

Influence of Vit.C on Egyptian Baladi Goats (*Capra Hircus*) with Gentamicin-Induced Nephrotoxicity

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Abstract

Nephrotoxicity is the main problem associated with gentamicin. So this work aimed to evaluate the effect of Vitamin C on gentamicin -induced nephrotoxicity in Baladi goats (*Capra hircus*) based on the clinical, haematobiochemical and histopathological changes. To achieve this aim, ten clinical healthy Baladi goats were allotted into two groups, each of five. The first group was gentamicin-induced nephrotoxicity that injected with gentamicin while, the second group was injected with Vitamin C along with gentamycin. Jugular blood samples were collected at 0, 7, and 12 days post gentamycin injection. Dullness, decreased appetite and unable to stand and lie down were the main signs exhibited after gentamicin injection. However, these signs did not appear in Vitamin C treated goats. In addition, there was significant increase in serum urea, creatinine and serum MDA. While hematological examination showed a significant decrease in Hb content and RBCs content and erythrocyte SOD. In the meantime, histopathological examinations revealed severe renal damage. Marked improvement in the haematobiochemical changes were detected in gentamicin Vitamin C treated goats with mild renal damage. Our results suggest the cytoprotective role of Vitamin C on gentamicin-induced nephrotoxicity in goats that could be attributed to its anti-oxidant activity, a result of high importance in clinical application.

Keywords: Baladi goats, Gentamicin nephrotoxicity, Vitamin C.

1. Introduction

The aminoglycoside antibiotics are used, either alone or in combination with cell wall-active agents, for the treatment of severe/ life-threatening infections caused by Gram-positive and Gram-negative aerobes [1]. The most commonly used and studied aminoglycosides is the gentamicin (GM) [2]. However, the main problem associated with gentamicin is nephrotoxicity [3]. Gentamicin nephrotoxicity is characterized by tubular damage associated with tubular epithelial cell toxicity [4].

The oxygen free-radicals play a role in nephrotoxicity, and that the use of antioxidants decreases nephrotoxicity [5]. oxygen free-radical generation is associated with auto-oxidation of glucose, alterations in the antioxidant enzymes such as superoxide dismutase (SOD) and formation of lipid peroxides such as Malondialdehyde(MDA) [6].

Vitamin C (Vit. C) is an antioxidant supplement that displays its powerful scavenging effects against activated oxygen species and various free radicals by neutralizing ROS and decreasing oxidative damage to cell membranes. Therefore, Vit. C has been used as a protective antioxidant agent against numerous kinds of deteriorations produced by oxidative stress [5].

Goats are usually found in small holdings as mixed flocks with sheep and other farm animals. The Egyptian goats are classified into several breeds differing in color, size, and other morphological features, such as Zaraibi, Baladi, Sinawi or Bedouin, Barki and Saidi [7].

Therefore, this study aimed to evaluate the clinical, hematobiochemical and histopathological changes associated with gentamycin-induced

nephrotoxicity in Baladi goats. Further aim is to evaluate the antioxidant properties of Vit.C on GM-induced nephrotoxicity in Egyptian Baladi goats (*Capra hircus*).

2. Materials and methods

2.1 Experimental design

The experimental design was approved by the local committee of the Faculty of Veterinary Medicine, Benha University, Egypt and conformed to the guidelines of National Institute of Health (NIH) of Egypt. A total number of 10 clinically healthy adult Egyptian Baladi goats about 1-1.5 year and 20.05 ±0.49 KG Bwt were randomized into 2 groups, each of five. Goats in gentamycin induced nephrotoxicity group (GIN) were injected with gentamicin sulfate 10% (Gentacure-10)® manufactured by PHARMA SWEDE-EGYPT) at a dose rate of 80 mg/kg body weight/day divided into three doses, one dose was given S/C every eight hours over the ribcage to induce nephrotoxicity for 12 day according to [8]. Goats in gentamycin induced nephrotoxicity group treated with Vit.C (GIN-C) were injected with a similar dose of GM. plus Vitamin C(Cevarol)® which was manufactured by Memphis Co. For Pharm. & Chemical Ind. Cairo-Egypt. It was injected at a dose rate of 200 mg/ kg body weight for 12 days [9]. The goats were fed on green fodder and concentrate with free access to sufficient tap water in a good hygienically well ventilated place throughout the period of the experiment.

