

Deleterious Effect of Urografin on the Renal Tubules of Adult Albino Rats and the Possible Protective Effect of N-Acetylcysteine Light and Electron Microscopic Study

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ABSTRACT

Introduction: Urografin (UG) is one of several types of contrast media used through the extensive use of investigations as imaging and interventional procedures. Multiple complications were encountered from its usage especially kidney affection, in a condition described as Contrast-induced nephropathy (CIN) which may be prevented with the antioxidant N-Acetylcysteine (NAC).

Aim of the work: To study the effect of Urografin on the renal tubules of albino rats and evaluate the role of N-Acetylcysteine administration on the injured tubules.

Materials and Methods: Twenty four adult albino rats were used regardless sex and were divided into 4 groups; a control group, NAC group by its administration in a dose equivalent to the human dose twice daily, Urografin group; where rats received a high dose of Urografin 76% solution through rat tail vein infusion and UG + NAC group; where rats received the same dose of Urografin 76% and NAC. The obtained specimens were examined by both light and electron microscopy.

Results: NAC group showed the same normal histological picture of renal tubules as the control group I. Renal sections of UG group revealed tubular dilatation with the presence of cellular debris in their lumens. Some tubules showed destruction and displayed highly vacuolated cytoplasm and dark pyknotic nuclei. Ultrastructurally, damaged apical membrane with partial loss of microvilli and rarefaction of the cytoplasm were noticed. UG + NAC group showed evidence of improvement as compared to UG group. Most of the tubules showed a nearly normal histological picture except for a few dilated ones with cellular debris.

Conclusion: N-Acetylcysteine exerts a protective effect against renal tubular damage of the kidney that has been induced by Urografin injection. So, it may be a useful protective agent before and during imaging procedures.

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INTRODUCTION

The extensive use of investigations as imaging and interventional procedures is widely used all over the world to help in diagnostic and therapeutic purposes. This is associated with an increase in the use of contrast agents specially after the use of Contrast Media CM which began in medicine in the early 1950s^[1].

Several types of contrast media (CM) vary in their chemical and physiological properties which determine their application. Iodine-based contrast media increases the attenuation of X-ray beams, so they are frequently used for computed tomography (CT). Gadolinium-based contrast agents are frequently used for magnetic resonance imaging (MRI)^[2,3].

Iodinated contrast media is a substance that can be given by intravenous route during X-ray based radiographic diagnosis. Their uses help in vascular and organs visibility^[4]. The Contrast Media CM go through

the circulation then ,it is eliminated from the body after 24 hours through glomerular filtration in case of normal kidney functions^[5].

Unfortunately, like most other drugs, complications may follow the administration of CM. These complications usually affect the kidney because it is responsible for elimination of more than 90% of the media from the blood. This kidney affection is commonly described as Contrast-induced nephropathy (CIN) which can be defined as a complex form of acute kidney injury with an acute reduction in renal functions, but it might be reversible in some patients^[6].

The frequency of CIN increases in risk patients as those with hypertension, diabetes, renal insufficiency, old age and with concomitant administration of drugs that interfere with the renal perfusion, such as angiotensin-converting enzyme inhibitors. Some reports stated that CIN is linked to be higher with intra-arterial CM administration than after intravenous administration^[7]. Also, the concentration and

time of exposure play a role in its side effects, especially when large doses are used, as in percutaneous cardiac interventions^[8].

Urografin is an ionic monomer, high osmolar, radiographic CM. It contains a mixture of sodium amidotrizoate and meglumine amidotrizoate in a proportion of 10:66 in an aqueous solution, so, 1 ml of Urografin 76% contains 0.1 gm sodium amidotrizoate and 0.66 gm meglumine amidotrizoate. The usual human adult dose of Urografin is 20 ml. Increasing the Urografin dose to 50 or 100 ml considerably increases the diagnostic accuracy which is needed in some circumstances. The dose may be increased yet the rate of injection is 20 ml /minute infusion and time should not be less than 5 minutes^[9].

Several preventive strategies were planned to avoid CIN, but the precise preventive strategy has not been proven up till now. Studies reported the preventive effects of adrenomedullin, Enalapril maleate, Folic acid and Pioglitazone through its vasodilatory and anti-inflammatory properties, so can prevent the development of CIN^[6]. Some authors stated that oral rehydration solution with saline infusion or Statins administration can prevent CIN^[10-12].

Oral administration of the antioxidant N-Acetylcysteine (NAC) reduces the possibility of acute contrast-media-induced nephropathy^[7,13,14]. It has a strong antioxidant effects due to the ability of scavenging free reactive oxygen radicals which explain its reno-protective effects^[15]. It is a safe, inexpensive, and readily available antioxidant that has been proposed as a prophylactic intervention for CIN on top of optimal hydration^[16]. Therefore, the aim of the present work was to investigate the effect of Urografin on the renal tubules and evaluate the role of N-Acetylcysteine (NAC) administration on them.

MATERIALS AND METHODS

Experimental animals

In the present work, twenty four adult albino rats were used regardless sex and of average weight (150-200 grams). The animals were housed in Anatomy department, Faculty of Medicine, Tanta University. They were kept in an appropriate laboratory room with good hygiene and given a balanced diet. All animals were quarantined for 3-days and were inspected once in a day, and unhealthy rats were excluded. The experiment was approved by the local ethical committee of Faculty of Medicine, Tanta University, Egypt. The rats were randomly allocated into the following groups:

Grouping and treatments

1. Group I (Control group): consisted of 4 rats receiving a single normal saline dose equal to the Urografin dose, via tail vein injection.
2. Group II (NAC group): consisted of 4 rats receiving N-Acetylcysteine (Acetylcysteine effervescent) in a dose equivalent to the human dose twice daily by

orogastric gavage for 3 days^[13].

