HISTOPATHOLOGICAL AND BIOCHEMICAL EFFECTS OF IVERMECTIN ON KIDNEY FUNCTIONS, LUNG AND THE AMELIORATIVE EFFECTS OF VITAMIN C IN RABBITS

(*Lupus cuniculus)*

Khawla Bedan Al-Jassim * , Ala Al-Deen Hassan Jawad**

Eman Aboud Al-Masoudi*** , Saleh Khadim Majeed****

*Veterinary hospital in Basrah, Basrah, Iraq.

** Department of Basic Science, College of Dentistry, University of Basrah, Basrah. Iraq.

*** Department of Physiology, Pharmacology and Chemistry, College of Veterinary medicine, University of Basrah, Basrah, Iraq.

**** Department of Pathology, College of Veterinary Medicine, University of Basrah, Basrah, Iraq.

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ABSTRACT

The objective of this study was to assess the effects of repeated administration of ivermectin alone or with the combination of Vitamin C on kidney function and histopathological effects on kidney and lung of rabbits. Total of 48 mature female rabbits were used in this study. The rabbits were divided into eight groups of equal number (6). The 1st group was administered 0.9% Nacl which considers as control. The 2nd , 3rd , and 4th groups were administered (0.5mg, 1mg, and 2mg/Kg B.W Ivermectin) respectively. While the 5th group was administered 50mg/Kg B.W vitamin C only. The 6th , 7th , and 8th groups were given 50mg/Kg vitamin C in combination with Ivermectin (0.5mg, 1mg, and 2mg/Kg B.W) respectively. The ivermectin therapy was given S/C weekly, while the vitamin C was given daily and orally. The treatment in all groups were prolonged for 8 weeks.

The results showed significant increase ($P< 0.05$) in uric acid level in the 4th group. Also the level of urea and blood urea nitrogen were revealed significant decrease ($P< 0.05$) in 7th group. While the creatinine level clarified significant increase ($P< 0.05$) in the 3rd and 8th groups as compared with control group.

The histopathological changes as a results of ivermectin treatment in kidney included vacuolation of subcapsular tubules, atrophy of glomeruli. The lung showed dilated alveoli, bronchioles were aggregated with lymphocyte, dilatation of bronchioles, as well as, folding and thickening of bronchial epithelium. The administration of vitamin C with combination of Ivermectin ameliorate the harmful effect of ivermectin treatment. It can be conclude that the repeated administration of ivermectin causes hazardous effects on kidney function and many of histopathological changes were demonstrated in kidney and lung structure. The changes were increased proportionally with the dose. The administration of vitamin C can acts as protective agent.

INTRODUCTION

Ivermectin is abroad spectrum antihelminths drug which used to control of ectoparasites and endoparasites in sheep and goat(1).Ivermectin is used in human in the treatment of onchocerciasis and also it is effective against stronglyloidiasis, Ascaraisis, Trichuriasis, Filariasis, Entrobiasis and Scabies(2). The metabolism of ivermectin is primary via the oxidative pathway, and it has a high affinity to bind with protein, it may reach to 93%. Also reported that the ivermectin or its metabolites are excreted almost extensively in the faeces' but an estimated 12 days and with less than 5% of the administered doses excreted in the urine(3,4). The (5) showed the coadministration of ivermectin and Albendazole caused significant increase in serum urea and creatinine in rats. The administration of vitamin E caused reduction in urea, creatinine level in rats (6). As well as, (7) concluded that vitamin C could prevent and relief the toxic effect of Tamoxifen therapy. Also (8) clarified that vitamin C exhibits a protective effect against free radical induced oxidative stress damage. The objective of this study was to assess the effects of repeated administration of ivermectin alone or with the combination of Vitamin C on kidney functions and histopathological effects on kidney and lung of rabbits.

MATERIALS AND METHODS

The Ivermectin 10% purchased from local market (VET Product Office, KIPRO Company, Holland) and Vitamin C(AlShahba Labo, Syria). The uric acid was measured according to PAP – Method,enzymatic colorimetric test for uric acid with lipid clearing factor (LCF).The Enzymatic colorimetric test for urea was done by

hydrolyzed of urea in the presence of water and urease to produce ammonia (NH3) and carbon dioxide (CO2). Creatinine was measured based on Jaffe-Reaction photometric colorimetric test for kinetic measurement, while the blood urea nitrogen was calculated according to following equation: (absorbance of sample/ absorbance of standard X37.28 mg/dl).

Animal housing and Experimental Design

Forty eight female rabbits (*Lepus cuniculus*), (1200-2000gm) body weight and (8-12 months) of age were brought from the local market in Basra Province in Iraq. The rabbits were housed (6 rabbits / cage) in a wire silk cages measuring (100 X 50 X 50 cm) under controlled animal house condition at temperature (25 ± 3 C^o) and relative humidity (50 ± 5 %) in the animal house of Veterinary Medicine College in Basra University. The rabbits were kept under observation for one month. The animals were offered *add libitium*a rabbit's diet, alfa-alfa, green leaves during all period of the experiment.