2.2 Clinical examination

Goats were subjected to a daily veterinary clinical examination after gentamycin injection

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observing the changes in clinical symptoms [10]. Confirmatory diagnostic tools including ultrasonography and electrocardiography were also applied.

2.3 Blood samples

Blood samples were collected from jugular vein as previously described (Radostits et al., 2010). Whole blood was collected for hematological analysis while clear sera were separated and stored at -20 C° pending biochemical examination.

2.4 Haematological examination

Total RBCs count, WBCs count, HB concentration and PCV% were carried out by using Hematology Analyzer (Perlong Medical Machine Co., Ltd., Model XF9080) .

2.5 Biochemical analysis

Serum urea, creatinine, total proteins and albumin were determined spectrophotometrically (Clinical Chemistry Analyzer ERBA CHEM 7, Germany) by using of commercial kits provided by Spectrum Diagnostics (Obour City, Cairo, Egypt). Serum Malondialdehyde (MDA) concentration and Erythrocyte superoxide dismutase (SOD) were colorimetrically measured using commercial kits (Biodiagnostic Research and Diagnostic Agents, Giza, Egypt).

2.6 Histopathological examination

Specimens from the kidneys of about 0.5 cm thickness were collected immediately after scarification in 10% neutral buffered formalin and used for histopathological examination. Before collecting specimens, macroscopic changes of kidneys of necropsied goats was carefully observed by naked eye for detection of any gross lesions then histopathological specimen were processed for histological examination [11].

2.7 Statistical analysis

The data were statistically analyzed using Repeated Measures Analysis of Variance (ANOVA) and independent-samples T test in the experimental study as previously described [12]. SPSS version 16 software was used to conduct this analysis. Values were represented as means \pm standard error (SE). All differences were considered significantly different among groups of the experimental study when ($p < 0.05$).

3. Results

3.1 Clinical findings

GIN Goats showed decrease in the appetite and dullness from the 6th day of the experiment. On the 9th day, they became unable to stand and recumbent in sternal and lateral position. On the other hand, GIN+C goats did not show clinical changes except

dullness and depressed appetite after one week of treatment.

3.2 Hematological finding

GIN group Table (1) showed significant decreased in total RBCs count and Hb concentration while significant increase in WBCs count and PCV% compared to GIN +Vit.C group was observed.

3.3 Biochemical findings

Serum total proteins, albumin, sodium, chloride and calcium Table (2) in GIN group showed significant decrease continued till reached the minimal level at the end of the experiment in addition to decreased level of erythrocyte SOD. Whereas there was significant increase in serum MDA, Serum urea and creatinine from 7th day and continued till reached the maximal level at the end of the study compared to GIN+ Vit.C group.

3.4 Histopathological findings

Macroscopic examination of cut surface of affected kidneys (Fig. 1) of GIN goats showed presence of small size necrotic areas which taken grayish white color and hemorrhage at corticomedullary junction while in GIN +Vit.C goats mild congestion at corticomedullary junction with absence of necrotic foci were observed.

Microscopical examination of the kidneys of GIN goat (Fig.2, 3, 4) demonstrated severe thickening and hyalinization of the renal capsule. The renal blood vessels and the inter-tubular blood capillaries were severely congested and filled with blood. The glomeruli showed severe congestion of the glomerular tuft with the presence of eosinophilic debris in the glomerular space. Moreover, segmentation of the glomerular tuft was also detected. Some of the glomeruli appeared shrinkage or even complete degeneration of the tuft. The renal tubules manifested severe degree of necrotic changes of their epithelial cell lining. Complete desquamation of the epithelial cell lining of the renal tubules including proximal, distal and loop of henel as well as collecting tubules were also seen. Most of these desquamated epithelium were become hyalinized and filled in the tubular luminae forming eosinophilic casts. Severe intertubular haemorrhage with focal mononuclear cellular aggregations was detected. Some of renal tubules showing cystic dilatation in which the lumen of the affected renal tubules become wide and lined by flattened epithelium. While, the histopathological findings in GIN + Vit.C goats was considered less severe than in GIN goats. The kidney (Fig.5) revealed mild thickening of the renal capsule. The renal glomeruli were mild congestion of their tuft with mild segmentation or shrinkage as well as the presence of few amount of eosinophilic debris in

the bowman's space. The renal blood vessels and intertubular blood capillaries were moderately congested, dilated and filled with blood. The renal tubules provoked various degrees of necrotic changes in the form of pyknosis of their nuclei and desquamation of the epithelial lining. Moreover, mild cystic dilatation of renal tubules was also seen. Few amounts of hyaline casts were observed in the lumen of the affected tubules.

