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Original Article

Morphological and Morphometric Study of Edaravone in Gentamicin-Induced Nephrotoxicity in Sprague Dawley Rats

Rajavel Varatharajan[1*], Lee Hui Jun[2], Tan Zhi Kai[2], Lim Wai Jian[2], James Anburaj[3], Venugopal Vijayan[4]
[1]Pharmacology Unit, Faculty of Pharmacy, AIMST University, Semeling, 08100 Bedong, Kedah Darul Aman, MALAYSIA.
[2]Undergraduate Students, Faculty of Pharmacy, AIMST University, Semeling, 08100 Bedong, Kedah Darul Aman, MALAYSIA.
[3]Pharmaceutics Department, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil, Srivilliputtur, 626126, Tamil Nadu, INDIA.
[4]Pharmaceutical Technology Unit, Faculty of Pharmacy, AIMST University, Semeling, 08100 Bedong,Kedah Darul Aman, MALAYSIA.

ABSTRACT

Background: Gentamicin is an antibiotic that exhibits a broad spectrum of activity against microorganisms. Now a days uses of gentamicin are limited due to it potentially induces nephrotoxicity by selective accumulation of gentamicin in the kidney. Edaravone is a potent anti-oxidant. It strongly scavenges free radicals, protecting the cells against oxidative stress. Due to the contribution of oxidative stress to the pathogenesis of nephrotoxicity, we tested the hypothesis of edaravone in gentamicin-induced nephrotoxicity in rats. **Methods:** Various parameters including animal body weight, kidney weight, body weight to kidney ratio, serum creatinine level, serum urea level and histopathology were analysed in nephrotoxicity animals (induced with gentamicin 100 mg/kg/body weight *i.p.,*) with and without edaravone (10 mg/kg/body weight *i,p.,*). **Results:** Gentamicin control rats shows that the body weight and kidney weight has been decreased, while kidney weight to body weight ratio, serum creatinine and serum urea were increased significantly while comparing with the normal control rats. Moreover marked renal histopathological abnormalities like glomerulosclerosis, glomerular hypertrophy, tubular cell degeneration and renal arteriolar hyalinization were seen in the gentamicin control rats. Edaravone attenuated the biochemical analyses such as, serum creatinine and serum urea. It also reduced the kidney weight to body weight ratio significantly. Edaravone treated groups showed slightly increase in the body weight and kidney weight but not statistically significant. Renal histopathological abnormalities were reduced in the edaravone treated rats as its compare with gentamicin control rats. Edaravone *per se* group shows no toxicity to normal rats. **Conclusion:** Our study suggests that edaravone ameliorated renal structural and functional abnormalities associated with experimental nephrotoxicity. With the biochemical parameters and histopathological studies, we concluded that edaravone reduced the toxicity caused by gentamicin and can be used against nephrotoxicity.

Key words: Gentamicin, Edaravone, Nephrotoxicity, Renoprotection

Correspondence :

Dr. Varatharajan Rajavel,

Pharmacology Unit, Faculty of Pharmacy, AIMST University, Semeling, 08100 Bedong, Kedah Darul Aman, MALAYSIA.