The rabbits were divided into eight groups (6 rabbits in each group). Each group was treated for 8week as follow: the 1^{st}group was Injected (0.9 % NaCl) which acts as a control, the 2^{nd} , 3^{rd} , and 4^{th} groups were injected with ivermectin in doses(0.5 mg/kg,1 mg/kg ,2 mg/kg B.W) respectively. While the 5^{th}group was administered 50mg/ Kg B.W Vitamin C. As well as, the 6^{th} , 7^{th} and 8^{th}groups were administered vitamin C in addition to ivermectin (0.5mg, 1mg, 2mg/Kg B.W) respectively. The Ivermectin were given subcutaneously and weekly, while vitamin C were given daily and orally. At the end of experiment (8 Weeks), the blood samples were taken directly from the heart by using disposable syringe and were put in screw tube without anticoagulant then centrifuged at 4000 rpm for 10 minutes to get serum for biochemical assays. After that the animals were sacrificed to get out kidney and lung which were preserved in10% formalin for histopathological studies.

Statistical analysis

The results were analysed by one- way ANOVA test. When significant differences were found, the means were compared using least significant difference (LSD). All statistical calculations were carried out by the aid of the statistical SPSS V. 22 (SPSS Inc.)

RESULTS

In Table (1),the uric acid level showed significant increase ($p< 0.05$) in the 4th group as compared with control group, while the urea and blood urine nitrogen (BUN)levels clarified significant decrease ($p< 0.05$)in the 7th group. As well as, the creatinine level reported significant increase ($p< 0.05$) in the 3rd and 8th groups as compared with control group.

The examination of the kidney of control rabbits revealed normal glomeruli with thin glomerular basement membrane, normal cellularity and patent capsular space surrounding proximal and distal convoluted tubules (Figure 1). The 2nd group showed vacuolation of subcapsular cortical tubules (proximal convoluted tubules) (Figure 2), atrophy of glomerulus (Figure 3), while the 3rd group showed in addition to vacuolated of subcapsular cortical tubules (Figure4), it undergo dilated cortical tubules (Figure 5), and atrophic glomerulus (Figure 6).

The 4th group which treated with high dose of ivermectin (2mg/Kg) revealed marked vacuolation of cortical tubules (Figure 7), and atrophy of glomeruli (Figure 8). Furthermore, the 5th group (50mg/Kg Vit.C) showed normal cortical tubules and glomerulus (Figure 9). The 6th group showed minimal dilated/ vacuolation of cortical tubules (Figure 10), as well as, the 7th and 8th groups revealed dilated/vacuolated cortical tubules (Figure 11, 12).

The examination of the lung of control rabbits showed alveoli, bronchiole within normal limits (Figure 13). The 2nd group showed minimal folding and thickening of bronchiolar epithelium (Figure14). The 3rd group showed bronchioles with papillary proliferation of mucosal epithelium, aggregate of lymphocytes and dilated alveoli (Figure 15). The 4th group revealed thickening and folding of bronchial epithelium and dilated alveoli (Figure 16), whereas the lung section in 5th group within normal limit (Figure 17).The 6th group showed bronchiole with folded epithelium with proliferation (Figure 18), as well as, the lung section of 7th group revealed peribronchial aggregated with lymphocyte, dilated alveoli and dilated bronchiole (Figure 19), an area of alveoli with mononuclear cell, thickening alveolar septa and congested pulmonary artery (Figure 20). Finally the 8th group showed an area of alveoli with inflammatory cell mostly mononuclear cell (Figure 21), bronchiole with folded proliferated bronchial epithelium and dilated alveoli (Figure 22).

DISCUSSION

The statistical analysis demonstrated significant increase in uric acid in 4th group which treated with 2mg/Kg Ivermectin , as well as, the urea and blood urine nitrogen revealed significant decrease in 7th group (1mg/Kg Ivermectin + vitamin C), while the creatinine level showed significant increase in 3rd and 8th group (1mg/Kg IVM, 2mg/Kg IVM +Vit.C).

It is well documented that the uric acid is the end product of protein and purine metabolism. In present study, the increase of uric acid and creatinine level it occur may be due to nephrotoxicity due to ivermectin treatment and may suggest reduction in glomerular filtration and dysfunction of the renal tubules and these results are closely matching with histological changes in kidney which observed in current study like vacuolation of cortical tubules and atrophy of glomeruli. The urea and blood urine nitrogen level decrease in current study may be due to effect of vitamin C which ameliorate the effects of ivermectin treatment.

Generally, (9) demonstrated the administration of 500mg/day of vitamin C for 2 months caused decrease in serum concentration of uric acid.

The results in our study is in agreement with (10) who proved the therapeutic and double therapeutic doses of Ivermectin (0.2mg and 0.4mg/Kg S/C) when given to male albino rats caused significant elevation in uric acid and creatinine. Similarly, Herd and Kociba,(11) postulated the I/M injection of 0.2mg/Kg for horse caused significant increase in urea level after 8 day of treatment, while the creatinine level showed significant decrease from day 4 of post treatment. Some investigators (12) found that the avermectin could interfer with the Malpighian tubules and hormones that acts on water balance. On the other hand,(13) claimed that the supplementation of vitamin C caused lower serum uric acid. Other group of investigators found that vitamin is very important in preventing the oxidative renal damage and stress (14).Moreover,Vitamin C was found to be effective in the protecting chemically induced oxidative renal damage in animals, they reported the high dose of vitamins significantly protect from renal damage induced by anticancerdrug (15, 16).

Generally ,kidney is regarded a vital organ responsible for reabsorption of substances and then excretion outside the body through urine. In present work ,the main features which can be observed due to ivermectin therapy are vacuolation of subcortical tubules (proximal convoluted tubules) and atrophy of glomeruli, in addition these lesion was reduced by vitamin C administration. This finding may be due to oxidative stress as a results of ivermectin treatment which produce free radicals and it may be accumulated in kidney tissues and impair its function.