4. Discussion

Gentamicin is a well-established aminoglycoside antibiotic for the treatment of infection produced by gram-negative organisms. However, Nephrotoxicity of gentamicin has been documented due to obvious accumulation and retention of aminoglycosides in the proximal convoluted tubular cells [13]. This study was carried out to understand adverse effect of gentamicin on goat because of the wide use of gentamicin in treatment of different affections in goat.

The results of the current study revealed that gentamicin injected with 80 mg/kg body weight/day for 12 days induced alterations in the clinical behavior of goats including dullness, depression, decreased appetite with eventual recumbency. These results coincided with [14]. These findings could be attributed to the toxic effect of gentamicin that produce nephropathic changes. It was suggested that GM remains with a long-half life in the renal proximal tubular cells, leading to renal damage such as structural changes and functional impairments of the plasma membrane, mitochondria, and lysosome [15].

The reduction in Hb content and RBCs count Tabel (1) in GIN goats might be attributed to nephrotoxic effect of gentamicin on the kidney through decrease production of erythropoietin hormone which stimulates erythropoiesis [16].

This study showed that GIN goats represent high Serum urea, creatinine and low Serum total proteins, albumin, sodium, chloride and calcium. These results are supported by previous studies [14] that correlate these changes to the reduced tubular reabsorption or increased tubular secretion. Nephropathy developed after administration of gentamicin was associated with increased serum creatinine and blood urea nitrogen, proteinuria, urinary loss of sodium and potassium, and glomerulosclerosis as the result obtained by [14, 17]. Hypocalcemia observed herein could be attributed to following intracellular events between either inhibition of basolateral calcium ATPase, Na/K ATPase or blockage of intraluminal calcium channels and competition of gentamicin with calcium for binding brush border, these finding are supported by [14, 18].

Our result elucidated high serum MDA and low erythrocyte SOD. These findings might be attributed to generation of reactive oxygen species which led to lipid peroxidation with increased production of MDA as end product to this process [19, 20]. Along with increase production of ROS which reduces activity of renal antioxidant enzymes as SOD [21, 22]. The histopathological finding of the kidney in this study confirm the nephrotoxic effect of gentamicin as exhibit severe degree of necrotic changes of their epithelial cell lining of the renal tubules with Complete desquamation of the epithelial cell lining of the renal tubules including proximal, distal and loop of Henle as well as collecting tubules. These pathological changes complied with other studies [13, 23]

Vit. C is a naturally occurring powerful antioxidant [13] that exhibits its powerful scavenging effects against activated oxygen species and various free radicals [6]. The reactive oxygen species like hydroxyl radicals have an unpaired electron that renders the specie quite reactive towards the nucleic acid, lipids and proteins leading to the cellular oxidative damages [24]. Mechanism of antioxidant activity includes the conversion of vitamin C into its oxidized form (dehydro-ascorbic acid) by donating two electrons to reactive oxygen species [25] while the oxidized forms of ascorbate are relatively stable and unreactive and do not cause cellular damage [24] however, these reactive oxygen species are then reduced to water. Because of that role of Vit.C, it was proposed to use in our study to testify its antioxidant effect against gentamicin induced nephrotoxicity.