3. Group III (UG group): formed of 8 rats received single dose of Urografin 76% solution, equivalent to the high human dose (100 ml) via tail vein infusion for 5 minutes^[17].
4. Group IV (UG + NAC group): consisted of 8 rats received N-Acetylcysteine (NAC) the same as group II. Then, Urografin was injected the same as in group III and NAC was administered again twice for the next 24 hours after Urografin injection^[13,18].

Urografin (UG) 76% was obtained from Berlimed S.A. Spain. An ampoule contains 20 ml (1ml contains Sodium amidotrizoate 0.1g and Meglumine amidotrizoate). The human adult high dose of 70 kg person is 100 mg. Rats of groups III and IV were given an equivalent dose in the rat tail vein once by 5 minutes infusion. Then, the rats were kept for another 24 hours after the injection^[17].

N-Acetylcysteine (NAC) was obtained from Sedico, Egypt in effervescent form 600 mg per sachet. Rats of groups II and IV were given an equivalent dose of the human 70 kg adult dose 600 mg twice daily for 3 days by oral route before Urografin injection and for 24 hours after. The dose of Urografin and the oral Acetylcysteine was calculated as follows: Dosage = $(M \times Wr) / Wm$ where M= the amount of medication, Wr =weight of rat and Wm=weight of standard physiological man (70kg)^[17,18].

Examination Methods

After 24 hours of Urografin injection of group III and after NAC administration in group IV, rats of the all groups were sacrificed and the kidneys were collected. Half of the specimens were fixed in 10% formol saline and processed for paraffin blocks and prepared for light microscopic examination with Hematoxylin (H) and Eosin (E) stain^[19]. The other half of the specimens were fixed in 2.5% buffered glutaraldehyde and then prepared for transmission electron microscopic examination^[20].

RESULTS

All the rats have tolerated both the Urografin and the N-acetylcysteine NAC treatments well, and all of them survived till the experiment have been finished.

Light microscopic study

Light microscopic examination of H&E stained sections obtained from groups I & II (control group & NAC group) were the same and exhibited the normal histological structure for the renal cortex. The proximal convoluted tubules (PCTs) constitute much of the renal cortex and located near renal corpuscles. They had narrow lumens and were lined by cuboidal epithelial cells with indistinct boundaries and elaborated striated border. The cells had acidophilic granular cytoplasm and rounded vesicular nuclei. The distal convoluted tubules (DCTs) were less encountered than the PCTs. They showed a wide lumen and were lined with short cuboidal cells displaying an

acidophilic less granular cytoplasm and rounded nuclei with no brush border (Figure 1).

After injection of Urografin in group III (UG group) light microscopic examination of the renal cortex sections stained by H& E revealed severe destruction and exhibited tubulo-interstitial injuries. Most of the tubules were dilated with the presence of cellular debris in their lumens. Most of the tubular cells had vacuolated cytoplasm and vesicular nuclei. Some tubules revealed destruction of apical plasma membrane with obvious decrease of their height and displaying highly vacuolated cytoplasm and dark pyknotic nuclei. Some cells lost their nuclei whereas other cells were exfoliated in the tubular lumen. Some disparate tubules showed detachment of their basement membrane. Dilated peritubular space, congested capillaries, mononuclear inflammatory cells and inter-tubular hemorrhage were detected (Figures 2-5).

Examination of H&E stained-sections obtained from the renal cortex of rats treated with Urografin and N- Acetylcysteine (group IV) revealed evidence of improvement as compared to group III. Most of the tubules showed a nearly normal histological picture except for a few dilated ones with cellular debris in their lumens. Some tubular cells exhibited vacuolated cytoplasm and pyknotic nuclei (Figures 6 and 7).

Electron microscopic study

Electron microscopic examination of the control& NAC groups (I, II) revealed cells of the proximal convoluted tubules (PCTs) with apical closely packed long microvilli and basal numerous infoldings enclosing elongated palisade of mitochondria (Figure 8). Cells of the distal convoluted tubules (DCTs) appeared smaller than those of the proximal ones, with few or no microvilli and basal infoldings encompassed the elongated packed mitochondria (Figure 9).

By electron microscopic examination of group III (UG group), the cells of the PCTs showed multiple changes, in the form of damaged apical membrane with partial loss of microvilli. There were no basal infoldings and the mitochondria were disorganized and exhibited different sizes and shapes. In addition, the cytoplasm was rarified with presence of multiple cytoplasmic vacuoles. The nucleus was central with extended chromatin (Figure 10). Some cells appeared ruptured with extrusion of their cytoplasmic organelles into the lumen, as well as loss of basal infoldings (Figure 11). Most of the cells of the DCTs showed interrupted basal infoldings with dispersed pleomorphic mitochondria. Some mitochondria appeared swollen and degenerated with cristolysis. The cytoplasm displayed heterogeneous electron-dense bodies and plenty of cytoplasmic vacuoles. (Figure 12). Some cells revealed destructed apical plasma membrane with lack of microvilli.