This results is in accordance with Abdou and Sharkawy, (17) who observed the S/C injection of 0.2mg and 2mg/Kg of Ivermectin to goats caused pathological changes of kidney which characterized by partial necrosis of capillary tuft and degeneration of tubular epithelium. As well as, the administration of the 1/10 LD50 of Abamectin for 30 consecutive days in rats caused histological changes in kidney which includes interstitial nephritis, hyaline globules inside the tubules with thickening of membrane (18).Moreover, the oral administration of 10mg/Kg of Abamectin weekly to 210 day and 30mg/Kg to 30 days to rats caused histopathological changes in kidney in both concentration which include necrosis of renal tubular epithelium and vacuolation of endothelial lining of glomerular tufts (19).Some investigator proved that the S/C injection of 1mg/Kg of Ivermectin to donkey for 7day caused significant histopathological changes in kidney like hypercellular glomeruli, glomeruli appear hypercellular tuft, as well as, pinkish deposit in Bowman space(20). In addition, (10) demonstrated the therapeutic and double therapeutic dose of Ivermectin (0.2mg and 0.4mg/Kg) caused several harmful changes in the kidney of the male albino rats which includes hyper cellularity of glomerular tufts, vacuolation and hydropic degeneration of the lining of convoluted tubules. On the other hand, the administration of 500mg/Kg of vitamin C caused reduction in toxicity, and enhanced the animal's tolerance due to environmental stress (21).

In the current work, the histological examination of lung due to ivermectin therapy revealed dilated alveoli, aggregated of lymphocyte in bronchiole, bronchiolar dilatation and folding and thickening of bronchial epithelium. These changes occur may be due to oxidative stress occur due to repeat administration of ivermectin and its accumulation in lung tissue.

This results is in line with (17) who observed the S/C injection of 0.2mg and 2mg/Kg of Ivermectin to goats caused haemorrhage in the perivascular area of lung and alveoli.As well as, (19) noted the Abamectin caused interstitial pneumonia in lung of rats which treated for 30 day, while it caused diffuse focal haemorrhage associated with atelectasis which were noted in the lung of animals exposed to Abamectin for 210 days. The ameliorative effect of vitamin C administration on lung tissue in current study is well demonstrated.

This results is in accordance with (22) who proved the coadministration of vitamin C and E to rats caused reduce the pulmonary fibrosis lesion in lung of rats treated with hexavalent chromium. Also, (23) showed the vitamin C and E could reverse the histopathological changes due to dichlovos pesticide exposure in rats.

CONCLUSION

The repeated administration of ivermectin causes hazardous effects on kidney function and many of histopathological changes were demonstrated in kidney and lung structure. The administration of Vitamin C can acts as protective agent.

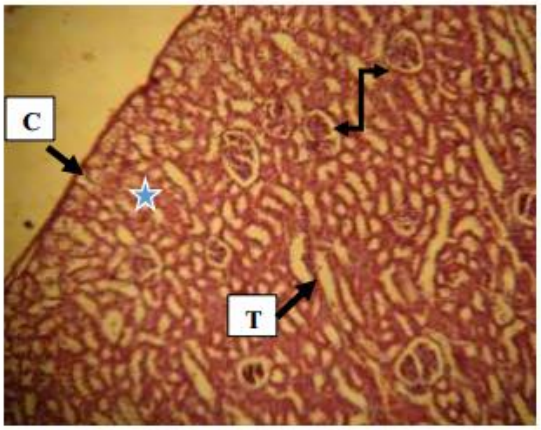

Figure (1): Kidney of control rabbit within normal limit stained with (H&E) X125. The pointer indicate capsule C, subcapsulular region (star) , glomerulus (curve arrow), tubules T.

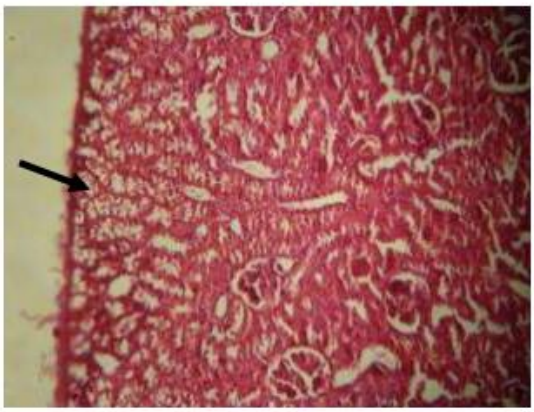

Figure (2): Kidney of rabbit treated with 0.5mg/Kg Ivermectin stained with (H&E) X125.. The pointer indicate vacuolation of subcapsular cortical tubules (PCT).

Table (1): Effect of ivermectin alone or with the combination of vitamin C on kidney functions of female rabbits after 8 weeks of treatment. (Mean ± SE), n=6/group.