GIN+ Vit.C goats showed milder signs of gentamicin nephrotoxicity along with palliation of clinical and hematobiochemical alteration observed in GIN goats. In addition to the histopathological finding of the kidney in GIN+VitC which revealed mild congestion of the renal glomeruli with mild segmentation or shrinkage of their tuft as well as the presence of few amount of eosinophilic debris in the bowman's space. The renal tubules showed various degrees of necrotic changes in the form of pyknosis of their nuclei and desquamation of the epithelial lining. Moreover, few amounts of hyaline casts were also seen in the lumen of the affected tubules. Our data were agreeable with [5, 26]

These finding suggested cytoprotective role of vitamin C on the renal tissue [27, 28] through reduction of cellular damage of the renal tubules [29]. Together with reduction of serum MDA and elevation of erythrocyte SOD in GIN+VitC goats this improvement could be attributed to role of vitamin C as antioxidant which reducing oxidative stress, scavenging free radicals and reestablishment antioxidative systems [13].

Table (1) Haematological parameters of gentamicin induced nephrotoxic (GIN) and gentamicin induced nephrotoxic + vitamin C (GIN+ Vit.C) goats for 12 days (Means ± S.E.)

Days Parameters	0 day		7 th day		12 th day	
	GIN group	GIN+ Vit.C group	GIN group	GIN+ Vit.C group	GIN group	GIN+ Vit.C group
PCV%	27.63±0.88 ^{3a}	28.1±0.26 ^{3a}	30.4±0.38 ^{2a}	29.5±0.29 ^{2a}	31.33±0.88 ^{1a}	30.07±0.47 ^{1a}
Hb g/dl	10.63±0.38 ^{4b}	10.27±0.52 ^{4b}	8.97±0.29 ^{2b}	9.47±0.18 ^{3b}	7.8±0.15 ^{1a}	8.97±0.17 ^{1b}
RBCs million/mm ³	12.10±0.36 ^{4b}	12.13±0.33 ^{4b}	10.77±0.37 ^{2b}	10.9±0.15 ^{3b}	7.6±0.32 ^{1a}	9.73±0.50 ^{1b}
WBCs thousand/mm ³	6.87±0.41 ^{3b}	5.47±1.28 ^{3b}	11.1±0.38 ^{1a}	7.93±0.79 ^{3b}	13.43±0.70 ^{1a}	9.5±0.61 ^{1b}

Values with different superscripts numbers within the same raw were statistically significant from corresponding values on day zero at p≤0.05.

Values with different superscripts letters within the same raw were statistically significant from corresponding values of GIN+ Vit.C subgroup at p≤0.05.

Table (2) Biochemical analysis of gentamicin induced nephrotoxic (GIN) and gentamicin induced nephrotoxic + vitamin C (GIN+ Vit.C) goats for 12 days (Means ± S.E.)

Days Parameters	0 day		7 th day		12 th day	
	GIN group	GIN+ Vit.C group	GIN group	GIN+ Vit.C group	GIN group	GIN+ Vit.C group
Urea mg/dl	20.00±0.57 ^{2b}	16.67±1.76 ^{3b}	92.00±5.19 ^{1b}	85.007±5.68 ^{1b}	210.00±5.19 ^{1a}	136.00±4.04 ^{1b}
Creatinine mg/dl	0.64±0.05 ^{7b}	0.52±0.07 ^{2b}	3.93±0.47 ^{1b}	2.81±0.15 ^{1b}	6.71±0.12 ^{1a}	3.89±0.08 ^{1b}
Albumin g/dl	3.87±0.12 ^{3b}	3.30±0.07 ^{2b}	1.63±0.15 ^{1b}	2.06±0.03 ^{1c}	0.98±0.07 ^{1a}	1.55±0.08 ^{1b}
T. proteins g/dl	7.44±0.12 ^{2b}	7.59±0.13 ^{2b}	5.34±0.29 ^{1b}	5.81±0.51 ^{1b}	4.41±0.11 ^{1a}	4.90±0.08 ^{1b}
Sodium mEq/l	142.67±2.03 ^{2b}	148.00±1.73 ^{2b}	88.67±1.20 ^{1a}	111.67±5.61 ^{1b}	73.67±3.18 ^{1a}	92.67±4.41 ^{1b}
Potassium mEq/l	4.84±0.20 ^{2b}	4.67±0.39 ^{2b}	9.85±0.59 ^{1b}	8.41±0.38 ^{1b}	11.06±0.12 ^{1a}	8.97±0.09 ^{1b}
Chloride mEq/l	125.67±6.69 ^{2a}	116.67±1.76 ^{2a}	86.67±1.76 ^{1a}	93.67±2.40 ^{1a}	66.33±4.48 ^{1a}	75.67±2.03 ^{1a}
Calcium mg/dl	9.84±0.33 ^{3b}	9.39±1.12 ^{2b}	4.32±0.15 ^{1b}	5.3±0.49 ^{1b}	3.48±0.33 ^{1a}	4.52±0.86 ^{1b}
Phosphorus mg/dl	5.85±0.05 ^{2b}	6.03±0.09 ^{3b}	10.46±0.41 ^{1b}	9.89±0.11 ^{1b}	11.23±0.18 ^{1b}	10.32±0.32 ^{1b}
MDA (n mol/l)	10.63±0.39 ^{3b}	13.11±0.11 ^{2b}	49.53±2.25 ^{1a}	38.17±1.24 ^{1b}	73.32±3.61 ^{1a}	57.68±2.72 ^{1b}
SOD (U/g)	32.10±1.88 ^{3b}	33.20±1.53 ^{3b}	10.62±1.25 ^{1a}	25.00±0.89 ^{2b}	4.65±0.70 ^{1a}	12.72±1.59 ^{1b}