Phone: 0060-173166982; Fax: 006 044268132

Email: varadharajeen@gmail.com

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INTRODUCTION

Nephrotoxicity is one of the most common side effects and therapeutical limitations of aminoglycoside antibiotics, particularly gentamicin (GM). In spite of rigorous patient monitoring, nephrotoxicity appears in 10-25% of therapeutic progresses. Conventionally, aminoglycoside nephrotoxicity has been considered to be mainly from tubular damage. Both lethal and sub-lethal alterations in tubular cells may lead to a significant tubular obstruction. Moreover, a reduced glomerular filtration is the symptoms of the disease. Reduced filtration is not solely the result of tubular malfunction and tubular obstruction, resulting in the renal vasoconstriction; tubuloglomerular feedback activation and mesangial contraction.[1,2] It is also associated with an induction of tubular necrosis, cellular desquamation, tubular fibrosis, epithelial edema of proximal tubules, perivascular edema, glomerular congestion and inflammation, which ultimately show the way to renal dysfunction.[3] Gentamicin-induced nephrotoxicity is characterized by slow rises in serum creatinine, tubular necrosis and marked decreases in glomerular filtration rate and in the ultrafiltration coefficient. Regulation of the ultrafiltration coefficient depends on the activity of intra-glomerular mesangial cells.[4] Gentamicin (GM) is still widely used against infections by Gram-positive and Gram-negative aerobic bacteria. Its therapeutic efficacy, however, is limited by renal impairment that occurs in up to 30% of treated patients. The drug may accumulate in epithelial tubular cells causing a range of effects starting with loss of the brush border in epithelial cells and ending in overt tubular necrosis, activation of apoptosis and massive proteolysis. GM also causes cell death by generation of free radicals, phospholipidosis, extracellular calcium-sensing receptor stimulation and energetic catastrophe, reduced renal blood flow and inflammation.[5] Many drugs have been shown to either ameliorate or potentiate GM nephrotoxicity. Green tea, garlic saffron, grape seed extracts as well as sesame and oleanolic oils are the agents that may augment GM nephrotoxicity include indomethacin, cyclosporin, uric acid and the Ca(++) -channel blocker verapamil. Because of their relative safety and effectiveness, antioxidant agents seem to be good candidates for testing in humans.[5]

Edaravone is chemically known as 3-methyl-1-phenyl-2-pyrazolin-5-one, it is a synthetic-free radical scavenger.[6] It was the first neuroprotective drug to be introduced in worldwide by Japan in treating patients with cerebral infarction.[6] Moreover it's has a potent free radical scavenging effects, edaravone possesses anti-necrotic and anti-apoptotic effects in varies diseases of animal models.[7] Therefore, it might be necessary to investigate its therapeutic potential in nephrotoxicity in associated with oxidative stress and cell death. In effect of several studies confirmed renal and cardiovascular beneficial actions of edaravone. Undeniably, edaravone administration just prior to reperfusion has reduced the oxidative stress and improved acute myocardial infarction by the long-term clinical outcomes.[8] Similarly, edaravone pharmacological post conditioning applied

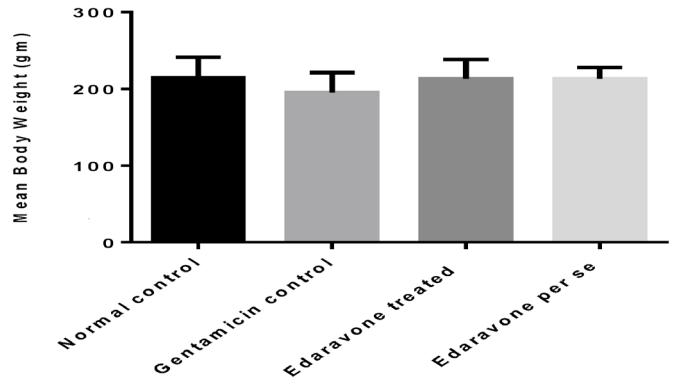


Figure 1: Effect of edaravone on mean body weight on 8 days study. Data are expressed as mean ± SEM. Body weight did not show statistically significant among the four groups (n=6 per group).

