; weighing 200 ± 20 g and aging 70 days
which were obtained from the breeding colony maintained at the animal house of the Nile Company for pharmaceuticals, Cairo, Egypt. All animals procedures were reviewed and approved by the Animals ethics committee, Al-Azhar University, based on the code of practice for the care and use of Animals for Scientific purposes, National Committee for Research, All animal experiments were carried out according to the guidelines and approval of Institutional Animal Ethics Committee. Rats were housed in the animal facility of Faculty of Medicine, Al-Azhar University under the normal conditions, each two rats were housed in a clear stainless steel cages. Each cage sized 20X32X20 cm. Rats were kept under constant and controlled temperature (23±3°C), humidity (about 60%), with normal light/dark cycle and fed on a standard rat diet and water ad libitum. Rats were acclimated and monitored under lab conditions for a week.

**Chemicals and stains:**

**Cisplatin:** was purchased from EMIC pharmaceutical industry (Cairo Egypt) in the form of parenteral vial with a concentration of 50mg/ml. Dose was calculated according to the body weight of each rat.

**Metformin hydrochloride (Glucaphage):** was purchased from Minipharma Merck Serono Company (500 mg metformin hydrochloride tablet). Dose was calculated according to the body weight of each rat.

**Periodic Acid-Schiff (PAS):** (Product Code: AR165 Staining Interpretation: PAS-positive structures: Magenta, Nuclei: Blue Background: Pink. Control Tissue: Kidney for basement membrane, Dako Corporation, Denmark). PAS was used to demonstrate the glomerular basement membrane (BM), tubular BM, brush borders, cell borders.

**Mallory’s stain kit (Staining Interpretation):** Collagen fibris: Deep Blue, Nuclei: Red, Erythrocytes: Gold yellow, Control Tissue: prostate, Dako corporation, Denmark). Mallory’s stain was used to demonstrate the collagen fibres in glomerular and tubular BM, and in the interstitium.

**Experiment design:** Rats were randomly divided into six equal groups:

**Group 1:** (Control group) was injected with 1 ml isotonic saline solution intraperitoneally (I.P).

**Group 2:** was injected with cisplatin I.P single dose 3.5 mg/kg on 4th day.

**Group 3:** was injected with cisplatin I.P single dose 7.5 mg/kg on 4th day.

**Group 4:** was given an oral dose of metformin (350 mg/kg /day) for 10 days.

**Group 5:** was given an oral dose of metformin 100 mg/kg/day for 10 days starting 3 days before giving cisplatin injection I.P at a dose of 7.5 mg/kg on 4th day and metformin was given for 7 days after.

**Group 6:** was given an oral dose of 350 mg kg/day metformin for 3 days before cisplatin injection I.P at a dose of 7.5 mg/kg on day four, and metformin was given for 7 days after.

Body weight of each rat was recorded on day 1, 4, 7 and 10. Average weight for each group was calculated. Blood urea nitrogen (BUN) and creatinine (Cr) levels were measured by a colorimetric method.
using commercial kits on an auto analyzer. On day of sacrificing, serum samples were obtained to measure blood urea nitrogen (BUN) and serum creatinine (Cr) for all the rats (Amini et al., 2012). At the end of specified duration (10 days) rats were sacrificed and both kidneys were excised, washed with saline and fixed in 10% neutral buffered formalin for 24 hours. They were processed in a sequence of ethanol solutions and finally embedded in paraffin wax blocks. Tissues blocks were sectioned at thickness of 4 ?m, followed by deparaffinization by xylene and stained with Hematoxylin & Eosin (H&E), Periodic Acid-Schiff (PAS) and Mallory stains.

**Statistical Analysis:**
All the statistical analysis were processed using Statistical Program of Social Sciences (SPSS) for windows (version 17, SPSS Inc., Chicago, IL, USA). Values of the measured parameters were expressed as mean value ± standard deviation (SD).