	Uric acid mg/dl	**Urea mg/dl**	**BUN mg/dl**	**Creatinine mg/dl**
1st Group Control 0.9% Nacl	7.286± 1.455 **ec**	41.869±2.104 **a**	19.490±0.982 **a**	0.868±0.091 b
2nd Group 0.5mg/Kg Ivermectin	5.651± 0.938 **c**	38.158± 3.277 **ac**	17.769±1.525 **ac**	1.136±0.125 **ab**
3rd Group 1mg/Kg Ivermectin	7.431± 1.330 **ec**	37.822± 3.964 **ac**	17.614±1.847 **ac**	2.553±0.418 **c**
4th Group 2mg/Kg Ivermectin	14.631± 3.377 **a**	44.566± 4.421 **a**	20.752±2.060 **a**	1.452±0.126 **ab**
5th Group 50mg/Kg Vit.C	12.909± 3.194 **abe**	43.677± 2.184 **a**	20.329±1.020 **a**	1.339±0.194 **ab**
6th Group 0.5mg/Kg Ivermectin + 50mg/Kg Vit.C	11.431± 2.199 **abc**	40.858± 1.929 **a**	19.024±0.902 **a**	1.285±0.183 **ab**
7th Group 1mg/Kg Ivermectin + 50mg/Kg Vit.C	10.840± 0.508 **abc**	31.380± 2.250 **bc**	14.607±1.046 **bc**	1.148±0.211 **ab**
8th Group 2mg/Kg Ivermectin + 50mg/Kg Vit.C	10.921±1.233 **abc**	37.363± 1.909 **ac**	17.406±0.889 **ac**	1.505±0.140 **a**

*Different letters denote significant differences (P< 0.05) between groups.

* Vit.C = vitamin C

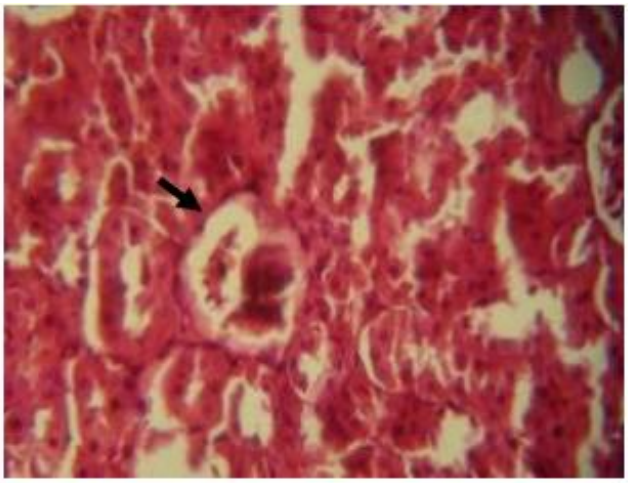

Figure (3): Kidney of rabbit treated with 0.5mg/Kg Ivermectin stained with (H&E) X500.. The pointer indicate atrophic glomerulus.

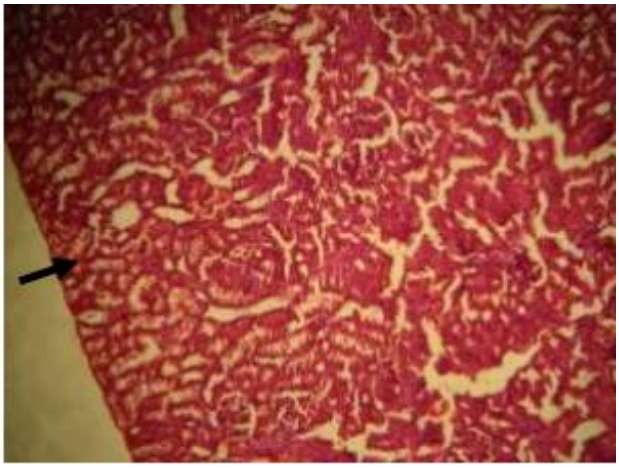

Figure (4): Kidney of rabbit treated with 1mg/Kg Ivermectin stained with (H&E) X125.. The pointer indicate vacuolation of subcapsular cortical tubules.

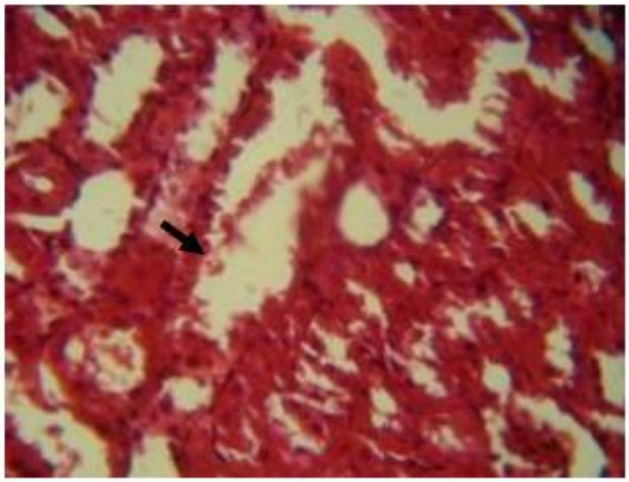

Figure (5): Kidney of rabbit treated with 1mg/Kg Ivermectin stained with (H&E) X500.The pointer indicate dilated cortical tubules.

