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The Modern Use of Stem Cells in Treatment of Renal Failure in Rat Model

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Stem cells are undifferentiated cells capable of proliferation and differentiation. They can yield a large number of differentiated functional progeny creating the tissue after injury. Stem cell therapy is a modern type of intervention strategy that is introduced to treat a specific disease. Renal failure is one of the most common causes of mortality and morbidity all over the-world. Treatment options of chronic renal failure (CRF) mainly involve renal transplantation in addition to dialysis. Kidney transplantation is hampered by shortage of donors while dialysis is encumbered by several limitations and is associated with several socioeconomic problems for the patients. We aim in this study to evaluate the use of stem cells in treating induced renal failure via kidney oxidation and apoptotic parameters. The subjects were classified into five groups that received cisplatin to induce renal damage, blood and tissue samples were collected. Stem cells decreased the elevated urea, creatine, cystatin c and interleukin 18 caused by cisplatin in addition to improving the oxidative reservoir measured by glutathione and MDA. This suggests that under the conditions of this study, stem cells could correct the renal damage induced by cisplatin in rats.

I. INTRODUCTION

Cisplatin is an anti-cancer agent; it is one of the most important drugs in chemotherapy with applications of 50% of human cancers among 700 FDA-approved drugs ***(Boulikas, 2007)***. It is one of the cheapest and most effective chemotherapeutic drugs used in treatment of various types of solid tumors such as testicular, ovarian, head, neck and lung carcinoma ***(Barabas et al., 2008 and Jia et al., 2011)***.

However, the use of such drug is limited in human therapy due to its serious side effects. Thus, prevention of these side effects is one of the major hurdles in treating cancer. Although, many trials to prevent the side effects of cisplatin such as the synchronous use of anti- oxidants have been tested, yet, there is no effective methods for its clinical use have histological architecture of the kidney***(Chang et al., 2002; Vickers et al., 2004).***

El-Sayed et al. (2008), Noori and Mahboob (2008) and Abdel Gawad and Mohamed (2010) confirmed that administration of cisplatin resulted in a significant increase in the levels of urea and creatinine in comparison to standard parameters. Moreover, cisplatin precipitated marked elevation in lipid peroxides as malondialdehyde (MDA) in addition to a decrease in glutathione (GSH) content of kidney tissue compared to control group. They also said that, morphologically, cisplatin caused a marked elevation in kidney weight and decreased total body weight.Microscopically, cisplatin affected all renal tubules especially the proximal convoluted tubules (PCT) that have been seenbeen established ***(Nishikawa et al., 2001).*** Renal damage is the major side effect preventing cisplatin application in cancer therapy ***(Miller et al., 2010).***

Davis et al. (2001) and Ganesan and Brian(2004)reported-that-the-nephrotoxic-effect-of-this chemotherapeutic drug is mediated by decreased protein synthesis, DNA damage, membrane peroxidation and mitochondrial dysfunction.

Many researches revealed that cisplatin administration induced structural and functional renal damage in the form of epithelial cytoplasmic vacuolization, necrosis and sloughing of lining epithelium that obstructed the tubular lumen. These lesions resulted in a significantincrease of serum creatinine and urea levels in addition to loss of normalmanifestation of luminal degenerative-trash.-Cytoplasmic-vacuolization alongwithout the brush border (microvilli) with can replace diseased or damaged areas in the body, with minimal side effects and rejection risk ***(Weissman, 2000 ; Lindvall and Kokaia, 2006).***

In last years, many contradictory researches were published regarding the medical use of bone marrow-derived stromal cells (BMSCs) in treatment of kidney diseases. Some results declared that BMSCs contributed

significantly to daily turnover of renal tissue and to a high degree during recovery from tissue insult ***(Morigi et al., 2004 ; Bi et al., 2007)***, whereas others indicated that this is rare event seen only in a very limited cases following injury ***(Brodie andHumes, 2005).***

Morigi et al. (2004) said that injury to a target organ can be recognized by bone marrow stem cells which transport from the site of origin to the site of damage then undergo differentiation and

with increased lysosomal bodies were noticed following cisplatin administration. Mitochondria had obscure crystals. Nuclei of most the of PCT epithelial cells showed corrugated nuclear envelope with frequent nuclear pores ***(Abdel Meguid et al., 2010; Ravindra et al., 2010).***

Stem cell therapy is a modern type of intervention strategy that is introduced into damaged tissue in order to treat a specific disease or injury. Many medical physicians believe that stem cells have the ability to change the future of human disease and terminate suffering. The potential of stem cells to proliferate and give rise to subsequent generations with different degrees of differentiation capacities, offers marked potential for the generation of tissues thatpromote structural and functional repair. They reported that mesenchymal stem cells injection had protected mice renal functions from cisplatin destructive effect.

Bi et al. (2007) mentioned that injection of BMSCs decreased the severity of cisplatin-induced acute renal failure, decreased tubular cell apoptosis and improved tubular cell proliferation following injury. These studies were agreed by ***Wan et al. (2010)*** who mentioned that BMSCs could differentiate into the tubular epithelial cells directly, improving the functions of kidney and healing acute renal failure in mice after cisplatin administration.

Bussolati and Camussi (2007), in opposite to the previous research, stated that BMSCs are capable of migration to the hurt kidney which seem to play a minor role in tubular regeneration as regard to the resident cells.