**RESULTS**

**Rat body weight:** as seen in table (1) both groups II and III shows that average rat body weight was progressively decreased after giving cisplatin injection. On giving cisplatin/ metformin in group V and group VI obvious less average body weight decrease was noted.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Day 1</th>
<th>Day 4</th>
<th>Day 7</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>244</td>
<td>251.4</td>
<td>256.4</td>
<td>260</td>
</tr>
<tr>
<td>Group II</td>
<td>243.6</td>
<td>239.5</td>
<td>230</td>
<td>227.2</td>
</tr>
<tr>
<td>Group III</td>
<td>244.2</td>
<td>235</td>
<td>230.5</td>
<td>225</td>
</tr>
<tr>
<td>Group IV</td>
<td>247</td>
<td>251.4</td>
<td>253.2</td>
<td>255</td>
</tr>
<tr>
<td>Group V</td>
<td>240.2</td>
<td>238.2</td>
<td>238</td>
<td>236.6</td>
</tr>
<tr>
<td>Group VI</td>
<td>246</td>
<td>241.2</td>
<td>238.6</td>
<td>237.5</td>
</tr>
</tbody>
</table>

**Biological markers:** Blood Urea nitrogen (BUN) and serum creatinine (Cr) levels were markedly increased in both groups II and III as seen in table (2) compared to control group I levels. More increase in BUN and serum Cr on increasing dose of injected cisplatin as seen in group III than that seen in group II. An obvious decrease in in levels of BUN and serum Cr in groups V and group VI compared to group II and group III on giving metformin with cisplatin.
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Table (2): Blood Urea nitrogen (BUN) and Creatinine

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serological Parameters</th>
<th>BUN (mg/dl)</th>
<th>Serum Creatinine (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td>22.6 ± 6.3</td>
<td>0.60 ± 0.3</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td>56.7 ± 5.5</td>
<td>1.34 ± 0.4</td>
</tr>
<tr>
<td>Group III</td>
<td></td>
<td>66.8 ± 6.7</td>
<td>2.23 ± 1.4</td>
</tr>
<tr>
<td>Group IV</td>
<td></td>
<td>46.4 ± 2.2</td>
<td>1.15 ± 0.02</td>
</tr>
<tr>
<td>Group V</td>
<td></td>
<td>51.2 ± 3.2</td>
<td>1.26 ± 0.23</td>
</tr>
<tr>
<td>Group VI</td>
<td></td>
<td>59.6 ± 2.6</td>
<td>2.1 ± 0.3</td>
</tr>
</tbody>
</table>

Histopathological results:
Light microscopical examination of H&E stained slides of kidneys showed the following:
- **Group 1 (Control):** normal histological structure of cortex and medulla (Figure 1 & Table 3).
- **Group II:** (cisplatin low dose): Mild glomerular deformity and hypercellularity with mild narrowing of Bowman's spaces. Tubular epithelium was markedly oedematous with scattered necrotic apoptotic epithelial cells. The interstitium showed markedly dilated congested blood vessels (Figure 2 & Table 3)
- **Group III:** (cisplatin high dose): Marked cortical necrosis, marked deformity and hypercellularity with obliterated Bowman's spaces were noted in viable glomeruli. Tubular epithelium is markedly edematous with numerous necrotic apoptotic tubular cells with numerous intra-tubular hyaline casts. Interstitium showed markedly dilated congested blood vessels (Figures 3, 4 & Table 3)
- **Group IV:** (metformin high dose): Mild glomerular cellularity with patent Bowman's space and normal histological architecture of tubules were noted (Figure 6 & Table 3)
- **Group V:** (cisplatin+ metformin low dose): as seen in (Figure 5 & Table 3) mild glomerular deformity and cellularity with patent Bowman's spaces, less oedematous proximal tubular epithelium with scattered necrotic apoptotic epithelial cells in contrary to distal tubular epithelium which were markedly edematous with few intra-tubular hyaline casts
- **Group VI:** (cisplatin+ metformin high dose): Marked glomerular deformity and moderate hypercellularity with narrow to patent Bowman's spaces are seen. Tubular epithelium is mildly oedematous with scattered necrotic apoptotic epithelial cells and few intra-tubular hyaline casts (Figure 6 & Table 3).

