Teratogenic Effect of Keppra (Levetiracetam) Drug on the Kidney in Albino Rat (*Rattus rattus*)

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Abstract

Levetiracetam (LEV) is new antiepileptic drugs (AEDs), usually used with other drugs in case of inadequate control of seizures. It is usually discharge with the breast milk.

This study was conducted for the evaluation of the effect of levetiracetam on the kidney after 3 and 7 day newborn albino rats (*Rattus rattus*).

A total of 20 rats were taken which were divided into two groups (A/control and B/ treated). The rat pregnant group (A) represents control group which has given distilled water orally during the pregnancy period and continued in taking of till one week newborn and (B) represents treated groups the drug was administered (350 mg/kg/day) orally during the pregnancy period and continued in taking of drug till one week newborn.

The statistical analysis of the result revealed that the mean values of the glomeruli diameter at 3 and 7 days newborn of the treated groups showed significant increase ($p<0.05$), and the mean values of the renal tubules diameter at 3 days newborn of the treated groups showed no significant increase ($p\geq0.05$), but at 7 day newborn of the treated group showed significant increase ($p<0.05$).

Histological study of the kidneys in treated group at 3, 7 days newborn, showed histopathological effect of kidney tissue represented by cortex damage where glomerulus emerged (degeneration , loss there nucleus, glomerular dead cell , small in size, glomerular cells accumulation and enlargement space was present between the glomerulus and glomerulus space , shrinking and atrophy of glomerulus). As well as, the damage was evident in the medulla where tubules emerged (swelling epithelial cells of collecting tubules , enlargement in size together narrow space between the proximal convoluted tubule, degeneration of collecting tubules , loss there nucleus and detached cells of collecting tubule from basement membrane).

This study disclosed that LEV can induce already not reported severe malformation if it is used constantly through the implantation, an organogenesis stages of pregnancy. Therefore, it is proposed that great caution should be practiced in using LEV during the early stages of pregnancy until further studies are performed to better understand these effects.

Keywords: kidney, levetiracetam drugs, Rat.

Introduction:

In a pregnant female, unrestrained epilepsy is a severe and serious threat for both mother and child. Commonly, at least one antiepileptic drug is required taken by pregnant female with epilepsy. Essentially, a healthy seizure-free mother and an undamaged child is the mean target for all concerns. However, the effect of the antiepileptic drug should be avoided or minimized on the developing child during pregnancy and lactation [1]. Recently, in case of uncontrolled seizures, a new levetiracetam (LEV), which is an antiepileptic drug (AED), has been used with specific pharmacologic characteristics. Usually it's used as a supplementary to other drugs. Eventually, levetiracetam (LEV) has been used as adjunction therapy for refractory partial-onset seizures, primary generalized tonic-clonic seizures, and myoclonic seizures of juvenile myoclonic epilepsy and partial-onset seizures with or without secondary generalization [2]. Significantly, it can pass through breast milk [3, 4, 5]. Few female pregnancies have been given the LEV drugs and there appears to be a substantial increase in clearance during pregnancy and a coloration fall of blood concentrations [4]. Its teratogenic risk is unknown [1]. Further, LEV is superbly absorbed after oral administration. Recently, it has been identified that the oral bioavailability level of LEV is more than 95%. More after one hour oral administration, its dose attains a peak plasma concentration [6]. Additionally, within 48 hours of starting therapy, it reaches a steady state concentration [6, 7]. Moreover, it has been reported that less than 10% of LEV is bound to plasma proteins and this protein binding is not clinically recant [7,8]. However, only 27% of LEV is metabolized and metabolism is not reliant on the liver cytochrome P450 enzyme system [7]. The plasma half-life of the LEV is (7 ± 1) hour in adults and it is predominantly excreted unaffected through the kidneys [7, 8]. Additionally, sixty-six percent (66%) of the dose is renal excreted unchanged. The glomerular filtration and active tubular secretion excreted on the metabolite [9]**.**

Material and Methods

Animal Breeding: Apparently healthy pregnant female Albino rats *(Rattus rattus*) strain (250-300 g) age (10-12 weeks) were utilized in this study. They were obtained from Al-Nahrain University / The High Institute of Infertility Diagnosis and Assisted Reproductive Technologies Animal House. All animals were housed at 21±4 Ċ. The rats were allowed adlibitum access to food and water throughout the gestational and lactation period [10].

Experimental Design: 20 pregnant female rats used in this study and they were divided into two groups: (A), (B) each contained ten rats:

Group (A): Represented control group, it is subdivided into two sub-groups (**A_1&A_2**) each included 5 rats.

Group (B): Represented treated group, it is subdivided into two sub-groups (**B_1&B_2**) each included 5 rats.