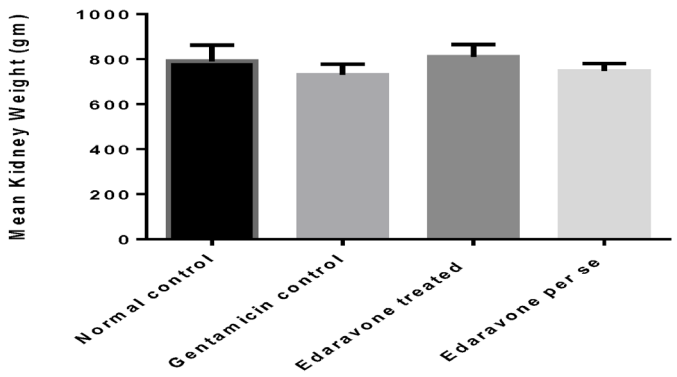


Figure 2: Effect of edaravone on mean kidney weight. Data are expressed as mean ± SEM. Mean kidney weight did not show statistically significant among the four groups (n=6 per group).

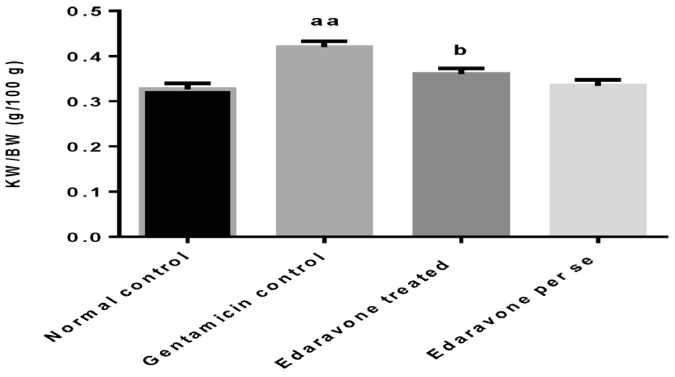


Figure 3: Effect of edaravone on kidney weight to body weight ratio (KW/BW). Data are expressed as mean ± SEM (n=6 per group). ^{aa}P< 0.01 vs Normal control; ^{b}P< 0.05 vs Gentamicin control.

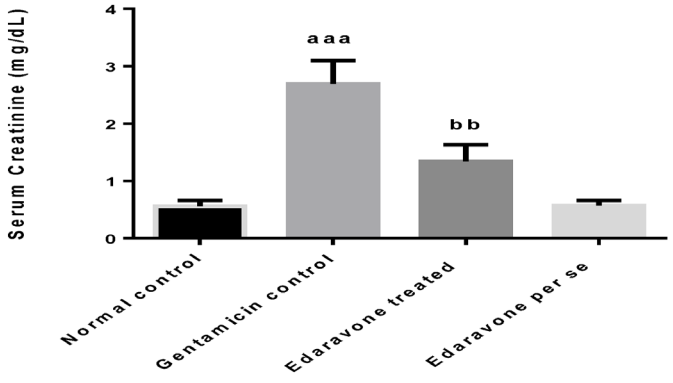


Figure 4: Effect of edaravone on serum creatinine (mg/dL) concentration. Data are expressed as mean ± SEM (n=6 per group). ^{aaa}P< 0.001 vs Normal control; ^{bb}P< 0.01 vs Gentamicin control.

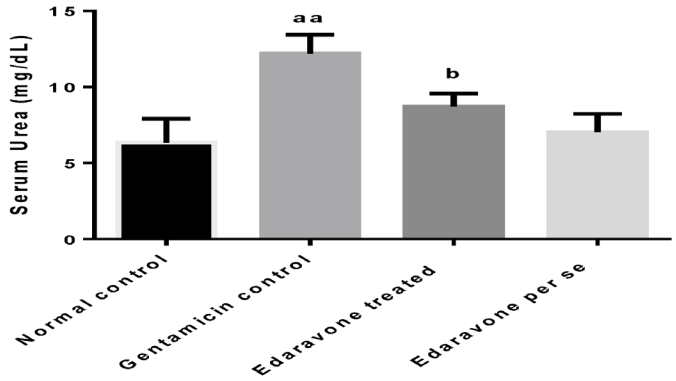


Figure 5: Effect of edaravone on serum urea (mg/dL) concentration. Data are expressed as mean ± SEM (n=6 per group). ^{aa}P< 0.01 vs Normal control; ^{b}P< 0.01 vs Gentamicin control.