II. MATERIALS AND METHODS

Work design

Fifty adult male albino rats were used in the study. The rats were housed in metal cages. All the ethical protocols for animal treatment were followed and supervised by the animal house, Faculty of science, Al- Azhar University. The rats were divided into five equal groups, ten rats each group:

Group A (plain control): did not receive any medication.**Group B (cisplatin):** received a single dose of intraperitoneal injection of **5mg/kg** body weight cisplatin then killed after 5 days to ensure renal damage ***(Chang et al., 2002).*****Group C: (Cisplatin and saline)**: each rat was intraperitoneally injected by a single dose of **cisplatin, 5mg/kg** body weight followed by a single dose of 1 ml saline (IV) after 5 days ***(Chang et al., 2002).*****Group D (Cisplatin and Mesenchymal stem cells treated-group)**-each-rat-was-intraperitoneally injected with a single dose of **cisplatin, 5mg/kg** body weight followed after 5 days by intravenous injection of **mesenchymal stem cells** in the tail vein of the animal, in a dose of **(10^6) cells / animal*(Tögel et al.,2005).***

Group E (Recovery group): each rat received-a-single-dose-of intraperitoneal injection-of-**5mg/kg**-body-weight-cisplatin and sacrificed at the end of the experiment to evaluate recovery.

Standard deviation (SD). Statistical significance and difference from control and test values were evaluated by analysis of variance (ANOVA) using SPSS. P values <0.05 was considered statistically significant,while P < 0.01 was considered statistically highly significant.

Isolation of BM-derived MSCs from rats:

Bone marrow was harvested by flushing the tibiae and femurs of 6 weeks old male albino rats with Dulbecco's modified Eagle's medium (DMEM,GIBCO/BRL)-supplemented-by-10%-fetal-bovine-medium (GIBCO/BRL). Nucleated cells were isolated with a density gradient[Ficoll/Paque-(Pharmacia)] and resus-pended-in complete-culture medium-supplemented-by-1%-penicillin-streptomycin(GIBCO/BRL).

The cells were incubated at 37° C in 5% humidified CO_2 for 12-14-days-as-primary-culture-or-upon-formation-of-large-colonies.When-large colonies developed-(80-90%-confluence),-cultures-were-washed twice with phosphate buffer saline (PBS) and cells were trypsinized with 0.25% trypsin in 1mm EDTA (GIBCO/BRL) for 5-minutes-at-37◦-C.-After-centrifugation (at 2400 rpm for 20-minutes)-cells-were-resuspended-in-serum-supplemented medium and incubated in 50 cm^2 culture flask (Falcon). The resulting cultures were referred to as first passage cultures **(Abdel Aziz et al., 2007)**.

Biochemical study

By the end of the experiment, serum urea and creatinine levels were measured using colorimetric method, serum IL18, cystatin C were measured by ELISA, glutathione, SOD and MDA were detected by spectro. The results were subjected to statistical analysis.

Statistical analysis

The results of morphometeric and biochemical studies were expressed as mean± standard

III. RESULTS

Control groups (Group I)

In control group, no differences were observed between morphological findings of such group and known normal rat kidney appearance.

Histological examination of the rat kidney specimens showed renal cortex containing Malpighian corpuscles and convoluted tubules. Each renal Malpighian corpuscle appeared as a rounded structure and formed of a glomerulus surrounded by Bowman's capsule. The glomerulus consisted of a capillary tuft which lined by endothelial cells with numerous nuclei. Bowman's capsule had visceral layerattached to the glomerulus and thin parietal layer which surrounded by a basement membrane and lined by simple squamous epithelium. Bowman's space (urinary or capsular space) existed between the visceral and parietal layer (figs.1). The cells of macula densa were seen near to vascular the renal corpuscle. Their nuclei appear to be much closer to each other (fig.1).

The proximal convoluted tubules had narrow lumens and lined by a few number of cuboidal cells with rounded nuclei as well as apical brush border (figs.1). The distal convoluted tubules had wide lumens and were lined by cuboidal cells with rounded nuclei and rested on basement membrane with no brush border (figs. 1).