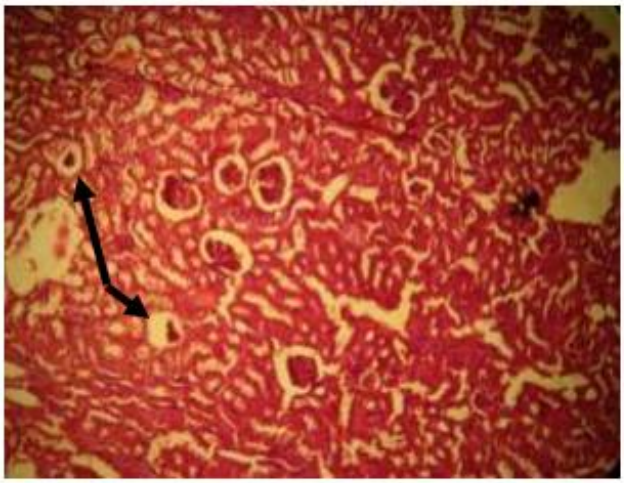

Figure (6): Kidney of rabbit treated with 1mg/Kg Ivermectin stained with (H&E) X125.The pointer indicate atrophy of glomeruli.

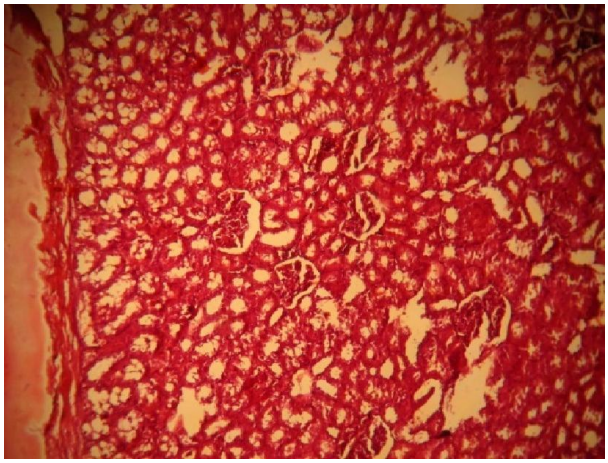

Figure (7): Kidney of rabbit treated with 2mg/Kg Ivermectin stained with (H&E) X125.The pointer indicate marked vacuolation of cortical tubules.

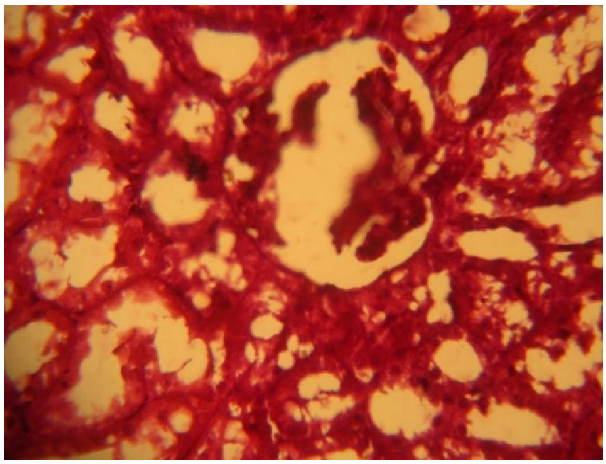

Figure (8): Kidney of rabbit treated with 2mg/Kg Ivermectin stained with (H&E) X500.The pointer indicate marked atrophy of glomeruli.

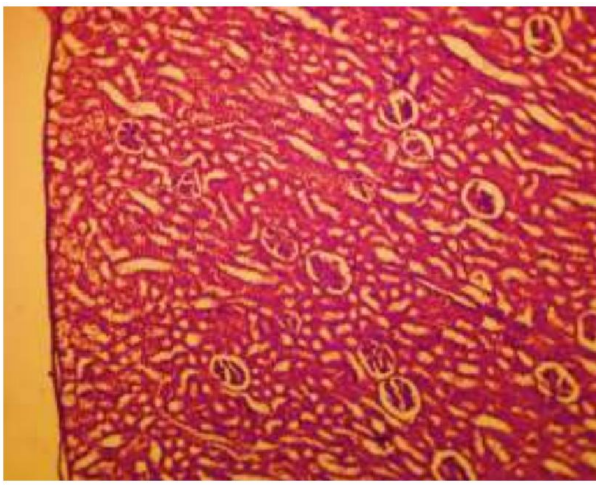

Figure (9): Kidney of rabbit treated with 50mg/Kg Vitamin C within normal limit stained with (H&E) X125.

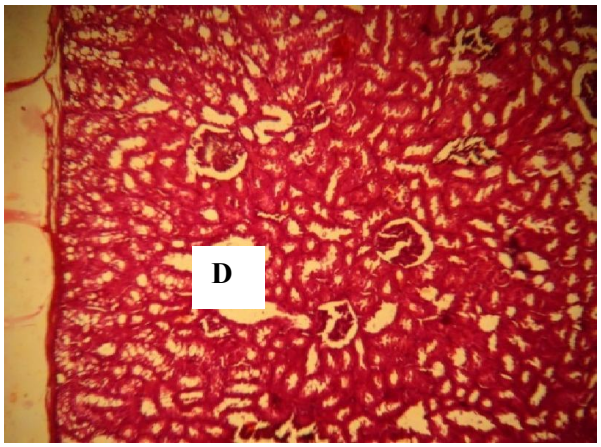

Figure (10): Kidney of rabbit treated (0.5mg/Kg IVM + 50mg/Kg Vit. C) Stained with (H&E) X125.The pointer indicate minimum dilation (D), vacuolation (arrow) of cortical tubules.