Treatment:

For the treatment, it has been used the syrup Keppra XR® (100mg/ml) UCB Pharma, Inc., Smyrna, Ga., USA (KEPPRA XR®)

Collect of Newborn:

Female pregnant were anesthetized by mixing solution (Ketamine 10 mg / kg and Xylazine 10 mg / kg) of body weight, an abdominal incision was made at the median line in order to extract embryos from placental sacs by cervical dislocation of uterus and remove the outer membranes of embryonic and then kidney birth reconstruction 3 and 7 days were taken of collection of the experimental and the control group, they fixed in Bouins fluid for (12-24 hours) and later washed several times with 70% ethyl alcohol and was kept until use[11]. Then, kidney was embedded in the paraffin wax, sectioning by rotary

microtome, stained with haematoxylin and eosin stain and periodic acid Schiff (PAS) [12]. Photographs were taken by a microscope imaging compound type MEIJI Canon camera and that in the developed embryos Laboratory in the Department of Biology/College of Education For Pure Sciences Pure (Ibn Al-Haitham) University of Baghdad.

Digital Image Analyzing Soft wares:

Digital Image Analyzing soft wares are designed especially for scientific analysis of a given image. Slides Images were captured by digital camera these sections were examined with light microscope and photographed type composite MEIJI Canon camera placed directly over the head of the microscope with a 40X objective and at least five images were captured for each sample.

Programs were used in this study:

Image J program *(http://imagej.nih.gov/ij/docs/guide)* **.**

Image J program is a public domain Java image processing and analysis program inspired by National Institutes of Health (NIH) Image for the Macintosh. It can read many image formats including TIFF, GIF, JPEG, and BMP. It can calculate area and pixel value statistics of user-defined selections. It can measure distances and angles. It supports standard image processing functions such as contrast manipulation, sharpening, smoothing, edge detection and median filtering. It does geometric transformations such as scaling, rotation and flips. Image can be zoomed up to 32:1 and down to 1:32. Image J main window is actually containing only a menu bar with all the Menu Commands, a Toolbar, a Status bar and a Progress bar.

Result:

1- Kidney newborn age of 3rd days:

The results showed that the mean value of the glomerular diameter in the control group of newborn was (16.00 ± 0.42), while the mean value in treated group was more with significant increase ($p < 0.05$) with mean of (18.97±0.62) (Table-1).

The results revealed that the mean value of the renal tubules diameter in the control group of infants was (8.64±0.18), the mean value of renal tubule diameter for the treated group showed no significant increase ($p \geq 0.05$) as mean value was (8.74±0.25) (Table-1).

In the control group, the histological study for kidneys showed there were continuous formations of mature glomerulus. There was a clear increase in the number of glomerulus in the cortical region. Where are emergence of the glomerulus and Bowman's capsule that is surrounded by cells mesenchymal and showed proximal convolute tubules (PCT) and distal convoluted tubules DCT lined of cuboidal epithelium (Fig. 1), while kidney in the treated group with (350 mg/kg/day) showed cortex damage where emerged enlargement space was present between the glomerulus and glomerulus space together glomerular cells accumulation , shrinking and atrophy of glomerulus , decreasing in cell size and damaged of glomerulus cell , loss there nucleus, glomerular dead cell. As well as, the damage was evident in the tubules emerged swelling epithelial cells of collecting tubules, damaged of collecting tubules cell , loss there nucleus and detached cells of collecting tubule from basement membrane (Fig. 2).

2- Kidney newborn age of 7th days:

The results revealed that the mean value of the glomerular diameter in the control group of newborn was (17.69±0.41), while the results showed the mean value of the glomerular diameter for the treated group a significant increase ($p < 0.05$) with mean of (23.77±0.97) (Table 1).

The results showed that the mean value of the renal tubules diameter in the control group of infants was (11.56±0.20), while the result showed the mean value of renal tubule

diameter for the treated group showed significant increase ($p < 0.05$) as mean value was (9.27±0.35) (Table 1).

In the control group, the histological study for kidneys showed the renal cortex and renal medulla, the cortical region was populated predominantly by later stages of developing glomerulus with a large number of the mature glomerulus emergence and the renal medulla emergence proximal convoluted tubules and distal convoluted tubules (Fig.3,4), while kidney in the treated group showed external layer damaged in Bowman's capsule , loss there nucleus in partial layer , the appearance of abnormal enlarged capsular space , damage in glomerulus , detachment glomerular cells and the glomerular cells accumulation together shrinking and atrophy of glomerular , decreasing in cell size. In the renal medulla which were damaged in collecting tubules , swelling cells together narrow lumen the proximal convoluted tubule without distal convoluted tubules, degeneration of collecting duct , detachment of epithelial lining from basement membrane and dead cell , loss there nuclei (Fig. 5,6).

Discussion:

The most critical period for teratogenic effects occurs during the embryonic period. In the fetal period, effect of drug exposure can cause fetotoxic effects such as growth restriction, change in size or functioning of certain organs, or development and behavioral abnormalities [13].

1. Histopathology of kidney in age 3rd day newborn:

The kidney of the newborn for the treatment with 350 mg/kg/day of LEV showed that there were differences between capsular spaces together glomerular cells accumulation which were appeared shrinking and atrophy of glomerulus which were characterized by decreasing in cell size of the control group. This result is in agreement [14], who reported that some glomeruli shrink or disappear. Also this result is compatible to what was obtained by [15], who mentioned that cell accumulation can either reduce the number of normal cells or increase the number of abnormal cells.