Values with different superscripts numbers within the same raw were statistically significant from corresponding values on day zero at p≤0.05.

Values with different superscripts letters within the same raw were statistically significant from corresponding values of GIN+ Vit.C subgroup at p≤0.05.

4. Conclusion

Our result suggested that gentamicin have a nephropathic effect at a dose of 80 mg/kg daily for 12 days causing disturbances in the clinical attitude, the biochemical parameters and the histological structure of the kidney in goats. Therefore, great attention should be given when use these drugs by estimating the therapeutic dose accurately. Moreover, we recommended using of vitamin C as

protective agent that helps in amelioration of gentamicin nephrotoxicity.

5. Acknowledgement

We are deeply grateful to Prof. Dr. Abdel Baset I. Al mashad, Professor of Pathology and Head of Pathology Department for their valuable help in histopathological examination.

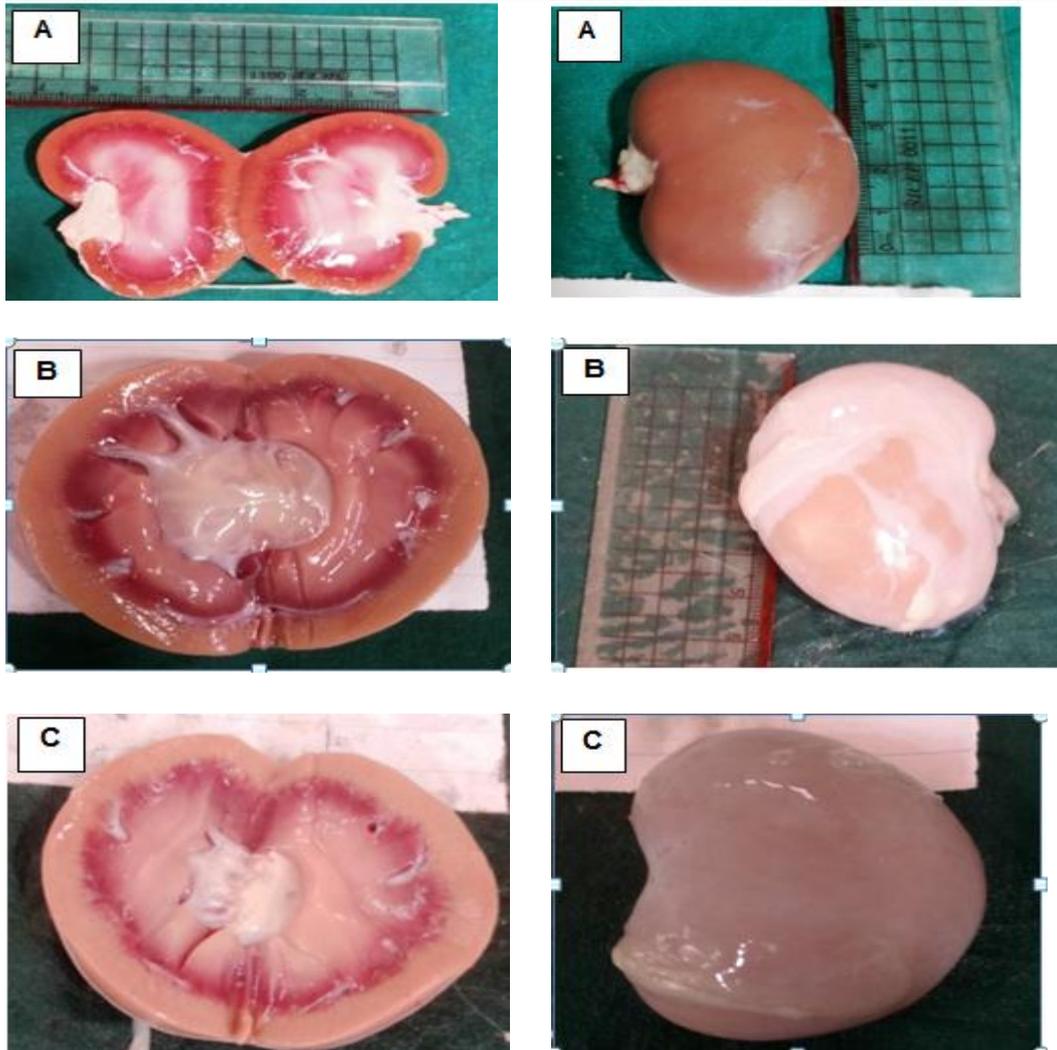


Fig (1) (A) Control normal kidney of goat. (B) Cut surface of kidney of GIN goat showing grayish white necrotic areas and haemorrhage at corticomedullary junction. (C) Cut surface of kidney from GIN+ Vit.C goat showed mild congestion at corticomedullary junction.

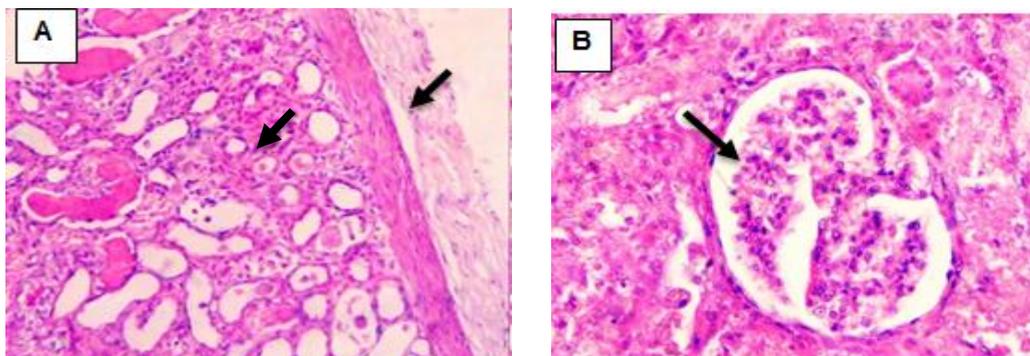


Fig (2) The microscopical examination of the kidney of GIN goats that after 12th day of injection showing severe thickening of the renal capsule with hayalinazation. The renal tubules showing sever degree of necrotic changes with the formation of hyaline cast in the renal tubules. (H&E stain × 200) (A), the glomeruli showing sever congestion and segmentation of the glomerular tuft. (H&E stain × 400)(B)