These cells showed absence of basal infoldings with abnormal mitochondrial deposition. Several cells exhibited rarified cytoplasm and the nucleus were hyperchromatic with irregular outlines (Figure 13).

Ultrathin sections of the renal cortex of group IV (UG + NAC) confirmed the light microscopic findings revealing a nearly normal renal ultrastructure. The lining epithelium of the convoluted tubules showed nearly normal appearance as rounded euchromatic nuclei and numerous elongated mitochondria in between basal infoldings. Few cells revealed some ultrastructural changes in the form of presence of heterogeneous electron dense bodies and dilatation of intercellular space (Figures 14 and 15). Regarding the DCTs, most cells exhibited a nearly normal appearance (Figure16).

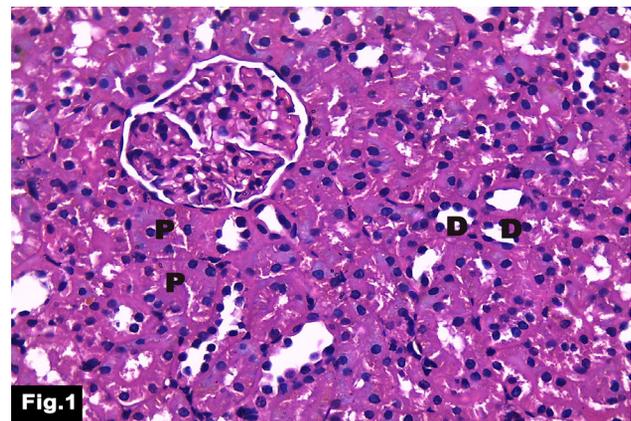


Fig. 1: A photomicrograph of a section in the kidney cortex of control group showing proximal convoluted tubules (P) with narrow lumens. The cells exhibit indistinct boundaries with apical striated border. The distal convoluted tubules (D) show wide lumens and are lined with short cuboidal cells with no brush border. (H&E X400)

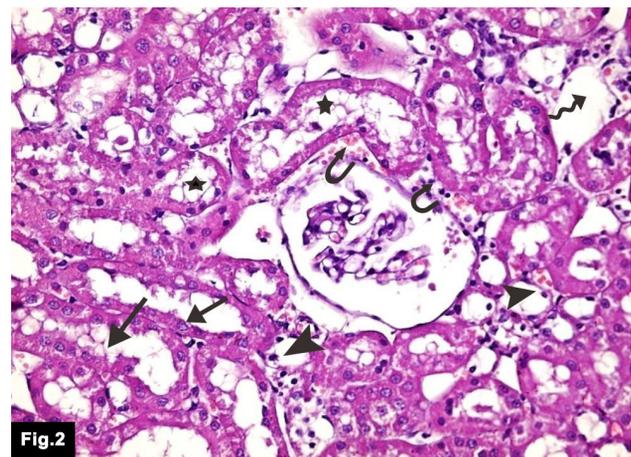


Fig. 2: A photomicrograph of a section in the kidney cortex of group III (UG group) showing dilated renal tubules with cellular debris inside the lumens (stars). The tubular cells have vacuolated cytoplasm and vesicular nuclei (arrows) while, some tubules have decreased cellular heights and pyknotic nuclei (arrow heads). Notice the dilated peritubular space (wavy arrow), peritubular hemorrhage and inflammatory cells (curved arrows). (H&E X400)

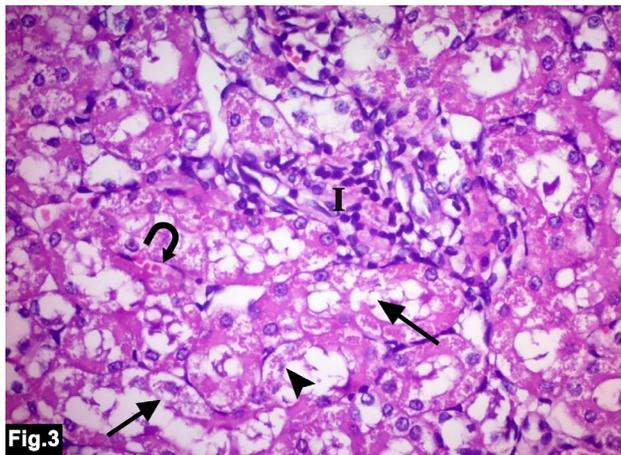


Fig. 3: A photomicrograph of a section in the renal cortex of group III showing severely damaged renal tubules with destroyed apical membrane (→) and vacuolated cytoplasm. Some tubular cells lose their nuclei (▶). Mononuclear inflammatory cells (I) and congested capillaries (curved arrow) are detected. (H&EX400)

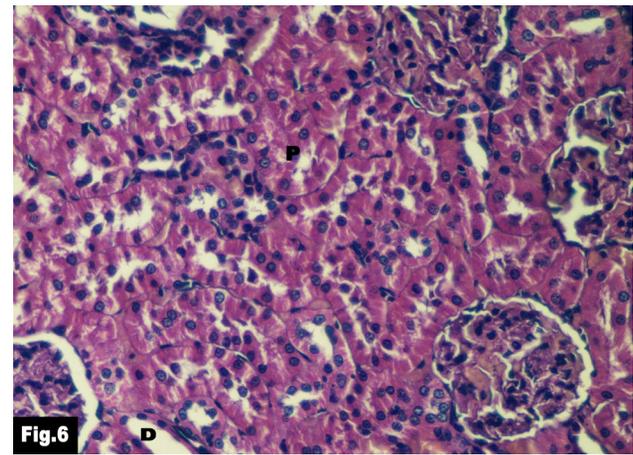


Fig. 6: A photomicrograph of a section in the renal cortex of group IV (UG + NAC group) showing, normal proximal convoluted tubules (P) with acidophilic cytoplasm and brush border. The distal convoluted tubules (D) appear normal with wider lumens. (H&EX400)

