EFFECTS OF ENFLURANE ON HISTOLOGICAL STRUCTURE OF LIVER AND KIDNEYS IN ADULT MALE ALBINO RATS AND THE ROLE OF VITAMIN E ADMINISTRATION

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ABSTRACT

Introduction: The aim of this study was to assess the probable hepatic and renal histopathological changes in rats following a 2 h of enflurane administration, which is still used for anesthesia and possible role of vitamin E supplementation. **Materials and Methods**: A total of 30 Wistar rats were used in the study. The rats were classified equally into 3 groups; control group, enflurane exposed group and vitamin E administrated group. The rats in the experimental group were anesthetized with 2% inhalational enflurane for 2 h. The third group was intraperitoneally administered with vitamin E (dl-alpha-tocopheryl acetate, 100 mg/kg body weight) that taken with enflurane anesthetic group. Following the anesthesia, rats were sacrificed and liver and kidneys were examined histopathologically. **Results**: Histopathological changes in the enflurane exposed group included degenerative and necrotic changes and inflammatory cell infiltration. The kidneys were more affected compared to liver. While in vitamin E administrated group, both liver and kidney were less affected. Consequently, it was assessed that enflurane had significant effects on the histology of liver and kidneys. So, renal function should be taken into consideration while using this anesthetic agent. In addition, we observed that vitamin E had a protective effect against this anesthesia complication.

Key Words: volatile enflurane; Anathesia; Liver hepatotoxicity; kidney nephrotoxicity

INTRODUCTION

Halogenated inhalational anesthetic agents undergo biotransformation in varying rates and as a result, metabolic products are formed and some of these products are excreted via kidneys[1-4]. Biotransformated agents cause hepatic injury by immunological reactions of reactive metabolites. The metabolites produce serious microsomal lesions by raising lipid peroxidation and malonyldialdehyde [2-5]. Enflurane (2-chloro-1, 1, 2,-trifluoroethyl-difluoromethyl ether) is a halogenated ether that is metabolized about 2%[1,4] and still used for inhalational anesthesia[1]. Inorganic fluoride formed due to metabolism of halogenated anesthetics, especially in long inhalation anesthesia in humans and animals, is the main cause for the changes in the kidneys. Inhalation anesthetics are more metabolized in rats when compared to humans[1,6]. However, experimental studies about the effects of enflurane on histology of liver and kidneys in rats are limited[3].

Vitamin E as a family of eight antioxidants: four tocopherols (alpha-, beta-, gamma-, and delta-) and four tocotrienols (alpha-, beta-,gamma-, and delta-). Alpha-tocopherol is the only form of vitamin E that is actively maintained in the human body. Therefore, it is the form of vitamin E found in the largest quantities in blood and tissues. Supplements of less than 2,000 mg of alpha-tocopherol daily has few side effects. The most worrisome possibility includes impaired blood clotting that lead to increased suseptability of hemorrhage in some individuals. So, some physicians recommend discontinuing high-dose vitamin E supplementation one month before elective surgery to decrease the risk of hemorrhage[7].

AIM OF THE STUDY

The aim of the present study was to assess the probable hepatic and renal histopathological changes in rats following a 2 h of administration of enflurane which has been still used for anesthesia and possible protective role of vitamin E administration.