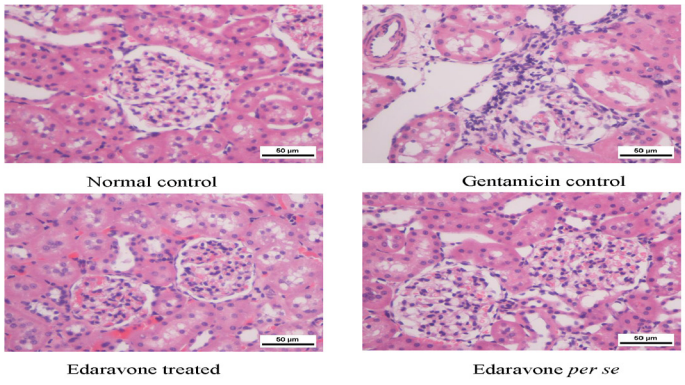


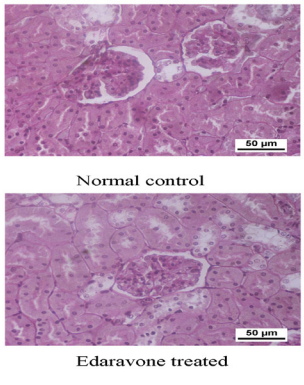
Figure 6: Effect of edaravone on renal histology using Haematoxylin and eosin staining.

before the onset of coronary reperfusion in rats provided decrease in the oxidative stress in myocardial infarct size.[9] It also shows significantly reduce the myocardial infarct size and to recover the cardiac function and left ventricular remodelling by reducing the cardiac oxidative stress during reperfusion in rabbits.[10] In effect, edaravone was proposed to be a novel option for the treatment of cardiovascular disease.[7] Interestingly, edaravone has been shown to protect canine kidneys from ischemia-reperfusion injury by improving the tubular cell function, renal vascular resistance and lowering the mean serum creatinine.[11] The present study aimed to investigate the effect of edaravone in renal toxicity (nephrotoxicity) in rats.

METHODS

Drugs and chemicals

Edaravone and Gentamicin were purchased from Sigma-Aldrich Ltd., St. Louis, MO, USA. All other chemicals used in the present study were of analytical grade. Gentamicin (100 mg/kg/day, *i.p.*) dissolved in freshly



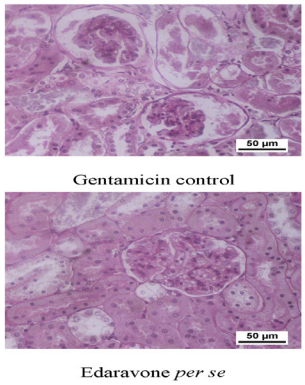
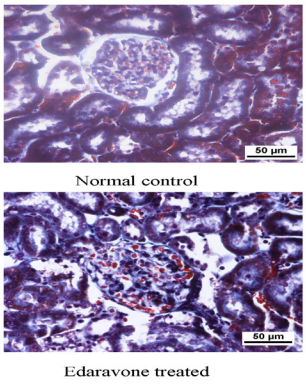


Figure 7: Effect of edaravone on renal histology using Periodic acid-Schiff staining.