And the treated caused cells death of glomeruli and collecting tubules which is characterized by decrease in cell size. This result is in agreement with [16], who reported that cell death essentially occurs when cellular damage may induce by toxicants. Also this result showed damage of glomerulus and cells of collecting tubule which is characterized by the loss of their nucleus. This result is compatible to what was obtained by [17], who mentioned that such inflammation of glomeruli may lead to failure. Also this result is compatible to what was obtained by [18], who mentioned that anti-inflammatory drugs caused allergic tubulointerstitial nephritis. And the treated caused swelling of cell which is characterized by enlargement of cells size.

This enlargement of cell may be due to the enlargement of the components of these cells and this swelling may be mostly due to the accumulation of water inside the cell [19]. This result is compatible with what was obtained by [20], who documented that such a type of cell swelling in kidney was mostly due to accumulation of water inside the cells. The cell that is moved toward the lumen showed the suicide of some cells and this result is similar to what was obtained by [21], who mentioned that such cell will die in their suicidal process. And the treated caused damage of collecting tubules cell which are characterized by detached cells of collecting tubule from basement membrane, this destruction may be due to the loos of cytoskeleton and destruction of plasma membrane [22].

2. Histopathology of kidney in age 7th day newborn

The kidney treated with 350 mg/kg/day of LEV showed external layer damaged in Bowman's capsule which are characterized by loss there nucleus in partial layer and damage in glomerulus which are characterized by the cells detachment in visceral layer. This result is compatible to what was obtained by [16], who reported that cell death essentially occurs when cellular damage may induce by toxicants. Also this result is in agreement with [23], who mentioned that the appearance of cell death that may be due to the plasma membrane destruction. And treated caused abnormal enlarged capsular space. This result is in agreement with [24], who mentioned that the role of cytoplasmic microtubules induce drug. And the treated caused the glomerular cells accumulation together shrinking and atrophy of glomerular which were characterized by decreasing in cell size. This result is in agreement with [14], who reported that some glomeruli shrink or disappear. And the treated caused swelling cells which are characterized by increasing in cell size together narrow lumen the proximal convoluted tubule without distal convolute tubules. This result is in agreement with [25], who mentioned that may be due to the effect of drug toxicity in kidney which may lead to deficit or a defect in the function, and narrow lumen of collecting tubule may be due to Hydropic degeneration [26]. And the treated caused degeneration of collecting duct which is characterized by detachment of epithelial lining from basement membrane. This result is in agreement with was documented by [27], who reported, that the tubular cells destruction will block the kidney function under the effect of drug toxicity. Also this result is compatible to what was obtained by [18], who mentioned that anti-inflammatory drugs cause allergic tubulointerstitial nephritis. And the treated caused death cell of collecting duct which is characterized by loss of nucleus. This result is in agreement with [28], who reported that the death of the tubular epithelial cells (lose their nuclei) may be due to the toxicity of the drug detected programmed cell death during embryogenesis.

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Table No (1): Effect of LEV (350 mg/kg/day) on glomeruli and renal tubules diameters (µm) of kidney of newborns aged 3 and 7 days:

Day of newborns	Glomeruli diameter Mean ±SE		Renal diameter Mean ±SE	
	Control	Treated	Control	Treated
3 days	17.69±0.41	23.77±0.97*	11.56±0.20	9.27±0.35*
7 days	16.00±0.42	18.97±0.62*	8.64 ± 0.18	8.74±0.25

*(P<0.05)