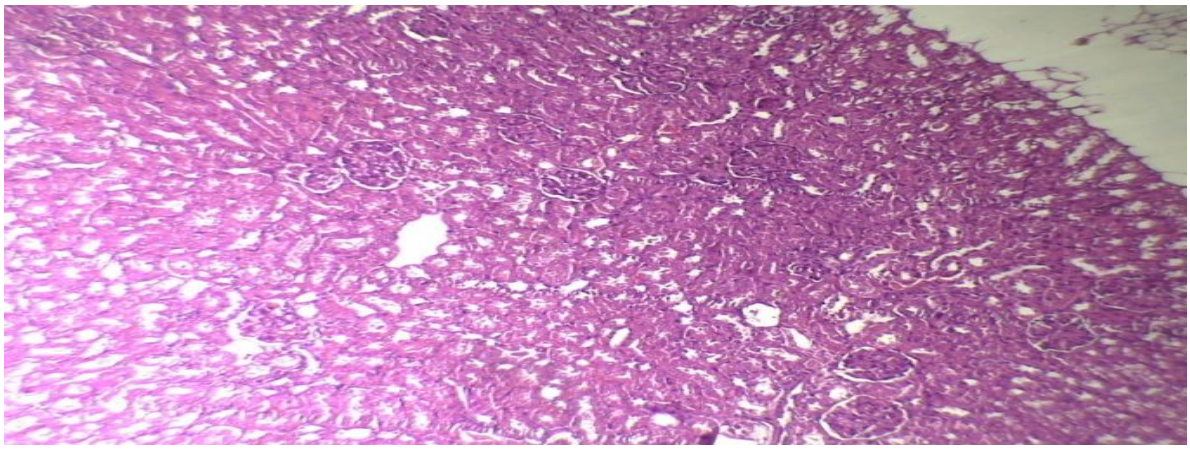

Fig. (1): Section from the kidney showing normal-sized, normocellular glomeruli, uniform tubules lined by cuboidal cells with no evidence of cystic dilation or cast formation (H&E, 100X)

Cisplatin administration group (Group II)

As compared to the control groups, light microscopic examination of kidney specimens of the animals exposed to cisplatin injection revealed degenerative changes in the form of shrunken glomeruli, with wide Bowman`sspace as well as thickening of parietal layer of Bowman`scapsule, ill-defined outline of some renal glomeruli (fig.2)

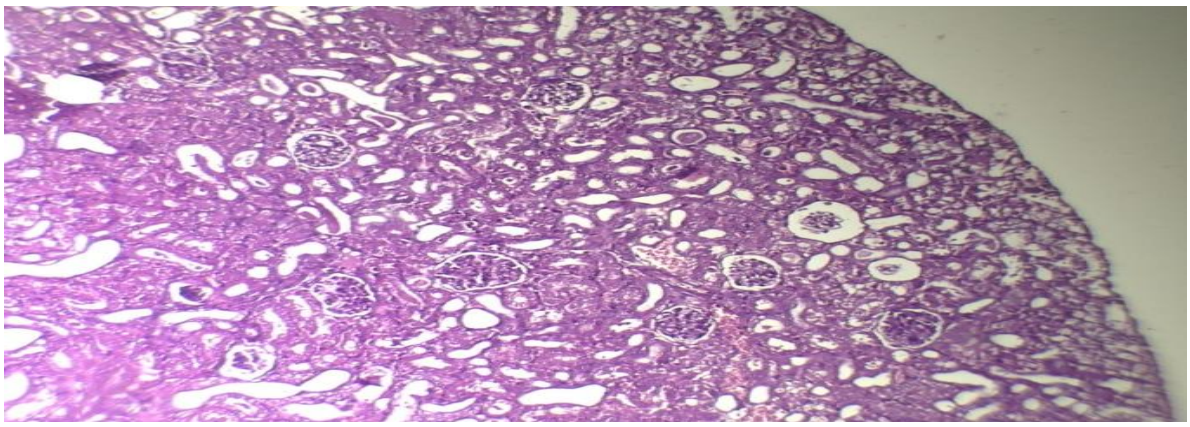

Fig. (02): Section from the kidney showing acute tubular necrosis with dilatation of tubules, epithelial flattening, brush border loss in proximal tubules, and sheddingof cells decreased number of glomeruli with scattered severe atrophic glomeruli (H&E, 100X)

Mesenchymal stem cells treated group after cisplatin administration (Group IV) As compared to the control groupsadministration of bone marrow derived stem cells one day after cisplatin injection resulted in reduction of the pathological changes as regard to the extent and degree-produced-by-cisplatin-administration-alone.

Light microscopic-examination of the rat kidney specimens revealed almost normal appearance of most of the glomeruli and renal tubules. Each renal glomerulus appeared rounded with preserved normal histological architecture. The glomerulus consisted of a capillary tuft with numerous nuclei (figs.3). The parietal layer of Bowman´s capsule was seen as single layer similar to the control group as well as normal appearance of the capsular space. However, mild shrinkage of some renal glomeruli and dilatation of Bowman`s (capsular) space were noticed (fig.3) denoting the variable degree of regeneration triggered by BMSCs.

Group injected with saline (group v)

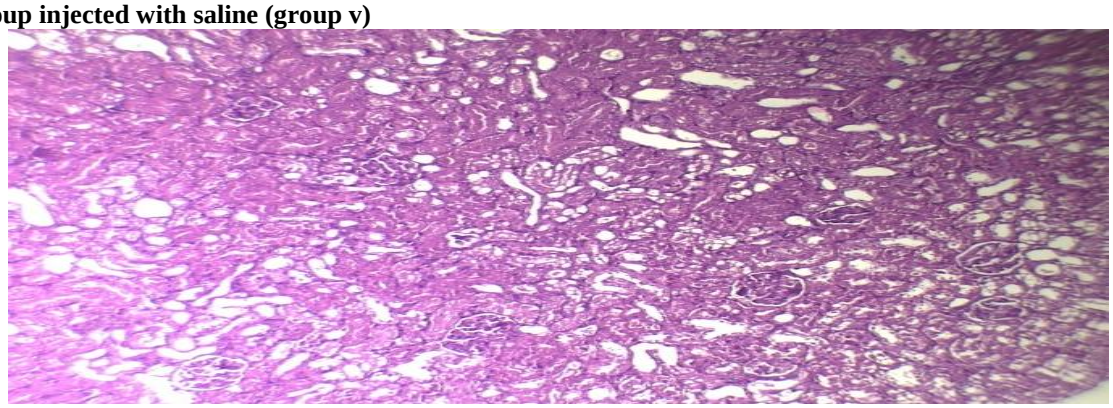

Figure 3 Fig. (03): Section from the kidney showing moderate dilatation of tubules, moderate atrophic glomeruli and few interstitial mononuclear inflammatory cell infiltrate (H&E, 100X)