Table (3): Histopathological results

<table>
<thead>
<tr>
<th>Parameters Groups</th>
<th>Glomeruli</th>
<th>Tubules</th>
<th>Interstitium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deformity</td>
<td>Cellularity</td>
<td>Bowman's space</td>
<td>Edema</td>
</tr>
<tr>
<td>Group 1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group II</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Group III</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Group IV</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Group V</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Group VI</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

0 = No, + = Mild, ++ = Moderate, +++ = Marked
Fig (1): (Control). Fig (2) (Cisplatin low dose): Mild glomerular deformity and hypercellularity with markedly dilated congested blood vessels. Fig (3) (Cisplatin high dose): Marked glomerular deformity and hypercellularity with obliterated Bowman's spaces and markedly dilated congested blood vessels. Fig (4): Numerous intra-tubular hyaline casts. Fig 5 (Cisplatin + Metformin low dose): Mild glomerular deformity with intra-tubular hyaline casts. Fig 6 (Cisplatin + Metformin high dose): Marked glomerular deformity and hypercellularity with mild tubular edema (H&E X400)

II- Histochemical results:
Light microscopical examination of PAS and Mallory stained slides of kidneys showed the following:
• **Group 1 (Control):** PAS showed average glomerular and tubular BM with preserved brush borders, cell borders, and nuclear details (Fig 7 & Table 4). Mallory’s stain showed no fibrosis.
• **Group II:** (Cisplatin low dose): PAS showed mild thickening of glomerular BM. Renal tubules showed partially
preserved brush borders with partially preserved nuclear details and indistinct (poor) cell borders (Fig 8 & Table 4). Mallory’s stain showed thin irregular glomerular and tubular BM (Fig 13 & Table 5)

- **Group III**: (Cisplatin high dose): PAS showed marked thickening of glomerular BM. Renal tubules showed partially preserved brush borders with loss of nuclear details (Fig 9 & Tables 4). Mallory’s stain showed thin irregular Bowman's capsule and tubular BM (Fig 14 & Table 5)

- **Group IV**: (Metformin high dose): PAS showed mild thickening of glomerular BM, with preserved tubular BM and brush borders (Fig 10 & Table 4). Mallory’s stain: showed thin irregular Bowman, s capsule and tubular BM (Fig 15 & Tables 5)

- **Group V**: (Cisplatin + Metformin low dose) PAS showed mild thickening of glomerular and tubular BM with partially preserved brush borders (Fig 11 & Table 4). Mallory’s stain showed thick irregular Bowman, s capsule and tubular BM (Fig 16 & Table 5).

- **Group VI**: (Cisplatin + Metformin high dose) PAS showed marked thickening of glomerular BM with preserved brush borders with loss of nuclear details of renal tubules (Fig 12 & Table 4).

<table>
<thead>
<tr>
<th>Groups</th>
<th>PAS Glomerular BM</th>
<th>Tubules Glomerular BM</th>
<th>Brush border</th>
<th>BM Cell borders</th>
<th>Nuclear details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Group II</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Group III</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Group IV</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group V</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Group VI</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Glomerular BM: 0 = Average  + = Mild/moderate thickening  ++ = Marked thickening
Brush border: 0 = Preserved  + = Partially preserves  ++ = Lost
Tubular BM: 0 = Average  + = Mild/moderate thickening  ++ = Marked thickening
Cell borders: 0 = Preserved  + = Partially preserves  ++ = Lost
Nuclear details: 0 = Preserved  + = Partially preserves  ++ = Lost

Mallory’s stain showed thick irregular formation (Fig 17) and medullary fibrosis (Fig 18 & Tables 5).
Fig 7 (Control): Average glomerular BM with preserved brush borders. Fig 8 (Cisplatin low dose): Mild thickening of glomerular BM with partially preserved brush borders. Fig 9 (Cisplatin high dose): Marked thickening of glomerular BM with partially preserved brush borders. Fig 10 (Metformin high dose): Mild thickening of glomerular BM with preserved brush borders. Fig 11 (Cisplatin + Metformin low dose): Mild thickening of glomerular BM with partially preserved brush borders. Fig 12 (Cisplatin + Metformin high dose): Marked thickening of glomerular BM with preserved brush borders (PAS stain X400)
Fig 13 (Cisplatin low dose): Thin irregular glomerular & tubular BM. Fig 14 (Cisplatin high dose): thick irregular Bowman’s capsule and tubular BM. Fig 15 (Metformin high dose): Thin irregular Bowman, s capsule and tubular BM. Fig 16 (Cisplatin + Metformin low dose): Thick irregular Bowman, s capsule and tubular BM. Fig 17 (Cisplatin + Metformin high dose): Thick irregular glomerular BM, Bowman, s capsule and tubular BM. Fig 18 (Cisplatin + Metformin high dose): Medullary fibrosis (Mallory’s stain X400)
DISCUSSION