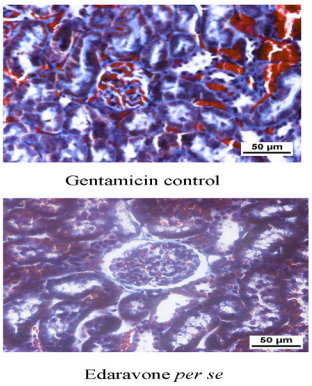


Figure 8: Effect of edaravone on renal histology using Masson trichrome staining.

prepared saline solution was administered to induce nephrotoxicity in rats. Edaravone (10 mg/kg/day, *i.p*) dissolved in freshly prepared saline solution was administered to treatment group and *per se* group. At the end of the study, the serum creatinine, serum urea level and other biochemical parameters were measured. The kidney was incised for morphological and histopathological studies.[12]

Animals

This study was carried out for 8 days. All the experimental procedures were approved by the AIMST University Human and Animals Ethics Committee (AUHAEC 19/FOP/2013) and complied with the guidelines of the care and use of laboratory animals at the AIMST University, Malaysia. Rats were acclimatized in the AIMST Central Animal House and allowed for access of water and food ad libitum. Rats were exposed to normal day and night cycles.

Effect of edaravone in gentamicin-induced nephrotoxicity

Twenty four healthy male Sprague Dawley (SD) rats, weighing between 140-170 g were used in the study. Four groups were employed in the study and each group comprised six rats.

Group I : **Normal control group:** Normal control rats were kept, maintained and allowed free access to water and food. No drug or treatment was given.0.9% normal saline was administered daily once *i.p*., according to their body weight.

Group II : **Gentamicin control group:** Gentamicin was administered to rats at a dose of 100 mg/kg/body weight *i.p*., daily once for the induction of nephrotoxicity.

Group III : **Gentamicin + Edaravone (pre-treated) group:** The rats were given edaravone via intraperitoneal route at a dose of 10 mg/kg/body weight daily once and 100 mg/kg/body weight of gentamicin daily once is also given via intraperitoneal route after one hour of pre-treated edaravone. [16,30]

Group IV : **Edaravone per se group:** Normal rats were injected with edaravone intraperitoneally route daily once at a dose of 10 mg/kg/body weight to test for any toxicity of the edaravone in normal rats.

Induction of experimental nephrotoxicity: Rats administered with Gentamicin (100 mg/kg/day *i.p.*) were allowed for 8 days to develop experimental nephrotoxicity.

Biochemical and morphological assessments of nephrotoxicity

The development of nephrotoxicity was assessed in rats by measuring the kidney weight to body weight ratio (KW/BW) g kidney weight/100 g body weight, serum creatinine level and serum urea level. The biochemical estimations were done using commercially available Reflotron strips assay kit employing Reflotron Plus Apparatus (Roche Diagnostics, Germany).

At the end of 8 days study, the treated and untreated rats were euthanized and sample was collected by cardiac puncture.[13] Blood sample from each rat was collected, centrifuged at 9000 rpm for 5 min and serum was collected. Using a micropipette, 30 µL of serum was drawn into the pipette (avoiding bubbles) and applied as a drop to the centre of the red application zone on the Reflotron assay strips, without touching the application zone. Before starting the analysis, a calibration for each parameter was done using standard calibration strips. The calibration value was in the range of (631~ 651), (632~652) and (624~644) nm. The assay strip was placed into the Reflotron apparatus for biochemical analysis. The concentrations of serum creatinine and serum urea were expressed in mg/dL.

Histopathological analysis

The isolated kidney was rinsed immediately in 0.9% normal saline and kept in 10% buffered formalin solution. After 10% neutral buffered formalin fixation, the renal tissue was embedded in paraffin. Tissue sections were cut at 4 µm thickness using a microtome, dewaxed, and stained using haematoxylin and eosin (H&E), Periodic acid-Schiff (PAS) and Masson's trichrome. Renal histological changes within the glomeruli, tubules and interstitial areas were assessed using Digital Binocular Microscope at 40X (Model: DN-117M, Brand-Inter Bridge, Quick Lab Sdn. Bhd, Malaysia).

Statistical analysis

The results were expressed as mean ± standard error mean (SEM). Data obtained from various groups were statistically analysed by one way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. The '*p*' value of less than 0.05 was considered as statistically significant.