MATERIALS AND METHODS

A total of 30 Wistar rats were used. The rats were 4 months old and weighed approximately 350-400 g. The rats were kept at temperature 21±2°C with humidity 50±9% and were fed with a standard diet for 10 days. Animals subjected to daily lightening regime of 12 h light followed by 12 h dark. Rats received standard rat chow and water *ad libitum*. The rats were classified randomly into 3 equal groups as control group, influrane exposed group and vitamin E administered group. The control group was administered with 50-50% oxygen-dry air for 2 h in 50x50x40 cm glass mechanism using an anesthesia device (Drager Cato Edition model, Germany). The rats in experimental group were anesthetized with 2% inhalational enflurane and 50-50% dry air-oxygen for 2 h with same mechanism. The rats in vitamin E administered group were anesthetized same like influrane exposed group as well as intraperitoneally administered with vitamin E (dl-alpha-tocopheryl acetate, 100 mg/kg body weight). Following the anesthesia, rats were killed by decapitated by cervical dislocation in conformity with the animal welfare law and tissue samples of liver and kidneys were fixed in 10% buffered formalin solution. Following the routine process, cross sections of paraffin blocks were stained with Heamtoxylin and Eosin (H and E) and PAS and examined under light microscope[8]. Histopathological changes in the liver were assessed with the modified scoring criteria of[11]. Briefly, 0-no histopathological changes 1-minimal degenerative changes, 2-moderate centrilobular degnerative and necrotic changes, 3-serious centrilobular cellular changes 4-centrilobular and moderate midzonal cellular changes, 5-severe centrilobular and midzonal cellular changes, 6-widespread and severe degenerative and necrotic changes in liver. Changes in kidneys were assessed with the modified scoring criteria (0-3) of Shigematsu (1997). Accordingly, 0-No histopathological change, 1-minimal; glomerular mesangial proliferation and congestion, 2-moderate; thicking in basal membrane, intratubular mass and interstitial cell infiltration 3-severe; thicking in basal membrane and widespread tubular nephrosis

RESULTS

The kidneys were more affected compared to liver in the rats exposed to enflurane anesthesia. Kidney in control group showed that each renal corpuscle is formed of a glomerulus surrounded by a narrow Bowman's space. Renal convoluted tubules were lined with cuboidal epithelium (**Fig. 1).** Transverse section in renal tubules at corticomedullary area of same group showed round and oval structure lined with cuboidal epithelium (**Fig.2).** Histopathological changes in kidneys of enflurane exposed group were glomerular congestion and Because of congestion, glomeruli filled the Bowman's capsule, widespread proximal and distal tubular necrosis with desquamated necrotic epithelial . cells in the lumen (**Fig.3)** Alterations of tubules at corticomedullary area of same group that contain remnants of cellular debris were observed. Extravascular haemorrhages were also seen (**Fig.4**). Histopathological changes in vitamin E supplemented group were glomerulus with minimal congestion. Structure of cortical renal tubules was preserved with few tubules that contain intra luminal cell debris **(Fig.5).** Corticomedullary tubules of same group preserved its shape and lined with cuboidal epithelium. Some tubules contained intraluminal hyaline casts **(Fig.6).** Liver in control group showed thin wall central vein surrounded by liver cells with round nuclei (arrow). Liver sinusoids with narrow lumens were observed (**Figs.7,8)** Histopathological changes in the liver of enflurane exposed group showed congested liver sinusoids, dilated central vein with dilated blood sinusoids (**Figs.9,**

10). Large vacuoles in the liver cells and shedding in central vein endothelium were observed (**Figs.11, 12).**

Histopathological changes in the liver of vitamin E supplemented group showed central vein that surrounded with preserved liver cells with rounded nuclei. Congested central vein was observed (**Fig. 13, 14**).

Liver of control group showed accumulation of glycogen content (Fig.15). While enflurane exposed group showed minimalglycogen content(Fig.16).

Kidney of enflurane exposed group showed glomerulus with less condensed capilaries . Thin

Kidney of control group showed glomerulus with condensed capillaries. Thick intact basement membrane (arrow) with strongly stained brush border (B) was observed in PAS staining Fig.17)

Kidney of enflurane exposed g showed glomerulus with less condensed capilaries . Thin interrupted basement membrane with weakly stained brush border was observed in (PAS staining) (Fig.18)

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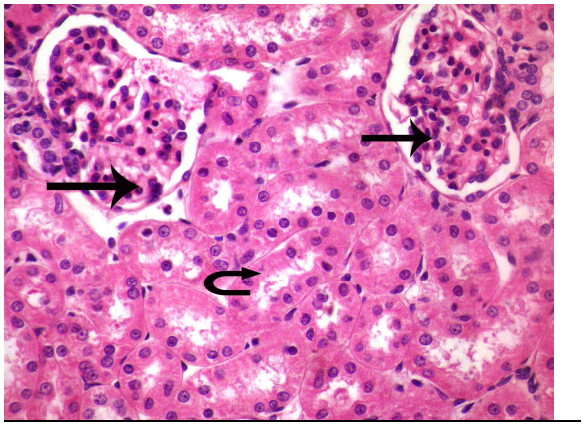


Fig. (1): A photomicrograph of a section in the kidney of a control adult male albino rat showing that each renal corpuscle is formed of a glomerulus(arrows) surrounded by a narrow Bowman's space. Renal convoluted tubules are lined with cuboidal epithelium (curved arrow).