Cisplatin is well known for its nephrotoxic effects producing many histopathological changes like vascular congestion, focal mononuclear cell inflammatory, cellular infiltrate, acute tubular injury with reactive atypia and apoptotic cells (Alhoshani et al. (2017) marked necrosis of proximal tubules and degeneration of the tubular epithelial cells which is related to an increase in lipid peroxidation, oxygen-free radicals, and inflammation in kidney (Kundan et al. (2013). Pezeshki et al., 2017, suggested that the cisplatin -induced nephrotoxicity started to develop almost 3 days after administration of the drug in rats.

Metformin had been suggested to have therapeutic or reno-protective effects against nephrotoxic agents (Nasri, 2013 and Rafieian-Kopaei & Nasri, 2013). Li et al. (2016) demonstrated that metformin may protect against cisplatin-induced tubular cell apoptosis. Sahu et al., (2013) showed in their study marked ameliorative effects of metformin on renal functions and attributed this improvement to antioxidant and cytoprotective effects of metformin.

Our study showed obvious decrease in average total body weight of rats given cisplatin injection. These results agree with results of the study of Akunna et al. (2018) who showed a significant decrease in final body weight of cisplatin treated rats. Our study showed that this average loss of body weight was noted to be less on giving metformin with cisplatin.

Sahu et al. (2013) reported that a single injection of cisplatin (7.5 mg/kg, i.p.) caused a significant increase in blood urea nitrogen and serum creatinine. These results were in accordance to our findings which showed marked increase in renal functions on giving cisplatin injection which were more elevated on increasing cisplatin injected dose from 3.5 mg/kg to 7.5 mg/kg. When metformin was given, blood urea nitrogen and serum creatinine levels were decreased. Amini et al. (2012) showed that post-treatment with metformin or co-treatment could prevent the elevation of serum BUN and that metformin may prevent or ameliorate gentamycin induced acute renal failure.

Our histopathological study showed marked histological changes as seen by H&E on giving cisplatin injection (3.5 mg/kg) and when the injected dose of cisplatin was increased from 3.5 mg to 7.5 mg; more cortical necrosis occurred, viable glomeruli showed marked deformity and hypercellularity with obliterated Bowman's spaces, tubular epithelia showed numerous necrotic/apoptotic tubular cells with numerous intra-tubular hyaline casts and Interstitial tissues showed markedly dilated congested blood vessels which agrees with the study of Sahu et al. (2013) who reported that a single injection of cisplatin (7.5 mg/kg, i.p.) caused a significant renal damage.

On giving single injection of 7.5 mg cisplatin + metformin 100 mg/kg/day, mild glomerular deformity and cellularity and patent Bowman's spaces were seen. Proximal tubular epithelia were less
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oedematous with scattered necrotic/apoptotic epithelial cells, while distal tubular epithelium was edematous with few intra-tubular hyaline casts. Obvious less necrosis/apoptosis was seen with narrow to patent Bowman's spaces and mildly oedematous tubular epithelial cells and less interstitial congestion and few intra-tubular hyaline casts were seen in rats which were given 7.5 mg cisplatin+ metformin 350 mg /kg/day for 10 days. It was also notable that the effects of 100mg/kg metformin + 7.5 mg/ kg cisplatin was much better than giving 350 mg/kg metformin with same high dose of cisplatin (7.5 mg /kg) for same 10 days period.