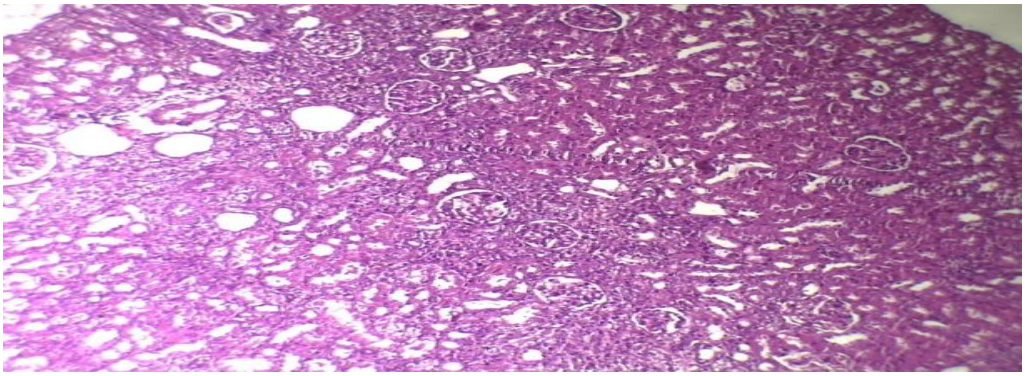

Fig. (4): Section from the kidney showing chronic pyelonephritis. Where, interstitial and periglomerular fibrous areas accompanied-of-mononuclear inflammatory cells. (H&E, 100X)

Recovery group (IV)

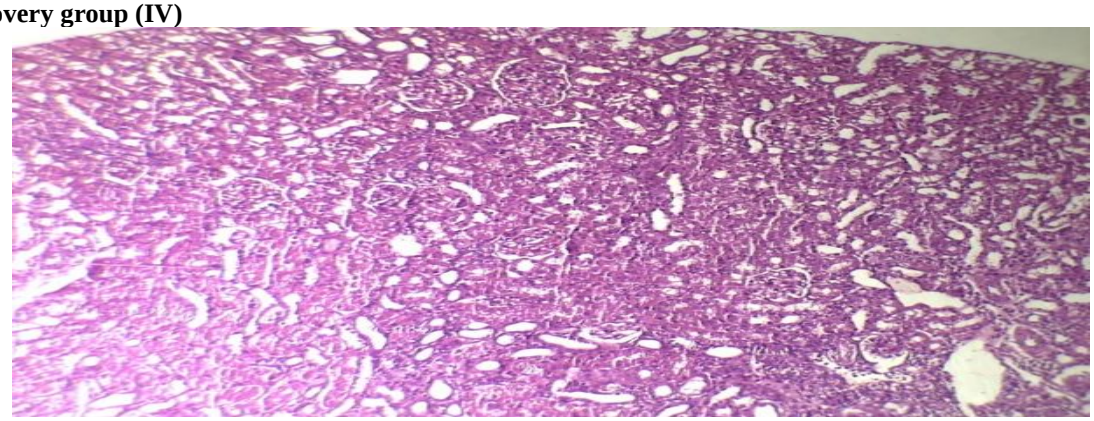

Fig. (5): Section from the kidney showing few atrophic glomeruli and glomerulonephritis, moderate tubular necrosis with dilatation of tubules and moderate interstitial mononuclear inflammatory cell infiltrate (H&E, 100X)

Table 1: concentrations of creatinine, urea, IL18, cystatin c, glutathione, SOD and MDA in normal, cisplatin,mesenchymal, saline and recovery groups.						
		Control (10)	Cisplatin (8)	Mesenchymal (8)	Saline (7)	Recovery (7)
Creatinine	(Mg-dl)	**0.464**	**2.464**	**0.87**	**1.57**	**1.31**
Urea	(Mg-dl)	**22.5**	**69.62**	**23.25**	**27.14**	**26**
IL18	(pg/ml)	**32.4**	**67**	**36**	**40.28**	**39.14**
Cystatin-c	(mg/l)	**4.752**	**7.795**	**3.15**	**4.61**	**4.44**
Glutathione in-tissues	(mmol/g)	**24.85**	**17.65**	**22.23**	**20.4**	**19.84**
SOD	(u/g-protein)	**1.604**	**0.99**	**1.45**	**1.21**	**1.086**
MDA in tissues	(nmol/g)	**60.6**	**121.37**	**65.58**	**76.81**	**73.28**