(H&E: X400).

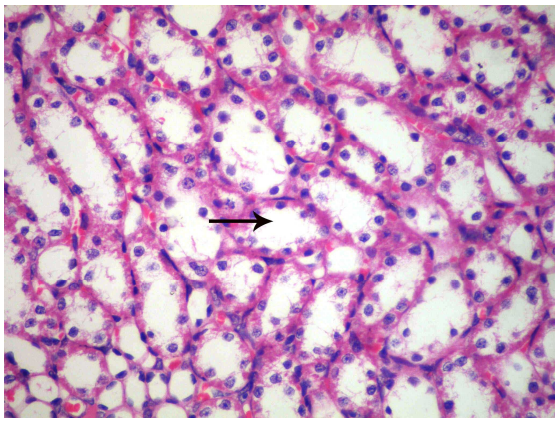


Fig. (2): A photomicrograph of a transverse section in the kidney of a control adult male albino rat showing renal tubules at corticomedullary area that lined with cuboidal epithelium (arrow).

(H&E: X400)

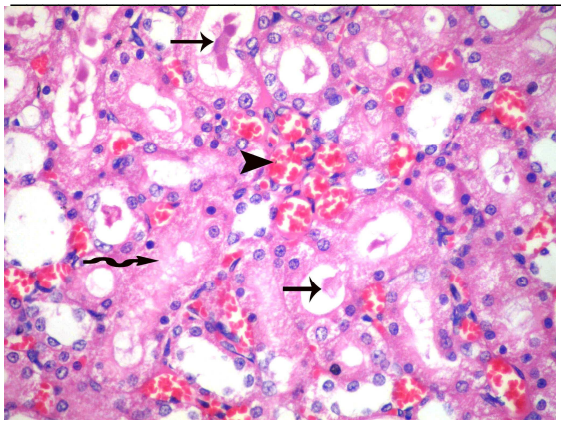


Fig. (4): Photomicrographs of a section in the kidney of adult male albino rat of enflurane exposed group showing alterations in corticomedullary tubules (twisted arrow) that contain cellular debris (arrows). Note extravascular hemorrhages (arrow head) are observed
(H&E: X400).

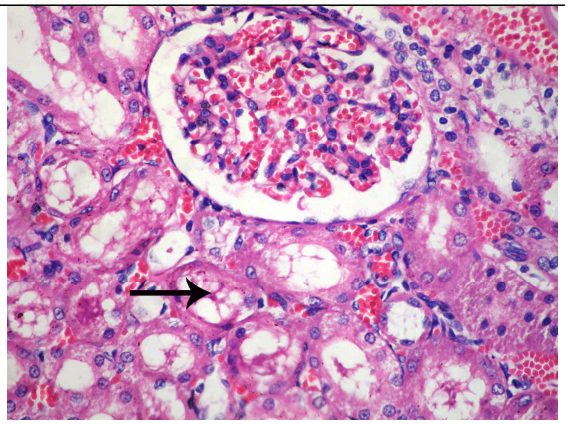


Fig. (3): Photomicrographs of a section in the kidney of adult male albino rat of enflurane exposed group showing alterations in most of the
renal corpuscles and tubules. The corpuscles appear with congested glomeruli that fill the Bowman's capsule (arrows). Proximal (p) and distal (D) tubules contain cellular debris (arrows).
(H&E: X400).