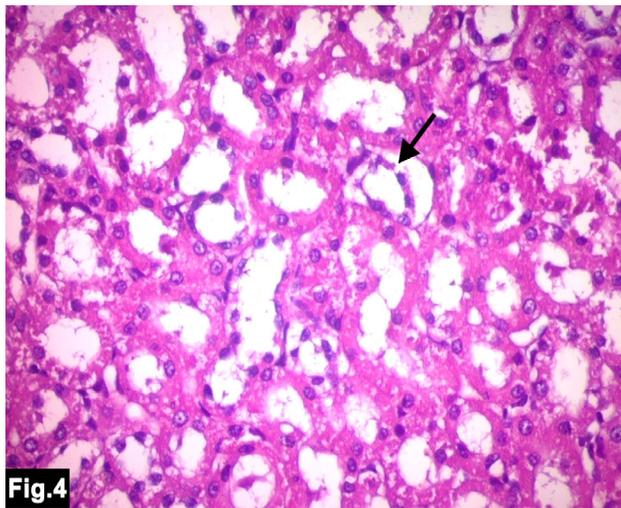


Fig. 4: A photomicrograph of a section in the renal cortex of group III showing disrupted tubular wall with detached basement membrane (→). (H&EX400)

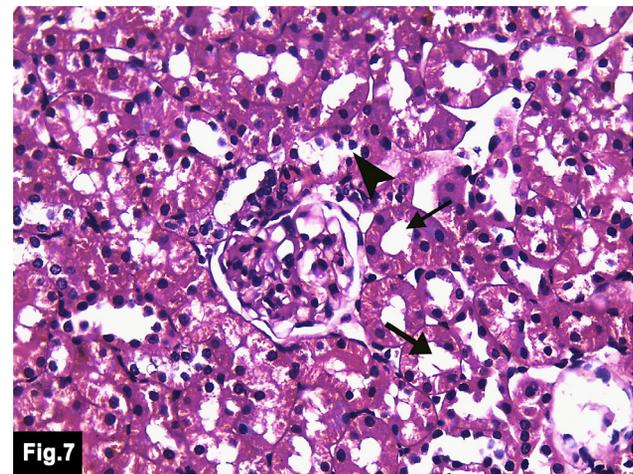


Fig. 7: A photomicrograph of a section in the renal cortex of group IV showing some dilated tubules with vacuolated cytoplasm and pyknotic nuclei (→). Few tubules contain intra-tubular cellular debris and detached cells (▶). (H&EX400)

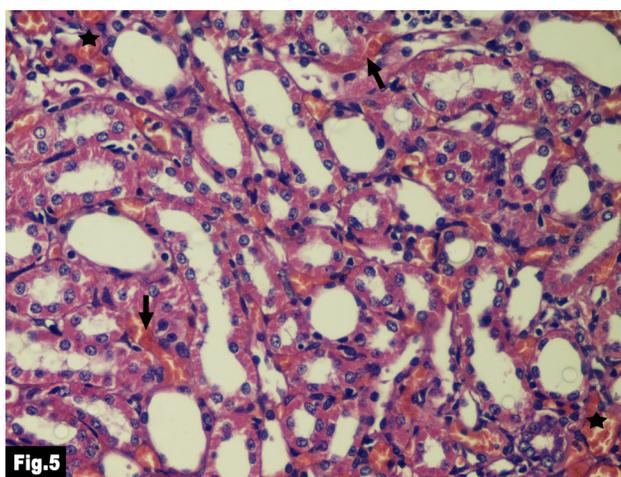


Fig. 5: A photomicrograph of a section in the renal cortex of group III showing congested blood vessels (stars) and intertubular hemorrhage (→). (H&EX400)

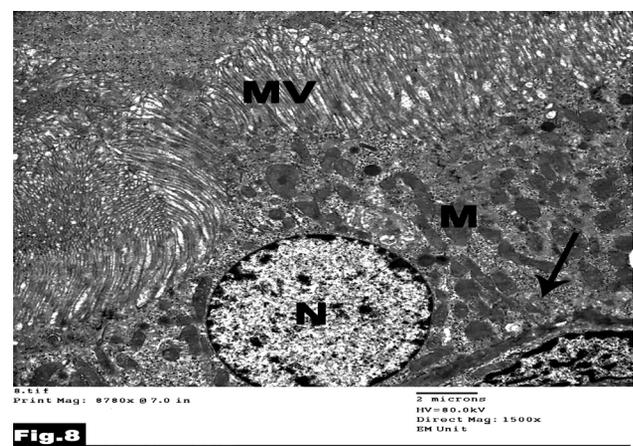
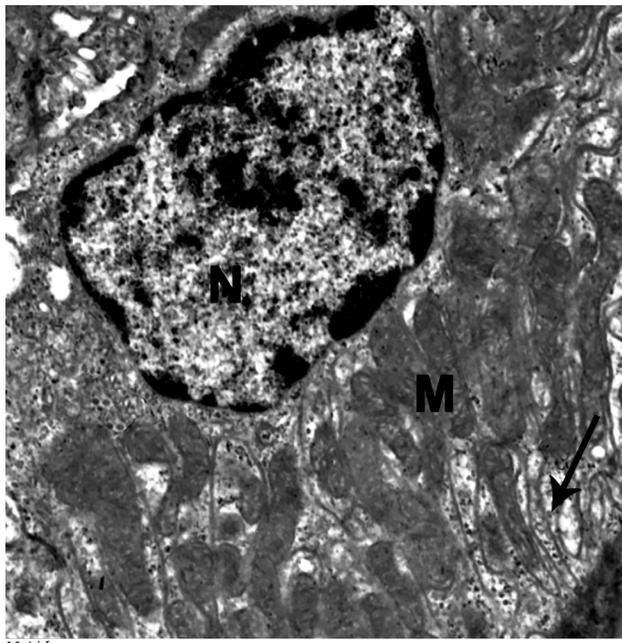