RESULT

Mean body weight

The mean body weight of normal control group, gentamicin control group edaravone treated group and edaravone *per se* group. *i.p.*,) are shown in the Figure 1. The mean body weight of gentamicin control group showed lesser than the normal control group, but it was not statistically significant (195.6 ± 11.48 vs 214.4 ± 12.06 gm). The rats

treated with edaravone showed slight increase in the body weight while comparing with gentamicin control group. However this increase was not statistically significant. Edaravone *per se* group showed no changes in the mean body weight.

Mean kidney weight

The mean kidney weight of animals in normal control group, gentamicin control group, edaravone treated group and edaravone *per se* group are shown in Figure 2. As compared to the normal control animals, the gentamicin control group showed a slight decrease in mean kidney weight, this decrease was not statistically significant. In contrast, there was an increase in the mean kidney weight when the edaravone treated group was compared to gentamicin control group but these mean kidney weight was not statistically significant. Edaravone *per se* group showed no changes in the mean kidney weight.

Kidney weight / Body weight (KW/BW)

The mean kidney weight/ body weight of animals in normal control group, gentamicin control group, edaravone treated group and edaravone *per se* group are shown in Figure 3. As compared to the normal control group, the gentamicin control group showed a significant increase in the KW/BW (g/100 g BW) (P<0.01). However, gentamicin animals treated with edaravone showed significant reductions (P<0.05) in the KW/BW as compared to gentamicin control group (Figure 3). Edaravone *per se* group showed no changes in the KW/BW as compared to the normal control group (Figure 3).

Serum creatinine

The serum creatinine of animals in normal control group, gentamicin control group, edaravone treated group and edaravone *per se* group are shown in figure 4. The serum creatinine level in gentamicin control group was increased significantly by 5 fold (P< 0.001) as compared to normal control group. In contrast, gentamicin rats treated with edaravone showed a significant (P< 0.01) reduction in the serum creatinine level as compared to the gentamicin control group (Figure 4). Edaravone *per se* group showed no changes in the serum creatinine level as compared to the normal control group (Figure 4).

Serum urea

The serum urea was noted to be significantly increased in gentamicin control group as compared to normal control group (P<0.01). Interestingly, edaravone treatment group showed an observable decrease in serum urea level (P< 0.05). The serum urea level in edaravone *per se* group shows no change in the serum urea level as compared to the normal control group (figure 5).

Histopathological study

Figures 6 to 8 shows histological observations of kidney sections stained with H&E, PAS and Masson's trichrome, respectively. Renal tissue sections of control rats showed normal glomeruli and tubules. However, glomerular injury, glomerulosclerosis, glomerular hypertrophy, shrunken nucleus, interrupted tubular basement membrane, hyaline, tubular necrosis and degeneration of cortical tubules were noted in renal sections obtained from gentamicin control group. These histopathological changes have been noted to be markedly reduced in the edaravone treatment group and edaravone *per se* group (Figures 6 to 8).

DISCUSSION

The drug gentamicin is widely used in clinical practice because of their efficacy against gram-negative bacterial infections, synergistic activity with β-lactam antibiotics, reduced cost, and tapered bacterial resistance. Recent reports have been shown that about 30% patients treated with gentamicin for more than a week, revealed certain symptoms of renal impairment.[14-16] The primary cause for gentamicin induced nephrotoxicity is believed by oxidative stress. It has been suggested that reactive oxygen species (ROS), formed due to oxidative stress have a vital role in the pathway of renal tubular necrosis. ROS are capable of stimulating nuclear factor kappa β that in turn triggers the instigation of inflammatory process.[2,17,18] Several other studies reported the role of reactive oxygen species in implicating the pathogenesis of gentamicin-induced nephrotoxicity.[19] Gentamicin-induced kidney damage is characterized by apoptosis, renal tubular epithelial cell necrosis, oxidative stress, inflammatory responses, and vascular contraction.[20,21] In the present study, we demonstrated the protective effects of edaravone in a gentamicin-induced nephrotoxicity model.