Our histochemical study using PAS and Mallory stains showed that 3.5 mg/kg injected dose of cisplatin led to mild thickening of glomerular BM, partially preserved cell and brush borders of tubules and that on increasing the injected dose of cisplatin to 7.5mg/kg marked thickening of glomerular BM with more loss of renal tubular brush borders were noted. Cisplatin + metformin groups showed more preservation of brush borders especially on increasing the dose of metformin to 350 mg/day where better preservation of brush borers of tubules was noted. Our findings were in accordance with other studies that proved that metformin preserved brush borders, decreased cell death and the damaging effects of cisplatin. Metformin proved to minimize the damaging effects of cisplatin. These findings were similar to findings of Fatemeh et al. (2012) who concluded from their study that metformin is a nephron-protective drug that could attenuate the tubular damage caused by gentamycin or other nephrotoxic agents.

Reduction of apoptosis, induced by oxidative stress, in endothelial cells and prevention of vascular dysfunction was found with metformin treatment (Nasri, 2013). Also, Taheri et al., 2012, reported found that there was an ameliorative property of metformin against unilateral ischemia–reperfusion induced injury in rats.

CONCLUSION

Metformin produced significant protection against cisplatin-induced nephrotoxicity especially in low dose.

REFERENCES


تقييم التأثيرات الوقائية المحتملة للميتفورمين على التسمم الكلوي المحدث من السيسبلاتين على الجرذان البيضاء

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خلفية البحث: استخدام مركب السيسبلاتين محدود نتيجة سُميته على الكلى لما يحدث من زيادة اضطراب الأكسدة، مما يؤدي في النهاية لخلل وظائف الكلى.

الهدف من البحث: تقييم التأثير الواقعي لمادة الميتفورمين من التسمم الكلوي المحدث من مادة السيسبلاتين لجرذان التجارب البيضاء البالغة.

مواد وطرق البحث: قُسم ستون جرذًا ألي旺ًا بعناية بأشكال عشوائي إلى ست مجموعات متساوية: المجموعة الأولى خُصقت بجرعة 1 ملغ/جرام من مخلل مذاب متساوي التطور بداخل تموج البرتينون، والمجموعة الثانية خُصقت بجرعة واحدة من السيسبلاتين 3.5 ملغ/جرام لكل كيلوغرام بداخل تشغيل البرتينون. المجموعة الثالثة خُصقت بجرعة واحدة 7.5 ملغ/جرام لكل كيلوغرام من مادة السيسبلاتين بداخل تشغيل البرتينون. المجموعة الرابعة أعطت جرعة 350 ملغ/جرام لكل كيلوغرام يوميًا من مادة الميتفورمين عن طريق الفم لمدة 10 أيام. المجموعة الخامسة أعطت جرعة 100 ملغ/جرام لكل كيلوغرام يوميًا من مادة الميتفورمين عن طريق الفم لمدة 10 أيام، ثلاثية أيام قبل حقنها اليوم الرابع مرة واحدة بمادة السيسبلاتين 7.5 ملغ/جرام لكل كيلوغرام بداخل تشغيل البرتينون، وسبعة أيام بعدها. أما المجموعة السادسة فأعطت 350 ملغ/جرام لكل كيلوغرام يوميًا من الميتفورمين عن طريق الفم لمدة 10 أيام، ثلاثية أيام قبل حقنها مرة واحدة اليوم الرابع بمادة السيسبلاتين 7.5 ملغ/جرام لكل كيلوغرام، وسبعة أيام بعدها. وتم وزن الجرذان في اليوم الأول والرابع والسابع والعشر من أيام التجربة، وتم حساب متوسط وزن أجسام الجرذان لكل مجموعة. وعند نهاية المدة المحددة (10 أيام) دُرحت الجرذان وتم استخلاص الكليتين من كل جرذة، ثم تم تحضيرها وصبغها بصبغة الأيوسين والهيماتوكسيلين لكي يتم دراسة أنسجتها، وكذلك صبغها بصبغة المالوري وشيف الحامضية الدورية لفحص أنسجتها كيميائيًا.
الخلاصة: مادة الميتفورمين لها تأثيرات تقلل من التناقش السمعي لمادة السيسبلاتين على كلى الجرذان الذكور البيضاء البالغة.