Fig. 8: An electron micrograph of the renal cortex of the control group, showing a cell of proximal convoluted tubule with characteristic apical long microvilli (Mv), characteristic basal infoldings (→) containing elongated mitochondria (M) and central rounded nucleus with extended chromatin (N). (Mic. Mag. × 1500)

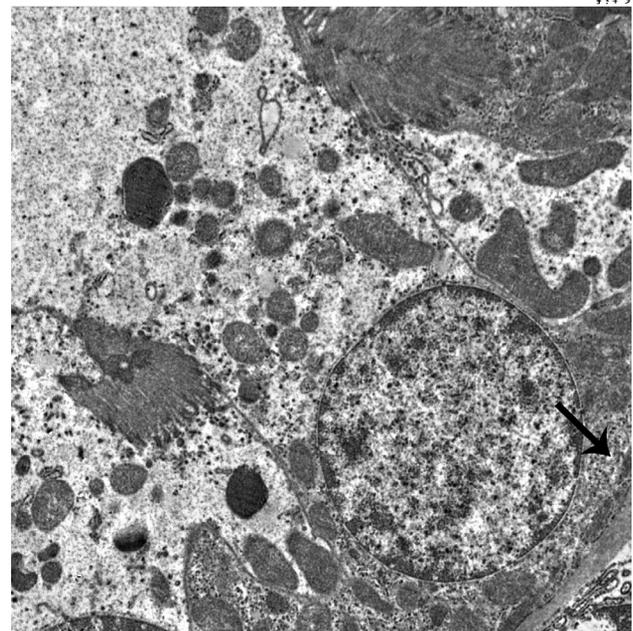


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Fig.9

Fig. 9: An electron micrograph of the renal cortex of the control group, showing a cell of distal convoluted tubule with no apical microvilli. Central nucleus exhibiting extended chromatin (N), basal infoldings (→) and elongated packed mitochondria in between (M) are noticed. (Mic. Mag. X3000)

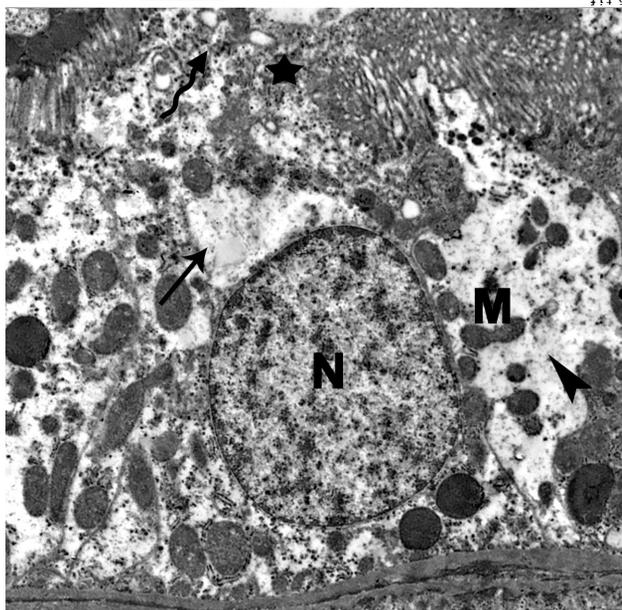
Fig.11



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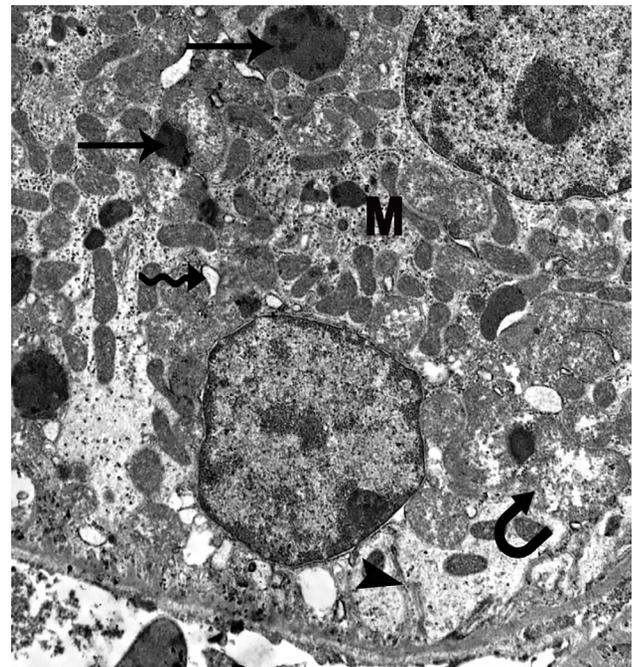
Fig. 11: An electron micrograph of PCT of group III showing ruptured cell with extrusion of cellular organelles and loss of basal infoldings (→). (Mic. Mag. X2000)