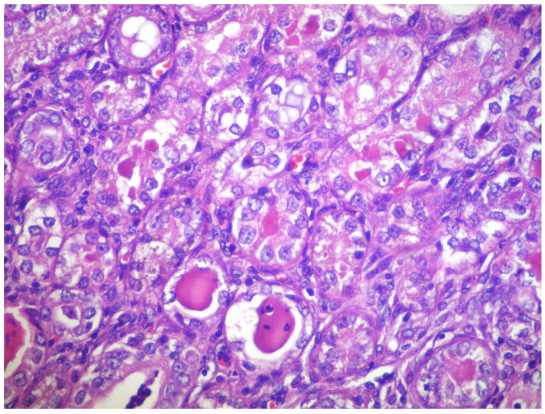


Fig. (6): A Photomicrograph of a section in the kidney of adult male albino rat of vitamin E supplemented group showing corticomedullary tubules that preserves its shape and line with cuboidal epithelium (arrow). Some tubules contain intraluminal hyaline casts (arrow head).
(H&E: X400)

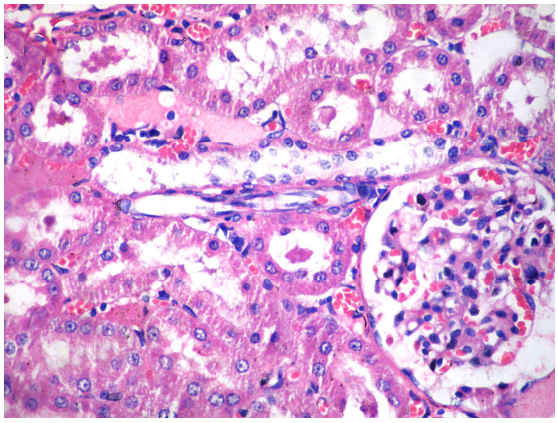


Fig. (5): A Photomicrograph of a section in the kidney of adult male albino rat of vitamin E supplemented group showing a glomerulus with minimal congestion. Structure of cortical renal tubules is preserved (arrow) with few tubules that contain intra luminal cell debris (arrow head
(H&E: X400)

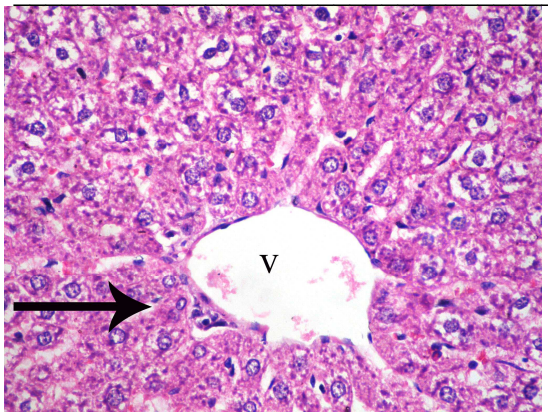


Fig. (8): A photomicrograph of a section in the liver of a control adult male albino rat showing thin wall central vein (V) surrounded by liver cells with round nuclei (arrow). Note, liver sinusoids with narrow lumens (curved arrow) are observed.
(H&E:X400)

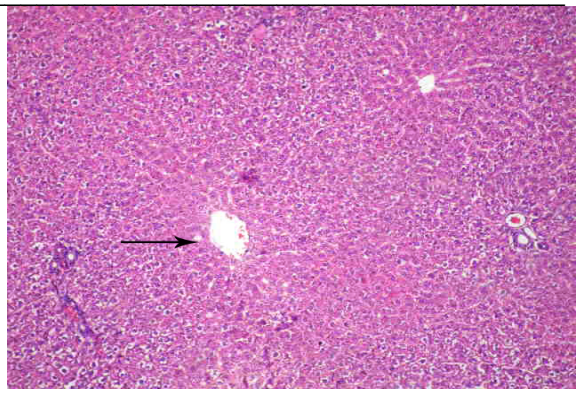


Fig. (7): A photomicrograph of a section in the liver of a control adult male albino rat showing thin wall central vein (V) surrounded by liver cells with round nuclei (arrow).
(H&E: 100)