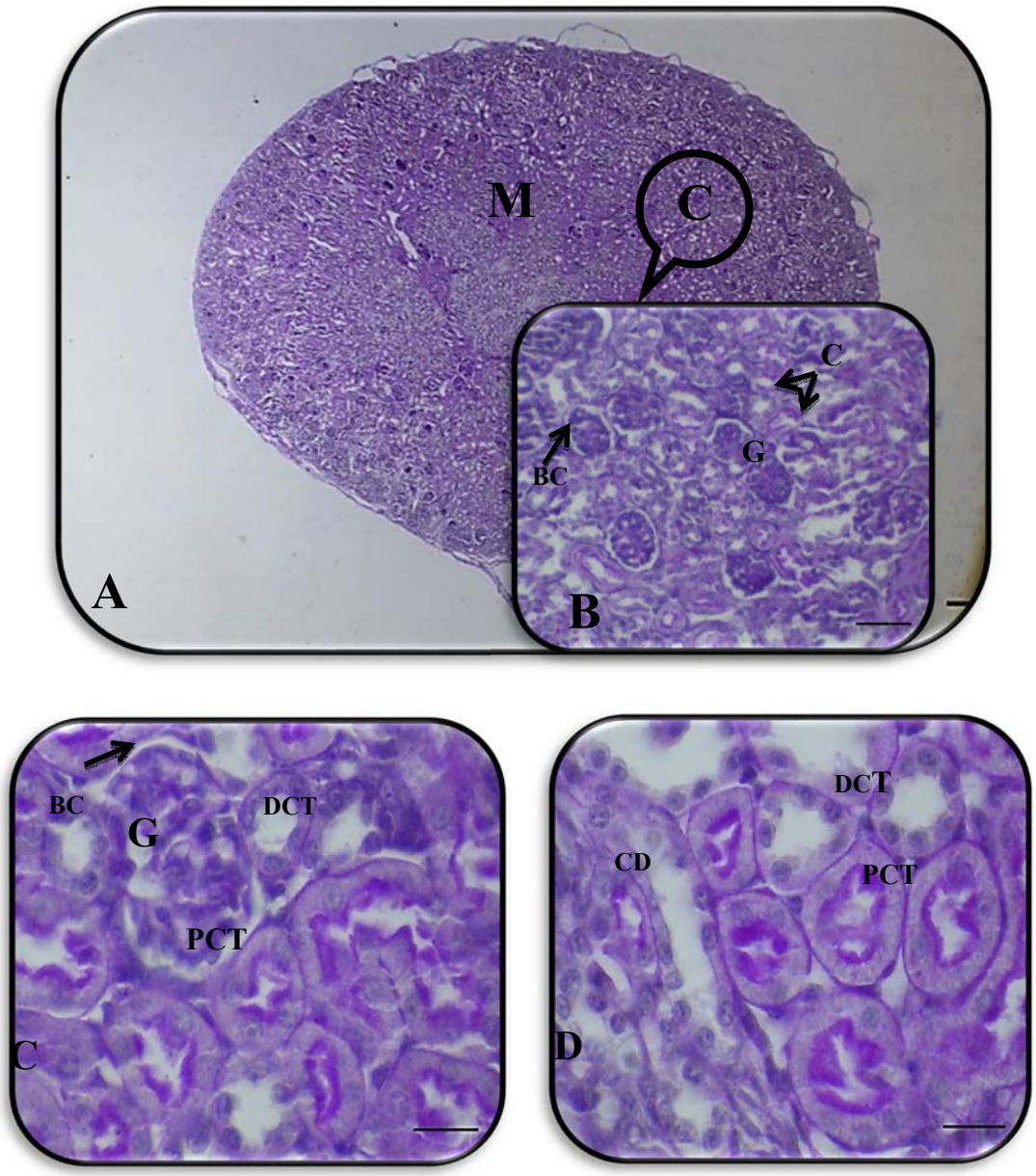
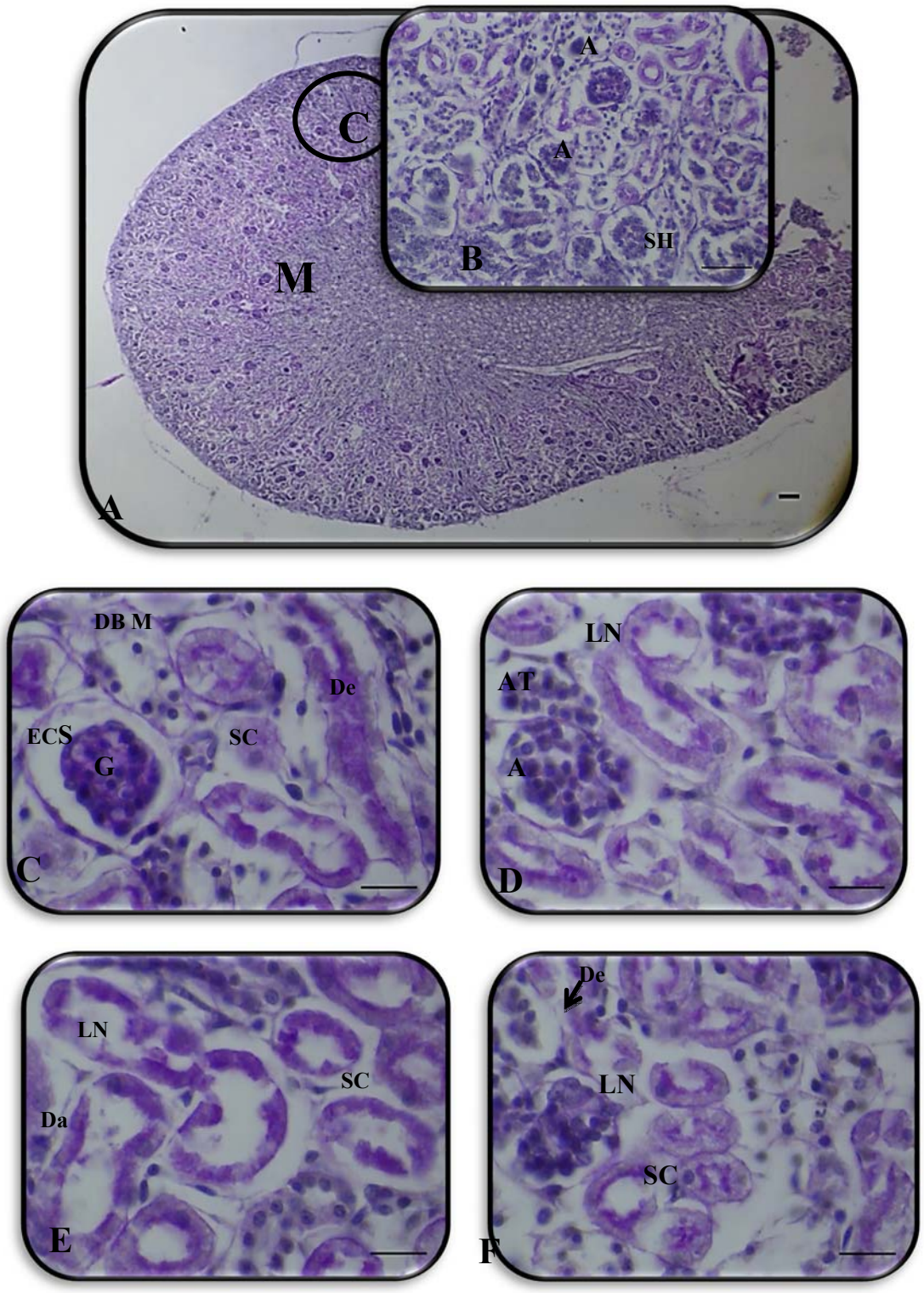