Fig.10



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Fig. 10: An electron micrograph of PCT of group III (UG group) showing damaged apical membrane (star) with partial absence of microvilli (wavy arrow) and loss of the basal infoldings. The mitochondria are disorganized and exhibiting different sizes and shapes (M). Notice the rarified cytoplasm (▶), cytoplasmic vacuole (→) and the central nucleus with extended chromatin (N). (Mic. Mag. X2000)



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Fig.12

Fig. 12: An electron micrograph of DCT of group III showing interrupted basal infoldings (▶), dispersed pleomorphic mitochondria (M). Some mitochondria appear swollen with cristolysis (curved arrow). Many heterogeneous electron-dense bodies (→) and cytoplasmic vacuoles (○) are observed. (Mic. Mag X 2000)

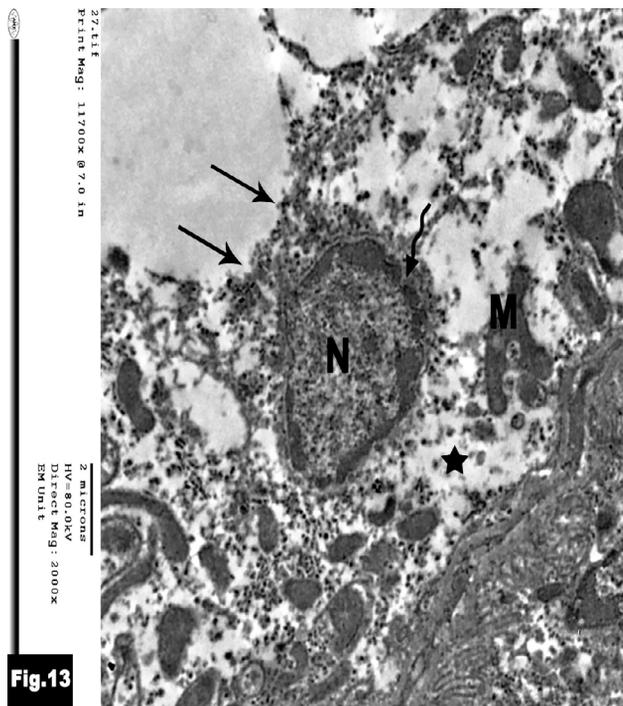


Fig.13

Fig. 13: An electron micrograph of DCT of group III showing rupture of apical plasma membrane (→), absence of microvilli, loss of basal infoldings (star) with abnormal arrangement of the pleomorphic mitochondria (M). The cytoplasm is rarified and the nucleus is hyperchromatic (N) with irregular nuclear outline (wavy arrow). (Mic. Mag X 2000)

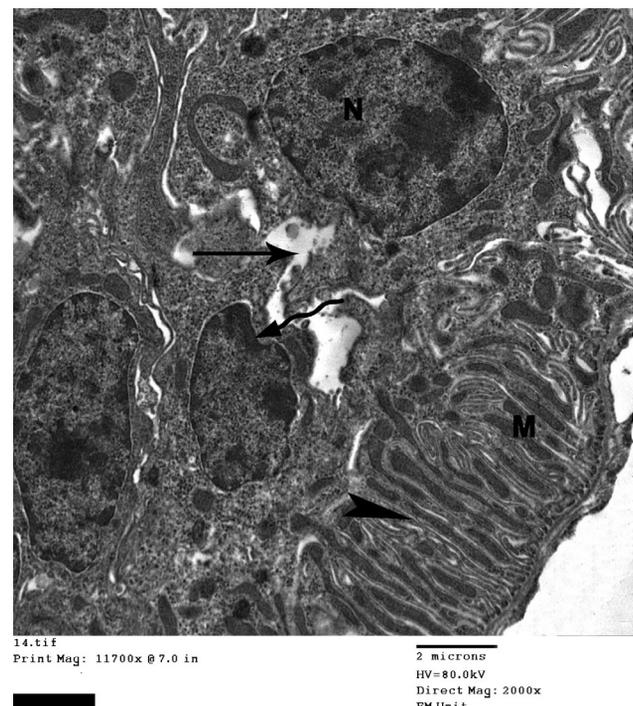


Fig.15

Fig. 15: An electron micrograph of renal cortex of group IV showing the cells lining the convoluted tubules with basal infoldings (▶) having longitudinally oriented mitochondria (M) and wide intercellular space (→). The nuclei (N) show euchromatic chromatin and few nuclei exhibit irregular outlines (wavy arrow). (Mic. Mag X 2000)