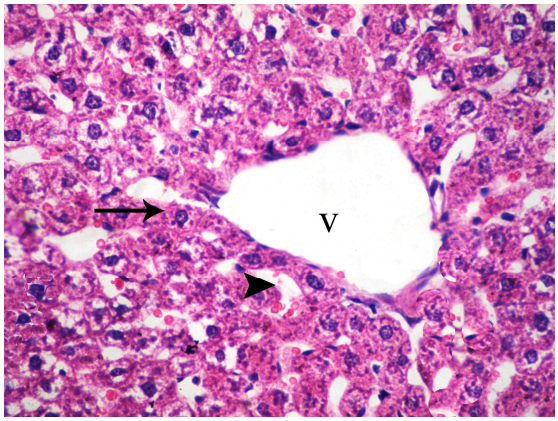


Fig. (10): A photomicrograph of a section in the liver of adult male albino rat of enflurane exposed group showing dilated central vein (V) with dilated blood sinusoids (arrow).
(H&E: X400).

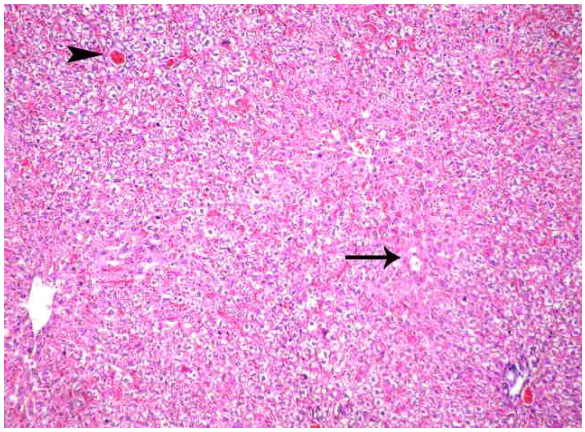


Fig. (9): A photomicrograph of a section in the liver of adult male albino rat of enflurane exposed group showing congested liver sinusoids (arrow).
(H&E: X100).

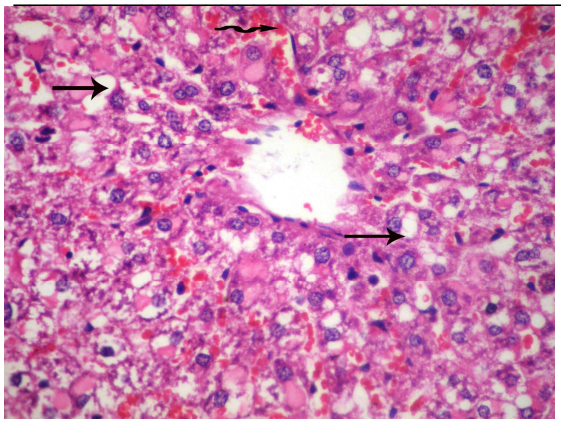


Fig. (12): A photomicrograph of a section in the liver of adult male albino rat of enflurane exposed group showing shedding in central vein endothelium (arrow head). Large vacuoles inside liver cells are observed.

(H&E:400)

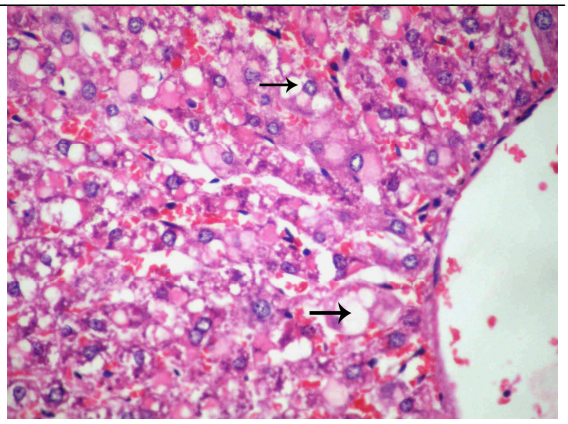


Fig. (11): A photomicrograph of a section in the liver of adult male albino rat of enflurane exposed group showing large vacuoles in the liver cells (arrow).