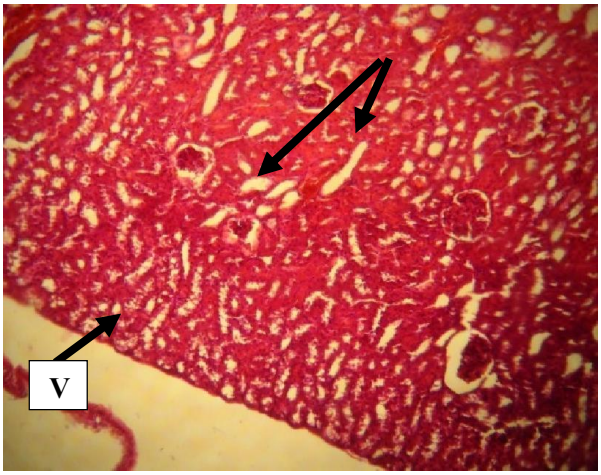

Figure (11): Kidney of rabbit treated (1mg/Kg IVM +50mg/Kg Vit. C) Stained with (H&E) X125.The pointer indicate dilated (arrow)/vacuolated (V) cortical tubules.

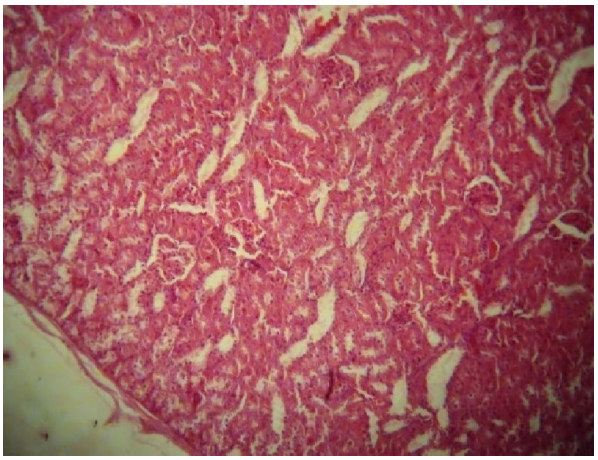

Figure (12): Kidney of rabbit treated (2mg/Kg IVM + 50mg/Kg Vit. C) Stained with (H&E) X125.The pointer indicate vacuolated cortical tubules (arrow), some dilated tubule (curve arrow).

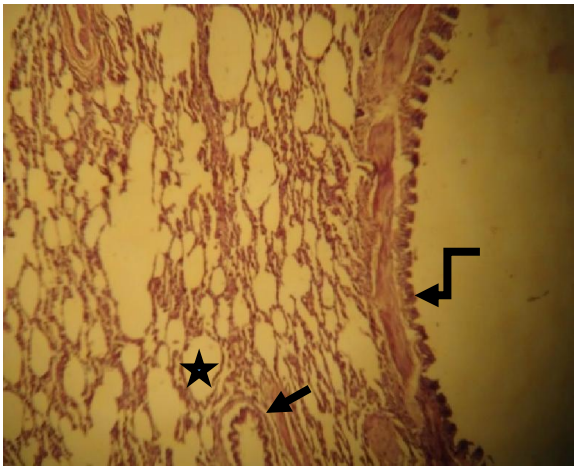

Figure (13): Lung of control rabbit bronchus and alveoli within normal limit stained with (H&E) X125. The pointer indicate bronchiole (arrow), alveoli (star), epithelial lining (curve arrow)

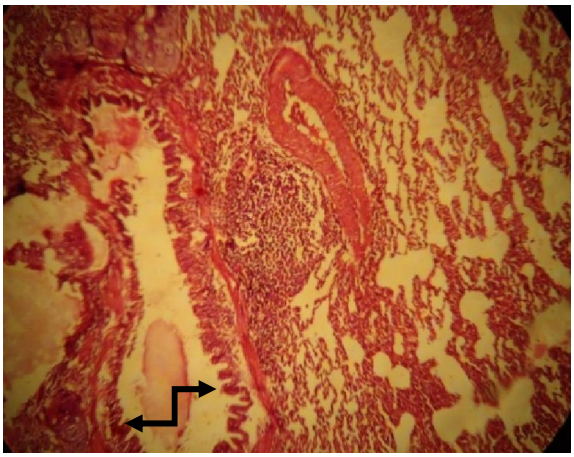

Figure (14): Lung of rabbit treated with 0.5mg/Kg Ivermectin stained with (H&E) X 125.The pointer indicate minimal folding (thickening)of bronchial epithelium.

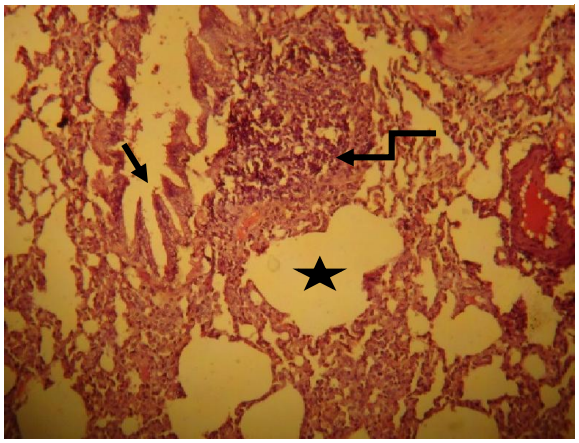

Figure (15): Lung of rabbit treated with 1mg/Kg Ivermectin stained with (H&E) X500.The pointer indicate bronchioles with papillary proliferation of mucosal epithelium (arrow), aggregated of lymphocyte(curve arrow), dilated alveoli (star),