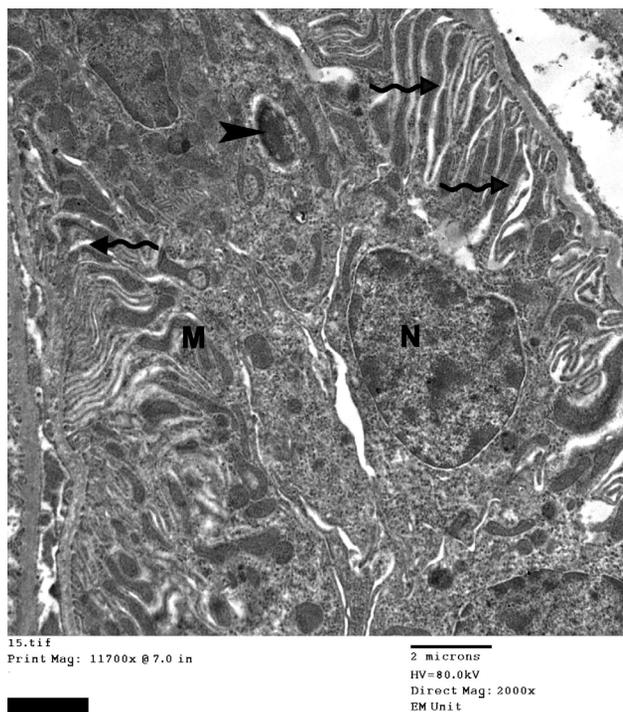


Fig.14

Fig. 14: An electron micrograph of renal cortex of group IV (UG + NAC group) showing renal tubule lining cell with normally rounded nucleus (N), normal basal infoldings (wavy arrows) with elongated mitochondria palisade (M). Notice a heterogeneous electron dense body in the cytoplasm (▶). (Mic. Mag X 2000)

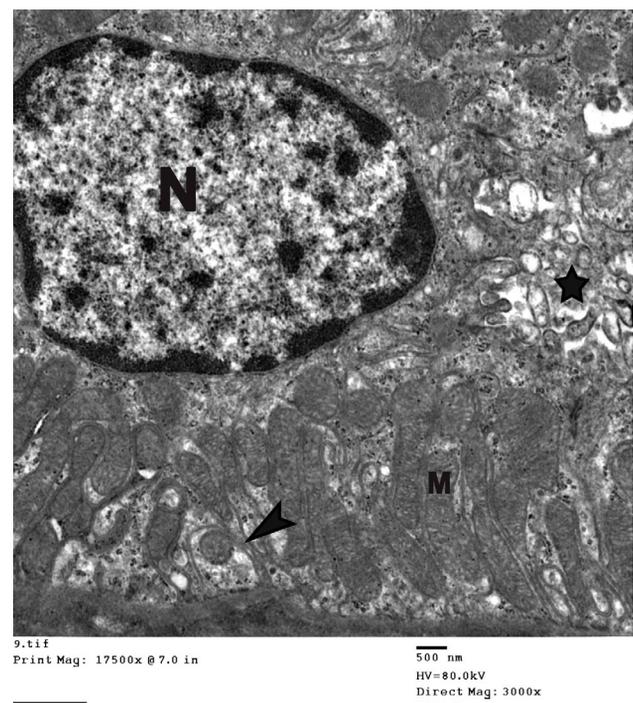


Fig.16

Fig. 16: An electron micrograph of DCT of group IV showing cell with preserved basal infoldings (▶) having a normally oriented mitochondrial palisade (M) and lateral cellular interdigitation (star). The nucleus is central, rounded with extended chromatin (N). (Mic. Mag X 3000)

DISCUSSION

Nowadays the extensive use of contrast media for imaging procedures, is unavoidable due to their major importance in medical diagnostic purposes, in spite of their reported side effects on different organs specially the kidney producing contrast-induced nephropathy^[21]. Therefore, our study attempted to address this problem by using N-Acetylcysteine as a preventive measure from contrast induced nephropathy^[22].

In the present study, after Urografin injection, the principal findings were in the form of tubular dilatation, or severe tubular destruction with appearance of intratubular debris. These results coincide with Xia *et al.*^[18] who reported similar changes in the form of collapse of the lumen of kidney tubules, presence of protein and cellular casts in their lumen or severe renal interstitial fibrosis.

In this work, after injection of Urografin, some tubules revealed destruction of the apical plasma membrane with obvious decrease of their height and displaying highly vacuolated cytoplasm with dark pyknotic nuclei. These results are in agreement with Kohli *et al.*^[23] and Xia *et al.*^[18] who reported similar results like destroyed microvilli, vacuolation of cytoplasm and renal tubular damage.

Moreover, the mononuclear inflammatory cells, inter-tubular hemorrhage and congested peritubular capillaries observed in Urografin group were explained by the strong systemic inflammatory response and the production of inflammatory cytokines in response of contrast media administration^[24].

Ultrastructurally, Urografin injection revealed destructed apical membrane with partial loss of microvilli, swollen degenerated mitochondria with cristolysis and plenty of cytoplasmic vacuoles. These changes are in agreement with Emad *et al.*^[25] who reported mitochondrial enlargement (ballooning) with partial to complete loss of their cristae and partial loss of the apical microvilli with vacuolations and rarefaction of the cytoplasm.

In addition, in our results several cells exhibited rarified cytoplasm and hyperchromatic nuclei with irregular outlines. These findings coincide with Romano *et al.*^[26] who reported cellular injury of the renal medulla in the form of extensive DNA fragmentation, and stated that the contrast media induce apoptosis which has been attributed to medullary hypoxia.