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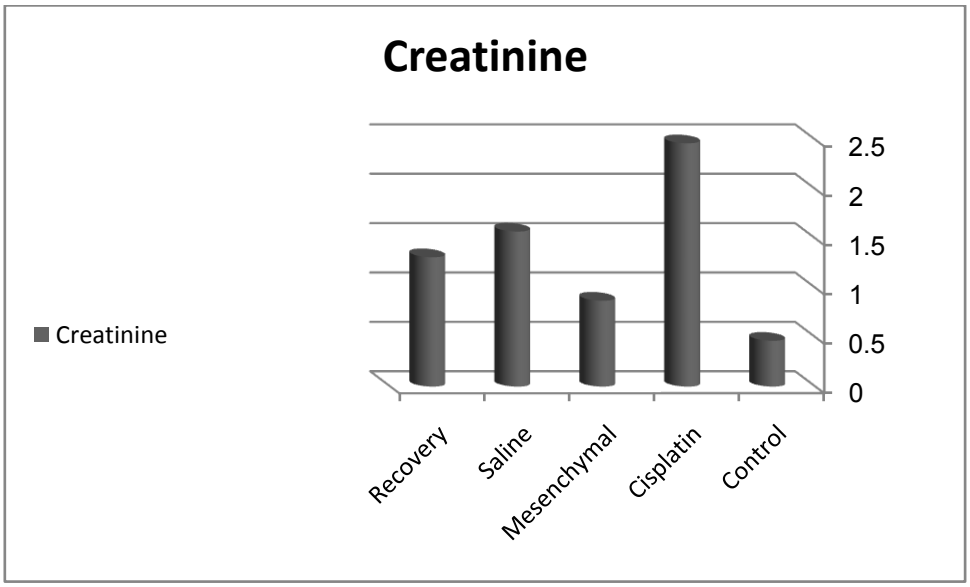

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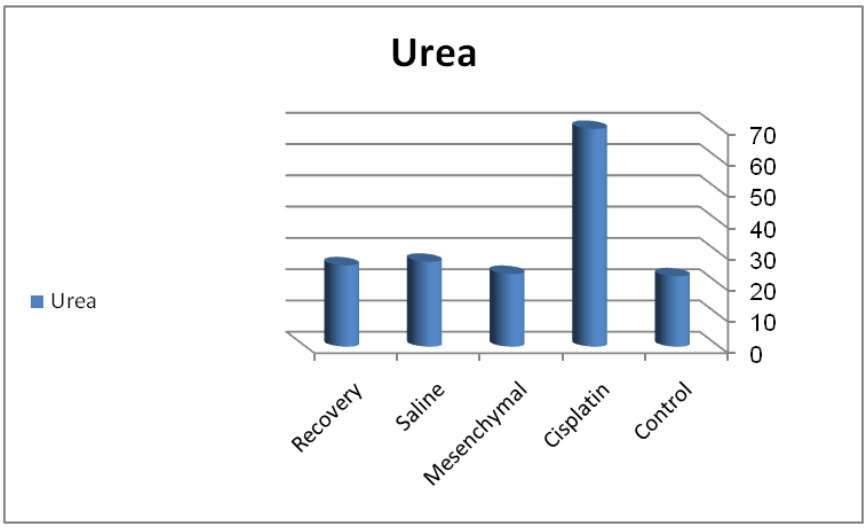

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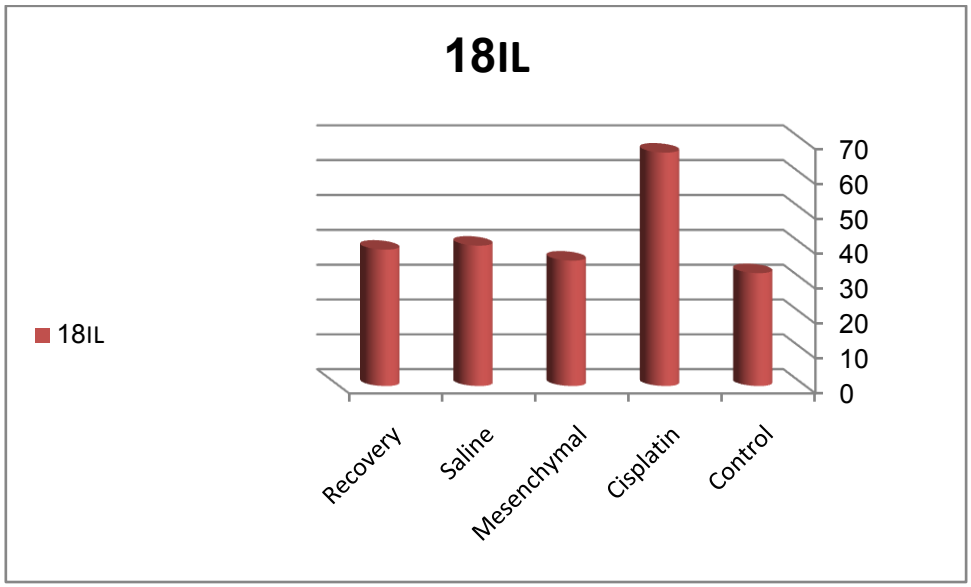