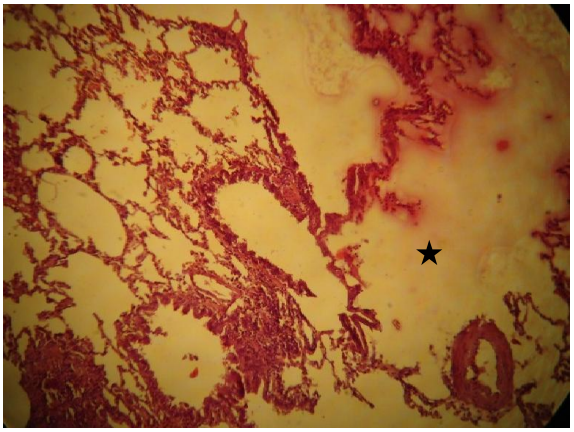

Figure (16): Lung of rabbit treated with 2mg/Kg Ivermectin stained with (H&E) X125.The pointer indicate minimum folding of bronchial epithelium (arrow), dilated alveoli(star), aggregated of lymphocyte(curve arrow)

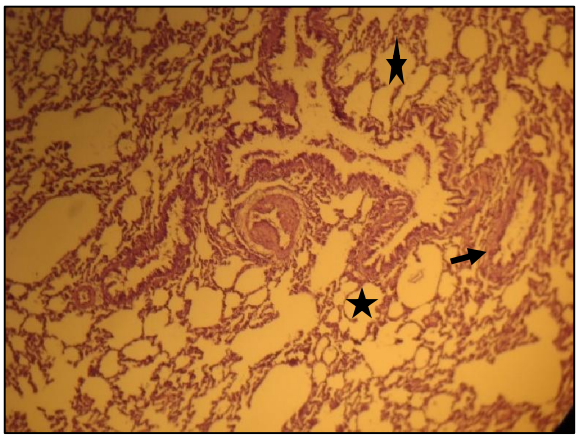

Figure (17): Lung of rabbit treated with 50mg/Kg Vitamin C within normal limits stained with (H&E) X125.the pointer
indicate bronchiole (arrow), alveoli (star)

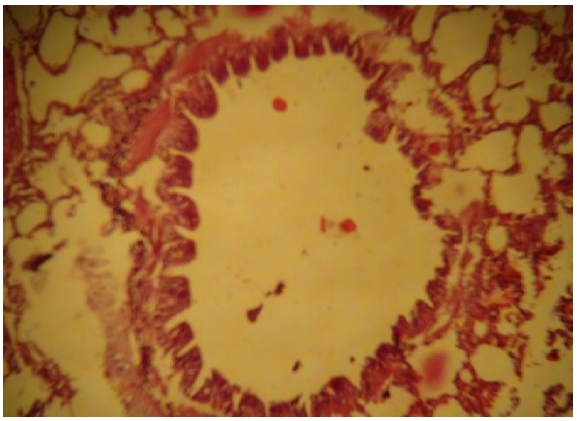

Figure (18): Lung of rabbit treated with (0.5 mg/Kg IVM + 50mg/KgVit.C) stained with (H&E) X125.The pointer indicate bronchiole with folded epithelium withproliferation.

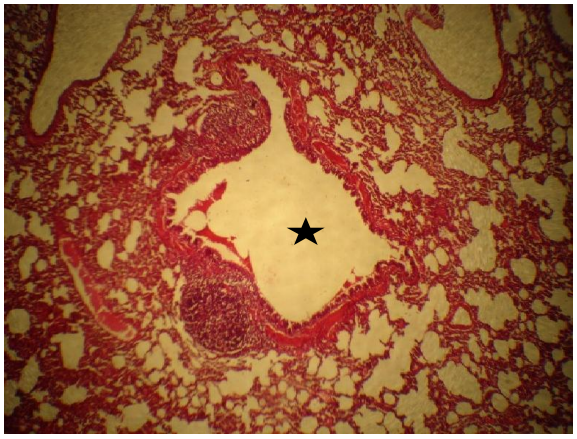

Figure (19):Lung of rabbit treated with (1mg/Kg IVM + 50mg/KgVit.C) stained with (H&E) X50.The pointer indicate peri bronchial aggregate of lymphocyte (arrow), dilated of bronchiole (star) , dilated alveoli (curve arrow)

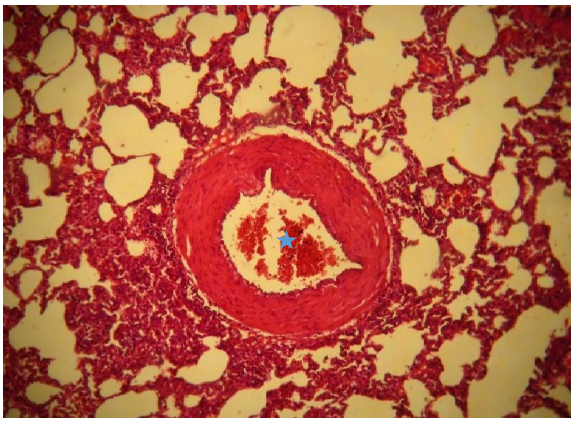

Figure (20): Lung of rabbit treated with (1mg/Kg IVM + 50mg/KgVit.C) stained with (H&E) X125.The pointer indicate anarea of alveoli with mononuclear cell with thickening alveolar septa and congested pulmonary artery(star)