Additionally, prominent increase in serum creatinine and urea concentration is suggested by a sign of significant impairment of kidney function in gentamicin induced nephrotoxicity.[22,23] In the present study, we have measured both serum creatinine and urea concentrations. Gentamicin control group shows a significant increase in serum creatinine and urea concentrations similar to that of other studies.[24-26] Administration of edaravone along with gentamicin in the curative groups assisted in restoring the serum creatinine and urea concentration to normal levels.

Histopathological studies are often used to analyse the renal structural abnormalities of the kidney. In the current study, the histopathological analysis using H&E, PAS and Masson's trichrome staining revealed the occurrence of mesangial cellularity with extracellular matrix accumulation in the glomerular structure, glomerulosclerosis, glomerular hypertrophy, hyalinization of the vessels and tubular cell degeneration in the kidney of treated rats. Moreover, the KW/BW was noted to be increased to some extent, which is significantly, in gentamicin control rats as compared to normal rats. These results confirm the development of renal structural abnormalities and nephrotoxicity in gentamicin control rats after 8 days of gentamicin administration. Remarkably, the aforementioned structural and functional abnormalities were significantly prevented by treatment with edaravone in nephrotoxicity rats, representative the therapeutic potential of edaravone in inhibiting the development of nephrotoxicity in gentamicin rats. It is worth mentioning that the renoprotective action of edaravone was noted to be similar to that of green tea[25] and cilostazol, a phosphodiesterase III inhibitor.[27]

By considering the oxidative stress in the pathophysiology of nephrotoxicity, antioxidants therapy opted to be an alternative choice in its management. The natural antioxidants such as β-carotene,[28] a terpenoid constituent of the crude extract can ameliorate the nephrotoxicity by its free radical scavenging activity. Edaravone, is a synthetic-free radical scavenger [6] besides its potent free radical scavenging effects, edaravone possesses anti-apoptotic and anti-necrotic effects in animal models of various diseases.[7] Edaravone possess nephroprotective property by promoting antioxidant enzyme system, thereby attenuating ROS generation and lipid peroxidation as similar to Wongmekiat *et al*., 2008.[29] In evidence of this, the edaravone treatment group can contribute to nephroprotection by its antioxidant activity. Thus, all together from the results of biochemical and morphologic pathology, edaravone treatment group has the ability to halt the gentamicin nephrotoxicity by having rich antioxidant and cellular anti-inflammatory property.[30-32]

CONCLUSION

Our study suggests that edaravone possesses a significant result in lowering the kidney weight to body weight ratio, serum creatinine level and serum urea level while comparing with the gentamicin control rats. Besides, from the result of this research which showed that edaravone *per se* did not show any changes in the normal rats, it can be concluded that

edaravone administer in the normal rats did not produce any toxicity. In addition, histopathology has proved that the edaravone treated animal shows with minimal toxicity in comparing with the gentamicin groups. In conclusion, edaravone treatment could reduce the risk of renal dysfunction by preventing injuries to the renal structure in gentamicin-induced nephrotoxic rats.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ABBREVIATION USED

GM: Gentamicin; **Ca:** Calcium; **SD:** Sprague Dawley; **KW/BW:** Kidney Weight to Body Weight ratio; **H & E:** Hematoxylin and eosin stain; **PAS:** Periodic acid–Schiff staining; **ROS:** Reactive Oxygen Species.

HIGHLIGHTS OF PAPER

Nephrotoxicity is one of the common most side effects and therapeutical limitations of aminoglycoside antibiotics, particularly gentamicin.

Edaravone is a potent anti-oxidant. It strongly scavenges free radicals, protecting the cells against oxidative stress.

The renal structural and functional abnormalities were significantly prevented by treatment with edaravone in nephrotoxicity rats.

Edaravone treatment group can contribute to nephroprotection by its antioxidant activity.

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