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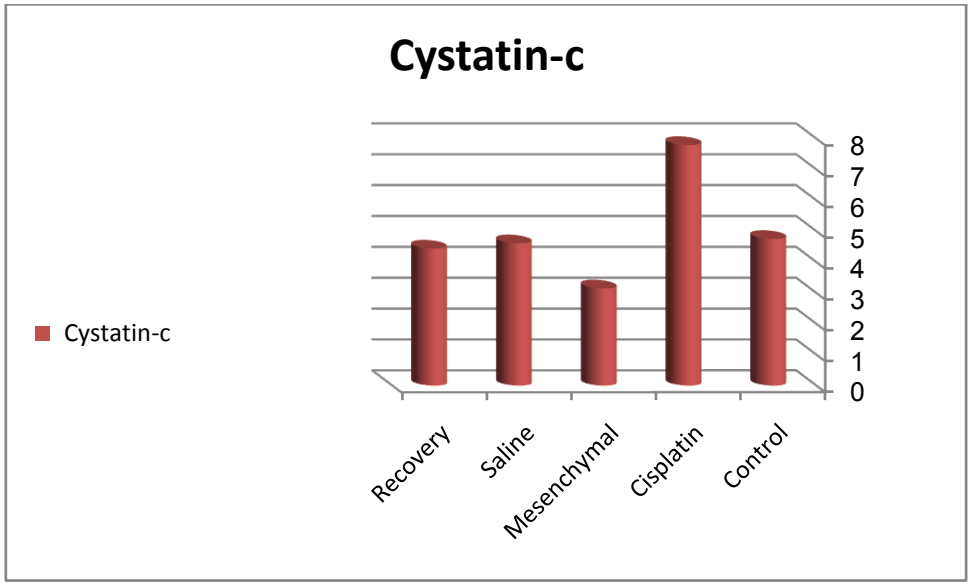

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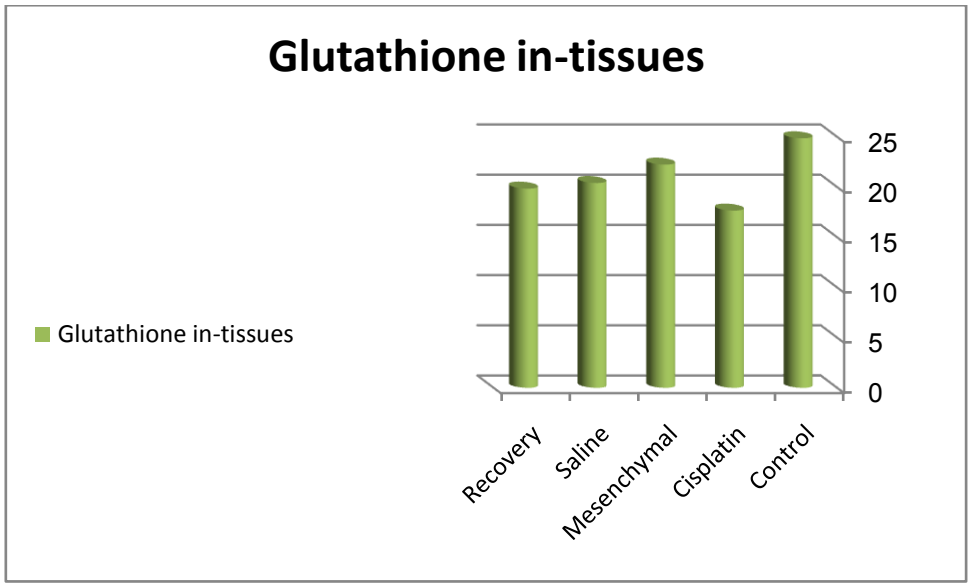

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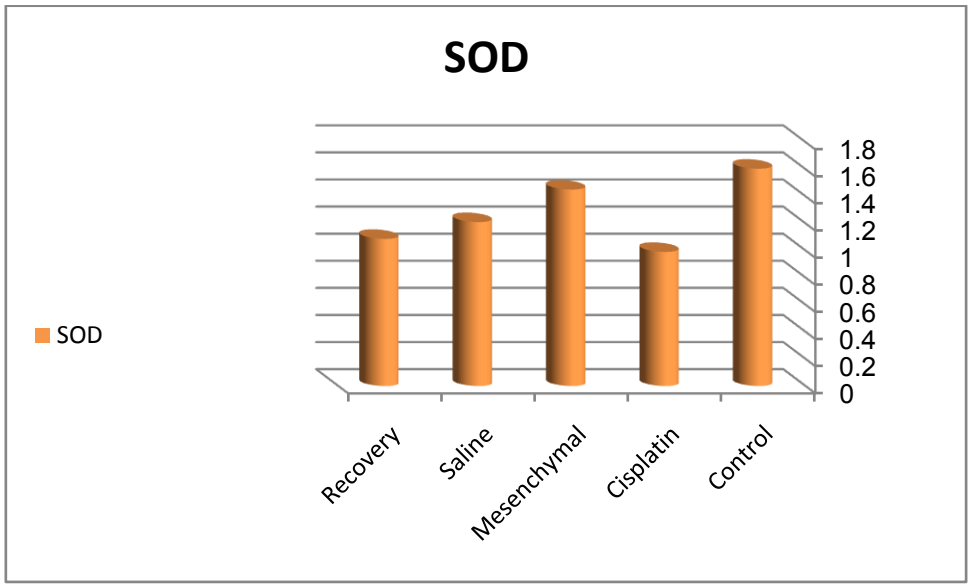