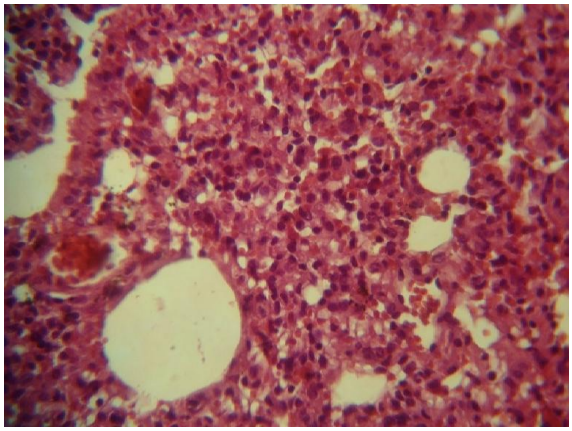

Figure (21): Lung of rabbit treated with (2mg/Kg IVM + 50mg/KgVit.C) stained with (H&E) X125.The pointer indicate an area of mononuclear cell in alveoli.

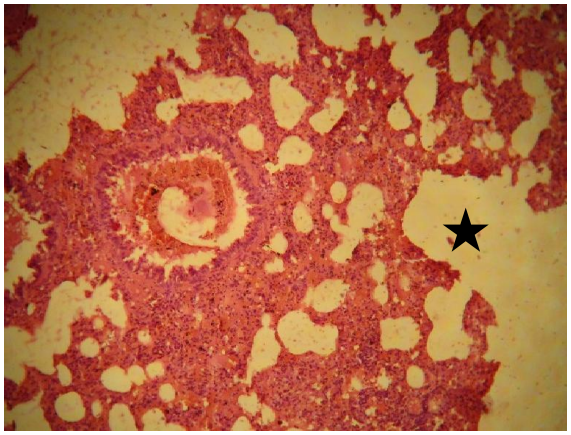

Figure (22): Lung of rabbit treated with (2mg/Kg IVM + 50mg/Kg Vit.C) stained with (H&E) X125.The pointer indicate bronchiole with folded proliferated epithelium(arrow), dilated alveoli (star).

التاثيرات النسجيه الامراضيه والبايوكيميائيه للايفرمكتين على وظائف الكلى،الرئه والدور المحسن لفيتامين سي على الارانب

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**** صالح كاظم مجيد
*المستشفى البيطري في البصره، البصره، العراق
** كليه طب الاسنان، فرع العلوم الاساسيه، البصره، العراق
*** كليه الطب البيطري، البصره ، العراق

الخلاصه

تهدف هذه الدراسه لمعرفه تاثيرات الجرع المتكرره من الايفرمكتين لوحده او مع فيتامين سي على وظائف الكلى والرئه في الارانب. استخدمت في هذه الدراسه 48 انثى ارنب بالغه. قسمت الارانب الى ثمانيه مجاميع وبعدد متساو كل مجموعه تتكون من سته ارانب. المجموعه الاولى جرعت ب 0.9% من كلوريد الصوديوم واعتبرت كمجموعه سيطره. المجموعه الثانيه والثالثه والرابعه جرعت ب(0.5 ملغم/كغم، 1 ملغم/كغم و2ملغم /كغم من وزن الجسم بالايفرمكتين) على التوالي.بينما جرعت المجموعه الخامسه ب 50 ملغم / كغم من وزن الجسم بفيتامين سي فقط. المجموعه السادسه ، السابعه والثامنه اعطيت 50 ملغم/ كغم من وزن الجسم فيتامين سي مع الايفرمكتين (0.5 ملغم/كغم، 1 ملغم/كغم و2ملغم /كغم) على التوالي. اعطي عقار الايفرمكتين تحت الجلد اسبوعيا، بينما اعطي فيتامين سي يوميا وعن طريق الفم. استمرالعلاج لمده 8 اسابيع في كل المجاميع المعامله.

اظهرت النتائج وجود زياده معنويه ($P< 0.05$)في حامض البوليك في المجموعه الرابعه. كذلك اظهر مستوى اليوريا و ومستوى نتروجين اليوريا في الدم نقصان معنوي ($P< 0.05$)عند المجموعه السابعه. بينما مستوى الكرياتنيين اظهر زياده معنويه ($P< 0.05$)في المجموعه الثالثه والثامنه عند مقارنتها بمجموعه السيطره. شملت التغييرات النسجيه الامراضيه في الكلى بسبب علاج الايفرمكتين تفجي في الانابيب تحت الكبسول للانابيب الكلويه و ضمور الكبيبه.اظهرت الرئه توسع في الاسناخ، تجمع الخلايا اللمفيه في القصبات، توسع القصبات، بالاضافه الى طي وتثخن الجدار الطلائي للقصبات. اعطاء فيتامين سي مع الايفرمكتين حسن التاثيرات الضاره الناتجه من المعالجه بالايفرمكتين. يمكن ان نستنج ان الجرع المتكرره من الايفرمكتين تسبب اضرار خطيره وخاصه في الجرع العاليه على وظائف الكلى وتسبب العديد من التغييرات النسجيه المرضيه في تركيب الكلى والرئه. والتغييرات تزداد بالتناسب مع الجرعه.وايضا اعطاء فيتامين سي يمكن ان يعمل كعنصر محسن.

مفاتيح الاستدلال: الايفرمكتين، فيتامين سي ، الكلى، الرئه، الانسجه، الارانب

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