Several theories explained the mechanism by which the CM can induce nephropathy especially high osmolar ones because its high osmolarity is related to acute adverse reactions^[3]. It may be due to direct cytotoxicity, vasoconstrictive stimuli following the release of prostaglandins and endothelin from endothelial cells exposed to CM. Moreover, Urografin leads to depressed activity of mitochondrial scavengers and enhances the formation of reactive oxygen species (ROS) that threaten oxygen balance and antioxidant functions, and directly

cause apoptosis and cell necrosis. Also, vasoconstriction leads to ischemia in renal medulla which increases the amounts of secreted reactive oxygen species(ROS)^[8,27].

Kohli *et al.*^[23] explained another patho-physiologic mechanism of contrast media induced kidney injury due to the strong systemic inflammatory response from its injection. Another route of kidney injury is hemolysis and release of free hemoglobin, transferrin and haptoglobin, resulting in renal tubular damage. Oxidative stress occurring with CM increases reactive oxygen species ROS that activate cytokine-induced inflammatory mediators, resulting in damage to proximal tubular cells^[28].

As a preventive tool from contrast-induced nephropathy, in the present work we tried to study N-Acetylcysteine protective effect and found that it decreased greatly most of the harmful effects of Urografin on the kidney tubules with apparent improvement in the histological renal picture. These results are in accordance with Xia *et al.*^[18] who stated that Acetylcysteine has apparently decreased apoptosis occurring in renal tubular cells of rats as a response to ureteric obstruction with CM, and ameliorates kidney injury.

Other researchers reported also the protective effect of N-Acetylcysteine against contrast media induced renal damage. Yayla *et al.*^[14] reported its protective effect against nephropathy in patients undergoing coronary angiography. Other studies confirmed the same results in NAC prevention of contrast induced nephropathy in patients undergoing peripheral angiography^[29]. Other in vitro studies have shown the ability of NAC to protect in a dose-dependent fashion the cultured renal tubular cells incubated with high concentrations of low and high osmolar contrast media^[27].

The mechanism by which N-Acetylcysteine can decrease kidney injury is controversial; it may be through the anti-vasoconstriction function, enhancing renal blood flow and so decrease incidence of cell injury, or may be due to the thiol group of NAC that can deactivate reactive oxygen species and plays antioxidant role directly and decreases the systemic and renal oxidative stress^[18].

In conclusion, the administration of N-Acetylcysteine shows promising results in our animal model research and exerts a protective effect against renal tubular damage of the kidney that has been induced by Urografin injection. So, N-Acetylcysteine may be a useful protective agent before the procedure and during it.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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المخلص العربي

التأثير الضار لعقار اليوروجرافين على الأنابيب الكلوية للفئران البيضاء البالغة والتأثير الوقائي المحتمل لعقار إن اسيتيل سيستين دراسة مجهرية بالميكروسكوب الضوئي والإلكتروني

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مقدمة: يعد عقار اليوروجرافين واحداً من عدة أنواع من وسائط التباين المستخدمة بصورة مكثفة في تحقيقات الأمراض كالتصوير بالأشعة وإجراءات تدخلية أخرى. ولقد تم اكتشاف مضاعفات متعددة من استخدامه وخاصة التأثير على الكلى في ما يوصف باعتلال الكلية الناجم عن وسائط التباين والتي يمكن الوقاية منها باستخدام مضاد الأكسدة إن اسيتيل سيستين.

الهدف من العمل: هو دراسة تأثير عقار اليوروجرافين على الأنابيب الكلوية للفئران البيضاء و تقييم دور عقار إن اسيتيل سيستين على هذه الأنابيب المصابة.

المواد والطرق: تم استخدام 24 فأراً أبيض بالغ بغض النظر عن نوع الجنس وتم تقسيمهم الى 4 مجموعات. مجموعة ضابطة ومجموعة إن اسيتيل سيستين بجرعة تعادل جرعة الإنسان البالغ مرتين يوميا ومجموعة اليوروجرافين المجموعة الثالثة عن طريق حقن جرعة عالية من عقار اليوروجرافين %76 في وريد الذيل للفئران عن طريق التسريب ومجموعة اليوروجرافين مع إن اسيتيل سيستين المجموعة الرابعة حيث تلقت الفئران نفس الجرعة من عقارى اليوروجرافين و إن اسيتيل سيستين ثم تم فحص العينات التي تم الحصول عليها باستخدام المجهر الضوئي والإلكتروني. **النتائج:** أظهرت المجموعتين الضابطة وإن اسيتيل سيستين نفس الصورة النسيجية الطبيعية للأنابيب الكلوية . كما كشفت مجموعة اليوروجرافين عن توسع أنبوبي مع وجود حطام خلوي في تجويفهم. كما أظهرت بعض الأنابيب تدميراً واضحاً وفجوات فى السيتوبلازم وأنوية داكنة للغاية .وباستخدام الميكروسكوب الإلكتروني تم ملاحظة الغشاء القمي تالفاً مع فقدان جزئي للزغيبات ووجود فراغات بالسيتوبلازم , فى حين أظهرت المجموعة الرابعة دليلاً على التحسن بالمقارنة بالمجموعة الثالثة حيث أظهرت معظم الأنابيب صورة نسيجية طبيعية تقريباً باستثناء عدد قليل من الأنابيب المتوسعة ذات الحطام الخلوى.

الخلاصة: أن عقار إن اسيتيل سيستين له تأثير وقائي ضد الضرر الكلوى الذى سببه حقن عقار اليوروجرافين لذلك قد يكون من العوامل الواقية المفيدة قبل وأثناء إجراءات التصوير بالأشعة.