Figure No.(1): Cross section of newborn Kidney at (3rd) day newborn (control group) showed: (BC) Bowman's Capsule, (C) Cortex, (CD) collecting duct, (CT) collecting tubules, (DCT) Distal Convoluted Tubule, (G) Glomerulus, (M) Medulla, (PCT) Proximal Convoluted Tubule. (A): (PAS), scale bare: 200µm 4X .(B) :(PAS), scale bare: 50µm, 40X. (C)&(D) : (PAS)، Scale bare: 20µm , 100X.



FigurNo.(2): Section of newborn Kidney at (3rd) day newborn (treated group) Showed: (A) Accumulation, (AT) Atrophy, (C) Cortex, (Di) Damaged of collecting cell, (De) detached cell, (ECS) enlargement capsule space, (LN) loss nucleus, (SH) shrinking glomerular.(A): (PAS)، scale bare: 200µm ،4X . (B): (PAS), scale bare: 50µm, 40X . (C)&(D)&(E)&(F) : (PAS), Scale bare: 20µm, 100X.

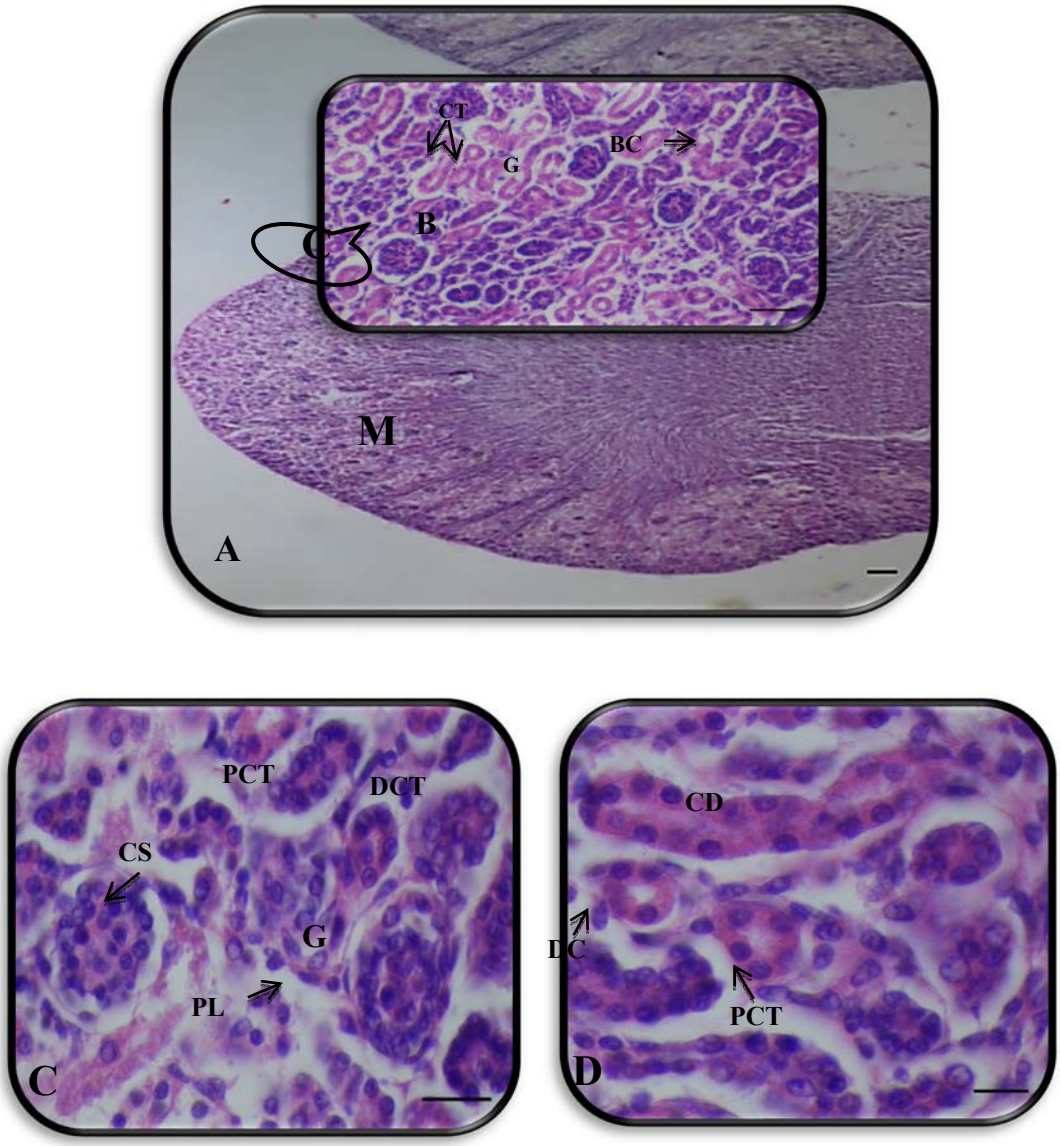


Figure No.(3): Section of newborn Kidney at (7th) day newborn (control group) showed: (BC) Bowman's Capsule, (C) Cortex, (CD) collecting duct, (CT) collecting tubules, (DCT) Distal Convoluted Tubule, (G) glomerular, (M) Medulla, (PCT)Proximal Convoluted tubule,(PL) Partial layer of bowman's capsule. (A): (H&E) stain, scale bare: 200µm,4X. (B): (H&E) stain,scale bare: 50µm ، 40X .(C)&(D) : (H&E) stain, scale bar: 20µm, 100X.

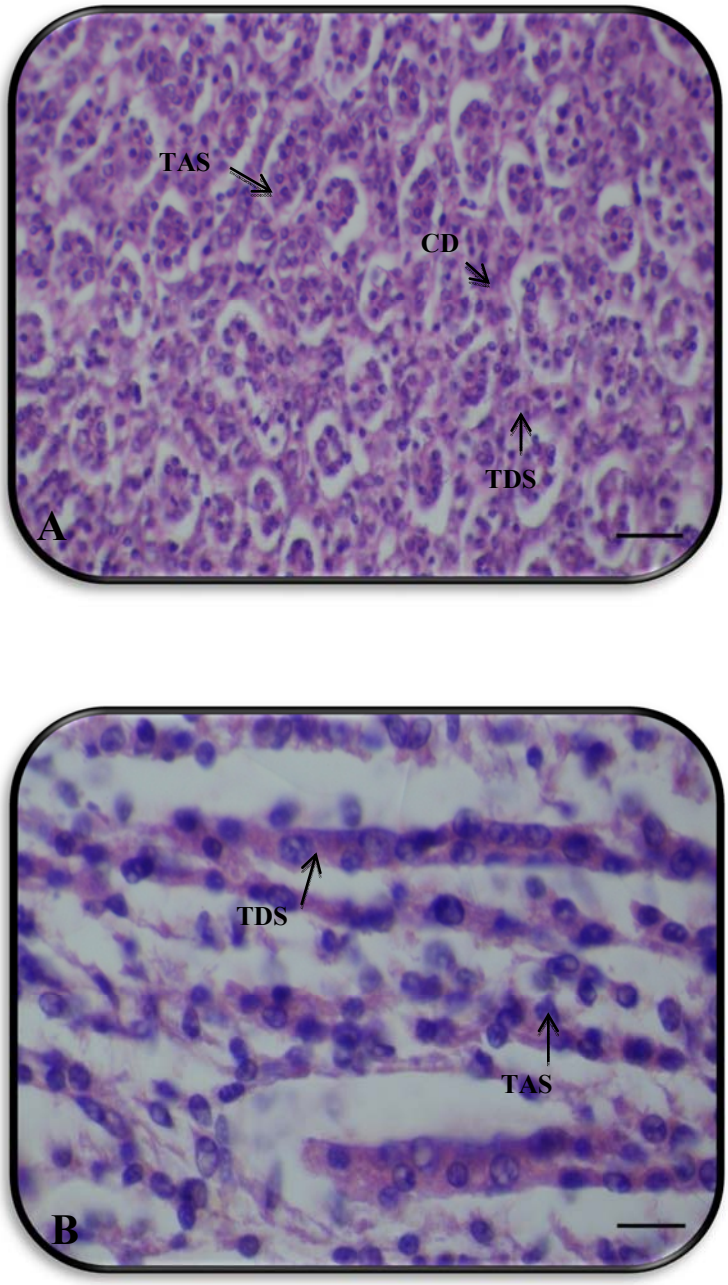


Figure No.(4): Section of newborn Kidney at (7^{th}) day newborn (control group) showed: (CD) collecting duct, (TAS) thick ascending segment, (TDS) thin descending segment. A: (H&E) stain, scale bar: 50µm, 40X. B: (H&E) stain, scale bar:20µm, 100X.