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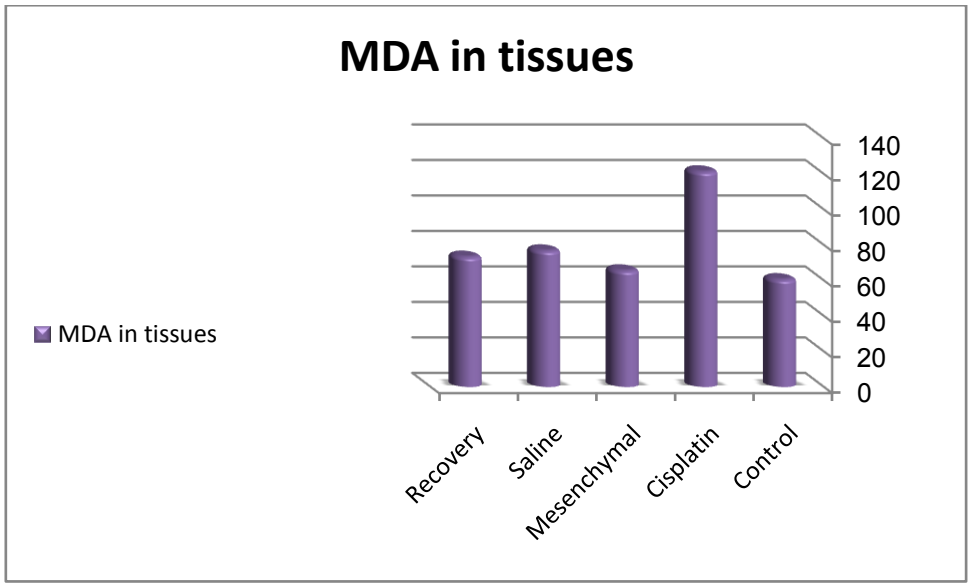

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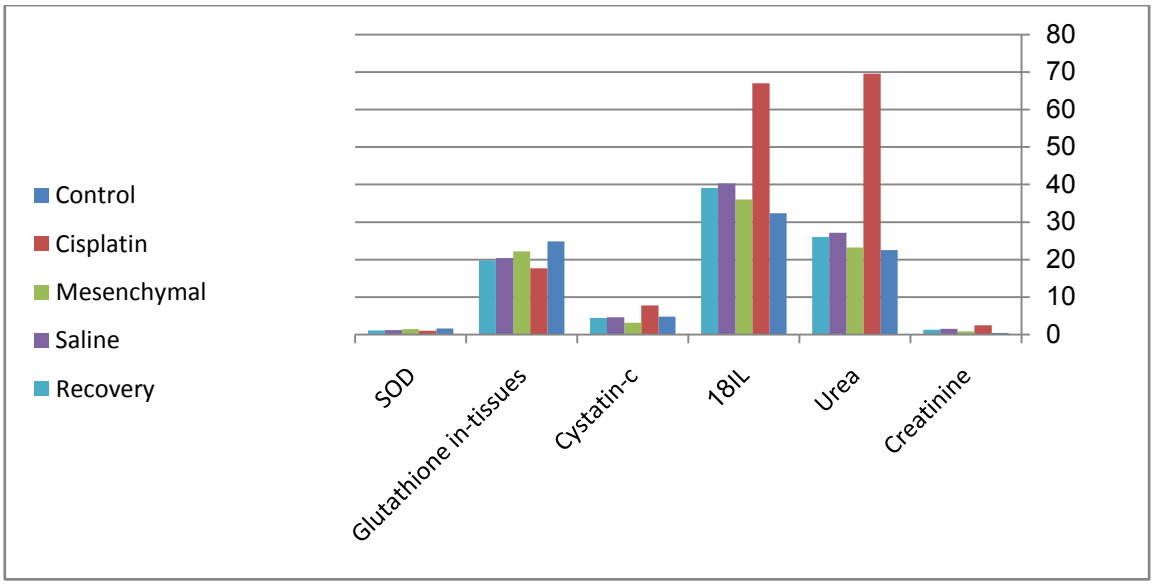

IV. DISCUSSION

In ongoing work, Fluromicroscopic examination of the kidney revealed that MSCs had been homed in the renal tissues.

BMSCs injection after cispaltin administration in the current work resulted in morphological, histologically and biochemical recovery, approaching the normal parameters group indicating its ability to differentiate and repair the damaged renal tissue.

Nephrotoxicity is a well-known complication of cisplatin which limits its use as anticancer drug. Acute kidney injury is one of the most serious and common complication induced by cisplatin administration which occurs in 20–30% of patients treated by this drug ***(Miller et al., 2010 and Al-Kharusi et al., 2013)***

In the present work, administration of cisplatin (5 mg/kg i.p.) resulted in an overt nephrotoxicity as evidenced by the detection of morphological and histological changes by light microscope in addition to biochemical manifestations of impaired renal functions.

Morphologically, rats intoxicated by a single injection of cisplatin showed no obvious changes in body weight as compared to control group.In similar study, ***Gautier et al. (2010)***reported that rats injected by cisplatin showed no changes in their body weights.

Contradiction to the present data, ***Abdel Meguid et al. (2010)*** mentioned that there was a significant decrease in the body weight as compared to control after cisplatin injection. They reported that in cisplatintreated rats, water and diet consumption was decreased which may be related to gastrointestinal disorders induced by cisplatin. Such discrepancy could be due to use of different period which was 2weeks.