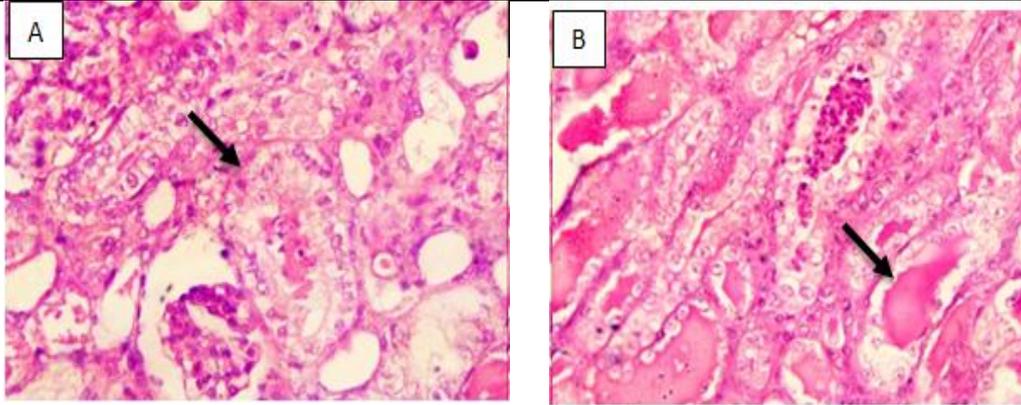


Fig (3) The microscopical examination of the kidney of GIN goats showing desquamation of the epithelial cell lining the renal tubules with the presence of desquamated epithelium and eosinophilic necrotic debris in their luminae. (H&E stain $\times 200$)(A). The desquamated epithelium were become hyalinized and filled in the tubular luminae forming eosinophilic casts.(H&E stain $\times 400$)(B).

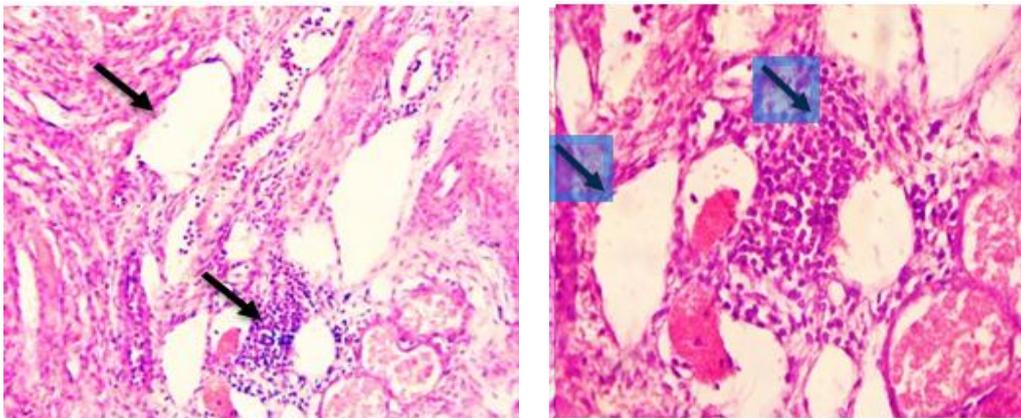


Fig (4) The microscopical examination of the kidney of GIN goats showing cystic dilatation of some renal tubules together with severe intertubular haemorrhage and focal mononuclear cellular aggregation was seen in the intertubular spaces. (H&E stain $\times 200$ and $\times 400$).

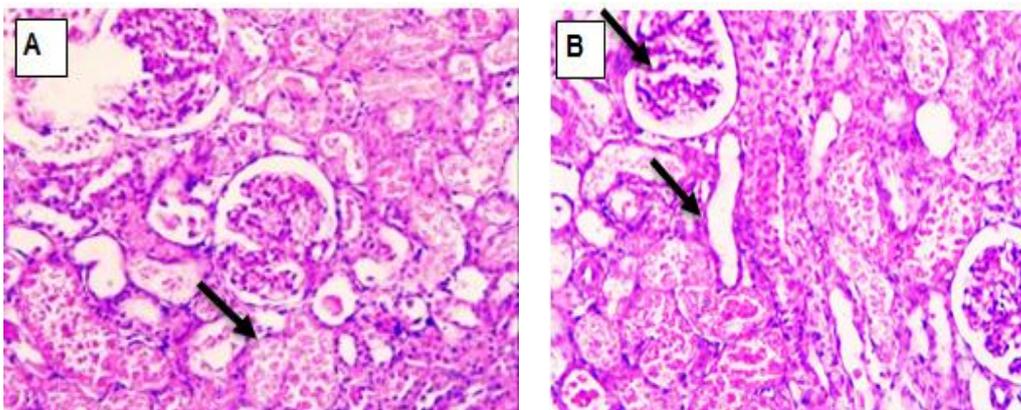


Fig (5) The microscopical examination of the kidney of GIN+ Vit.C goats showing congestion of the renal blood vessels and intertubular blood capillaries (A) and mild congestion of the glomerular tuft. Mild degenerative changes and mild cystic dilatation of the renal tubules was observed (B). (H&E stain $\times 200$).

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