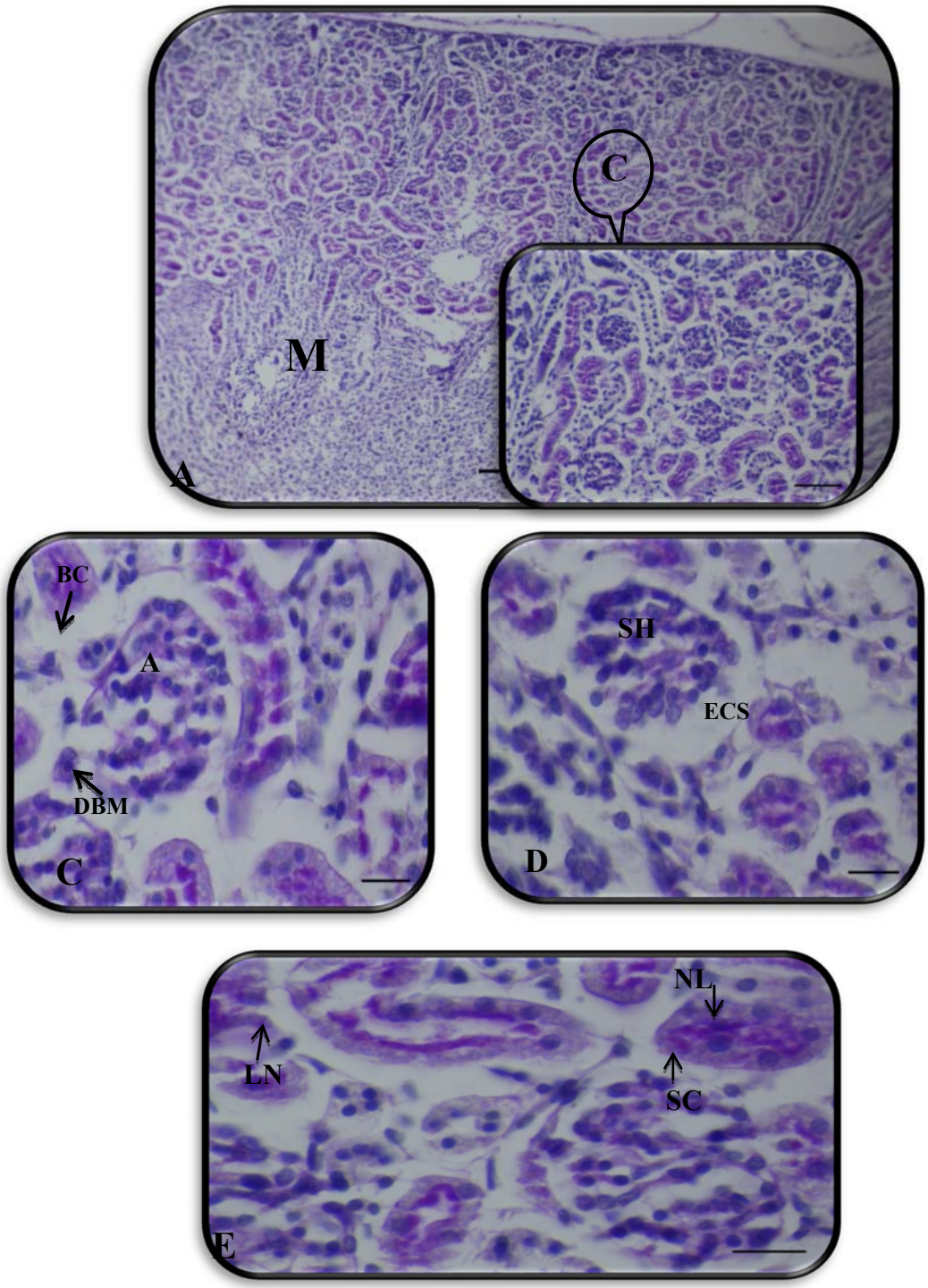


Figure No.(5): Section of newborn Kidney at (7th) day newborn (treated group) showed: (A) Accumulation, (AT) Atrophy of glomerulus, (BC) Damaged exterior of Bowman's capsule, (C) Cortex,(DBM) Detached of basement membrane,(ECS) Enlargement capsule space, (LN) Loss of nucleus, (M) medulla, (NL) Narrow lumen of proximal convoluted tubules, (SC) Swelling cell, (SH) shrinking of glomerular. (A): (PAS) stain, scale bar: 200 µm, 4X. (B): (PAS) stain, scale bar: 50µm, 40X. (C)&(D)& (F):(PAS) stain, scale bar: 20µm, 100X.