However, cisplatin induced nephrotoxicity was characterized by increased kidney weight in current work as compared to control group. Similar results obtained by ***Shimeda et al. (2005)***and ***Al-Kharusi et al. (2013).***The increase in kidney weight is thought to be due to cellular degenerative changes including cytoplasmic vacuolization of the proximal tubular cells, cellular infiltration, cast formation and tubular dilatation ***(Saad et al., 2000).*** On the contrary to the afore-mentioned findings, ***Lee et al. (2007)*** reported that cisplatin treatment resulted in a significant decrease in kidney weight Such discrepancy could be due to use of different species as they used mice as animal model.

In the current work, cisplatin injection caused structural alterations in the renal glomeruli which appeared shrunken with consequent widening of Bowman`s space as well as ill-defined outline of some renal glomeruli and obliteration of Bowman`s space. These findings were similar to that of ***Shirwaikar et al. (2003)***and ***Abdel Meguid et al. (2010).***The previous results of the present study explained by ***Giuseppa et al.(2009)*** who reported that the reduction in the glomerular size and glomerular collapse were a sequel of glomerular damage process.

Ravindra et al. (2010), also,explained that cisplatin intoxication caused a severe atrophy of glomeruluswhich led to reduction in its size. However, ***AbdelGawad and Mohamed (2010)*** reported that glomeruli were having normal structure after cisplatin injection. This is in contradistinction to the findings of the present work which could be due to use of different dose and period as they used cisplatin in a dose of 7.5mg/kg for five days.

In the present work, single intraperitoneal injection of cisplatin to rats broughtsignificant nuclear changes of both proximal and distal convoluted tubules, in the form of nuclear karyorrhexis, karyolysis and pyknosis which were signs of irreversible cell damage. Some cells lost their nuclei.This is in agreement with results reported by ***Abdel Gawad and Mohamed (2010)*** who stated that cisplatin administration causedrenal tubular necrosis which affected mainly proximal convoluted tubules.

Moreover,the cumulative effect of cisplatin and its by product culminate their cytotoxic effects through interaction with DNA leading to cell death. In an aqueous environment, the chloride ligands of cisplatin are replaced by water molecules generating a positively charged electrophile which reacts with nuclear DNA. The produced cisplatin-DNA intra-strand crosslinks resulted in cytotoxicity and were thought to be responsible for cellular death ***(Galea and Murray, 2002 and Boulikas andVougiouka, 2003).*** Another suggestion was that ROS in cisplatin induced nephrotoxicity directly acted on DNA and destroyed it ***(Ajith et al., 2007).*** These reports could explain the observed lesions in the present work.

Biochemically, this study demonstrated that treatment with cisplatin administration impaired renal functions which manifested by increased serum urea and creatinine levels as compared to control. Similar results obtained by ***Somani et al. (2000)and Aydogan et al. (2008)***, who suggested that tubular injury which include obstruction and back leak of glomerular filtrate could be involved in the decrease in glomerular functions in cisplatin-treated rats. The alterations in glomerular functions may also be secondary to ROS which induced mesangial cells contraction, altering the filtration surface area and modifying the ultrafiltration coefficient factors that decreased the glomerular filtration rate. Another postulation by ***Ozen et al. (2004) and Noori and Mahboobc (2010)*** who reported that administration of cisplatin to rats caused a reduction in glomerular filtration rate leading to increased urea and creatinine levels in plasma.

Moreover, serum levels of IL18 and cystatin c were significantly increased after administration of cisplatin in cisplatin group, while intravenous injection of stem cells caused a decrease in such parameters. This is agreed with***Sarah Faubel et al., 2007***who posted that cisplatin caused damage failure in rats measured by IL18 and this may be due to activation of inflammatory factors.

Significant depletion of anti-oxidant content was observed in our study in cisplatin group compared to normal control; this is agreed with ***Helen H. and MacusTienKuo. (2010)*** who noticed that this may be because cisplatin inhibits glutamylcysteine synthesis (γ-GCS), the rate-limiting enzyme for GSH biosynthesis.

Increasing in free radicles caused elevation in lipid peroxidation that could be measured by high levels of malondialdehyde(MDA) this is agreed by***Mashal M. Almutairi etal., (2017).***

The protective and regenerative mechanisms MSCs were incompletely understood. Some have reported that MSCs directly replaced injured renal tissues whereas other observations suggested that MSCs regulated the endogenous reparative mechanism without trans differentiation through paracrine and endocrine effects, including mitogenic, anti-apoptotic, anti-inflammatory and angiogenic influences***(Humphreys and Bonventre, 2008).***

Kotton et al. (2001) reported that MSCs can differentiate into various epithelial cell types after systemic administration. Moreover, ***Loeffler and Roeder (2002)***mentioned that mesenchymal cells can shift from one differentiation pathway to another under modified external conditions and can shift from quiescence to proliferative state.

Morigi et al. (2004)explained that injury to a target organ can be sensed by the injected bone marrow stem cells that migrate to the site of the damage, undergo differentiation and promote structural and functional repair. MSCs engrafted the damaged kidney and differentiated into tubular epithelial cells, thereby restoring renal structure and function indicating that the exogenous administration of MSCs could promote both structural and functional renal repair via the trans-differentiation of MSCs into tubular epithelium.***Rookmaaker et al. (2007)***declared that bone-marrow-derived stem cells may home to injured glomerular endothelium, differentiate into endothelial cells and participate in regeneration of the highly specialized glomerular microvasculature.

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