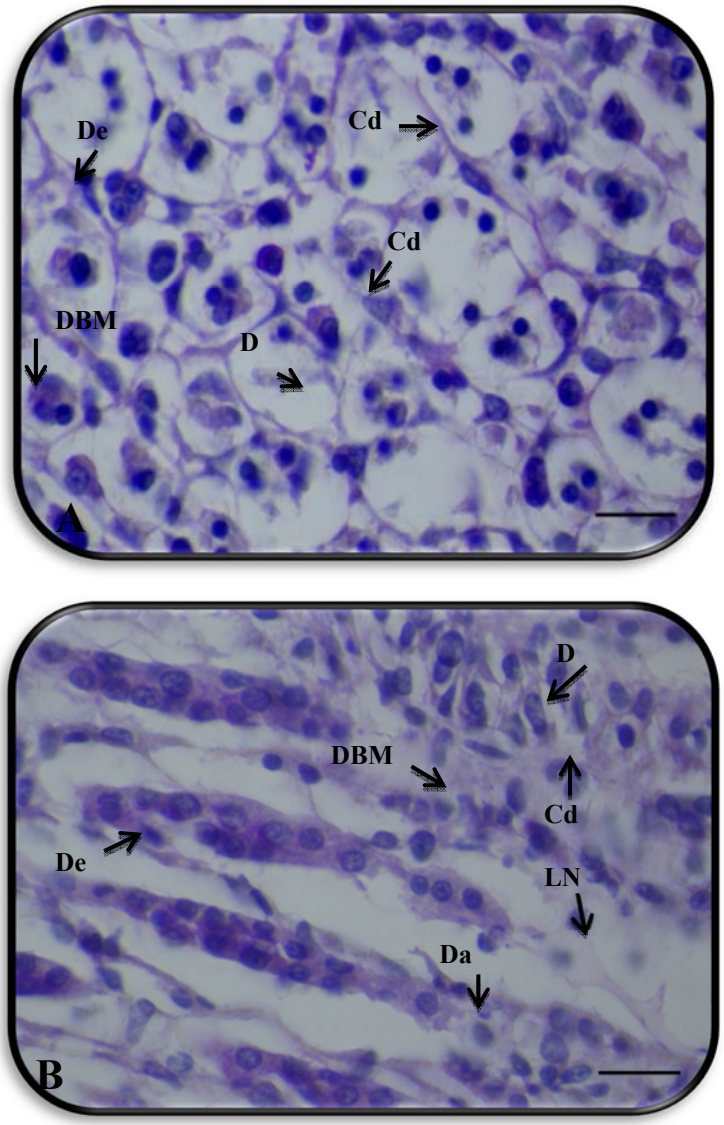


Figure No.(6): Section of newborn Kidney at (7th) day newborn (treated group) Showed: (Cd) cell death, (D) degeneration of thick ascending segment, (Da) damaged of thin descending segment, (DBM) detached cell, (De) decreasing size, (LN) loss nucleus. (A): (PAS) stain, scale bar: 50µm , 40X. (B): (PAS) stain, scale bar:20µm, 100X.

التأثير الماسخ لعقار الكيبرا (ليفيتيراسيتام) في كلية مولود جرذ Albino rats (*Rattus rattus*)

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استلم البحث في : ٢/٢٢ / ٢٠١٥ ، قبل البحث في :٣/٢٩ /٢٠١٥

الخلاصة

عقار ليفيتيراسيتام Levetiracetam (LEV) من العقاقير المضادة للصرع الجديدة، عادة مايستخدم مع العقاقير المضادة للصرع الاخرى في حالة عدم الكفاية للسيطرة على نوبات الصرع، وهو عادة مايفرز مع حليب الام.

اجريت هذه الدراسة لتقييم أثار عقار ليفيتيراسيتام LEV على كلى مواليد الجرذ الابيض Albino rats (*Rattus rattus*) بعمر 3 و 7 أيام، حيث استخدم 20 جرذاً حاملاً تم تقسيمها عشوائياً على مجموعتين (مجموعة A/ السيطرة ومجموعة B /المعاملة) ، جرعت الام الحامل في مجموعة السيطرة الماء المقطر منذ اليوم الاول للحمل وحتى نهاية الاسبوع الاول بعد الولادة ، و جرعت الام الحامل في مجموعة المعاملةعقار LEV تركيز (350 mg/kg/day) عن طريق الفم من اليوم الاول للحمل وحتى نهاية الاسبوع الاول بعد الولادة.

اظهرت نتيجة التحليل الاحصائي ان معدل القطر الكبيبي في مجموعة المعاملة للمواليد بعمر 3 و7 يوم وجود فروق معنوية ($p<0.05$) ، بينما اظهرت نتيجة التحليل الاحصائي لمعدل قطرالنبيبات الكلوية بعمر 3 يوم عدم وجود فروق معنوية ($p\geq0.05$)، في حين اظهرمعدل قطر النبيبات الكلوية بعمر 7 يوم وجود فروق معنوية ($p<0.05$).

اوضحت المقاطع النسجية لكلى مواليد التجربة بعمر 3 و 7 يوم وجود حالات مرضية نسجية متمثلة بحدوث ضرر واضح في القشرة حيث ظهر في الكبيبية (تنكس ، وفقدان النوى ، وموت خلايا الكبيبة ، وصغرحجمها، وتراكم الخلايا الكبيبية ، وتوسع واضح مابين الكبيبة والفسحة المحفظية ، وانكماش واضمحلال الكبيبات). وكذلك كان الضرر واضحاً في اللب حيث ظهرفي النبيبات الكلوية (انتفاخ الخلايا الظهارية للنبيبات الجامعة وكبر حجمها مع ضيق تجويف النبيبات الملتوية الدانية دون النبيبات الملتوية القاصية ، تنكس الخلايا الظهارية للنبيبات الجامعة وفقدان النوى و انفصال الخلايا الظهارية عن الغشاء القاعدي.

كشفت الدراسة الحالية ان عقار LEV يمكن ان يحدث تشوهات عديدة اذا ما تم استخدامه خلال مراحل انغراس الجنين، وتكوين الاعضاء في الحمل . لذلك تقترح الدراسة ان يأخذ الحذر الشديد عند استخدامه خلال المراحل الاولى من الحمل حتى يتم اجراء المزيد من الدراسات لفهم افضل لهذه الاثار.

الكلمات المفتاحية: الكلية ، عقار ليفيتيراسيتام، الجرذ.