(H&E:400)

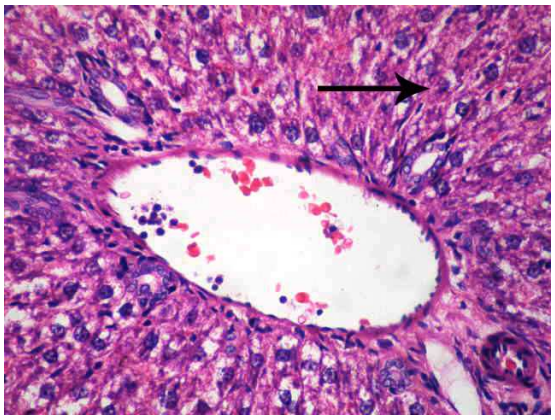


Fig. (14): A photomicrograph of a section in the liver of adult male albino rat of vitamin E supplemented showing well preserved liver cells with rounded nuclei (arrow) .Congested central vein is observed (v).

(H&E: X400)

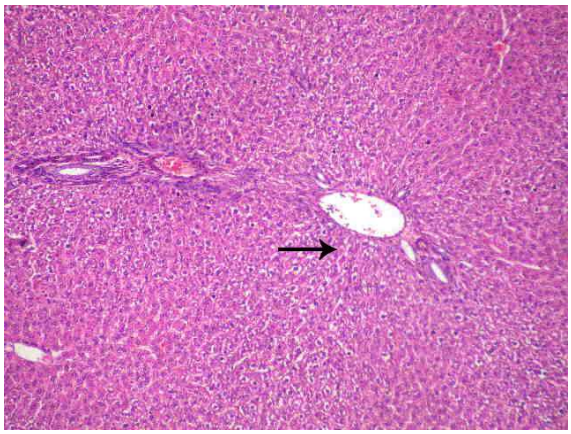


Fig. (13): A photomicrograph of a section in the liver of adult male albino rat of vitamin E supplemented showing central vein (V) that surrounded with preserved liver cells (arrow).

(H&E: X100).

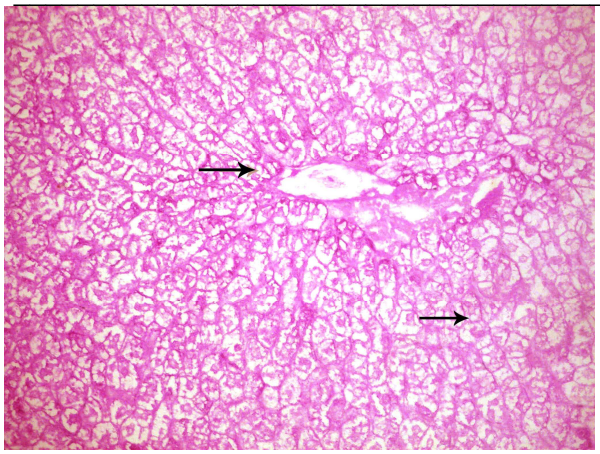
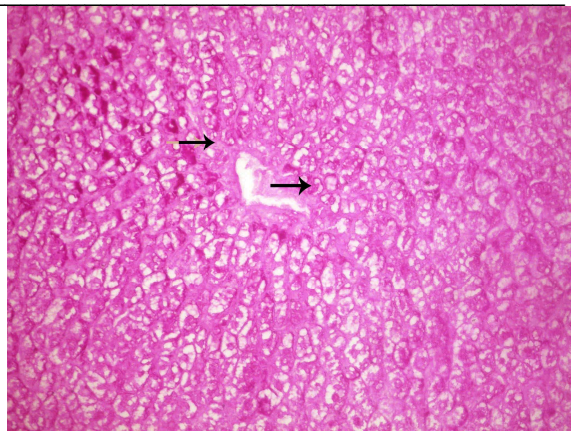


Fig. (16): A photomicrograph of a section in the liver of adult male albino rat of enflurane exposed group showing minimal glycogen granules (arrow). **(PAS X400)**.



.**Fig.(15):** A photomicrograph of a section in the liver of adult male albino rat of control group showing accumulation of glycogen granules (arrow). **(PAS X400)**.

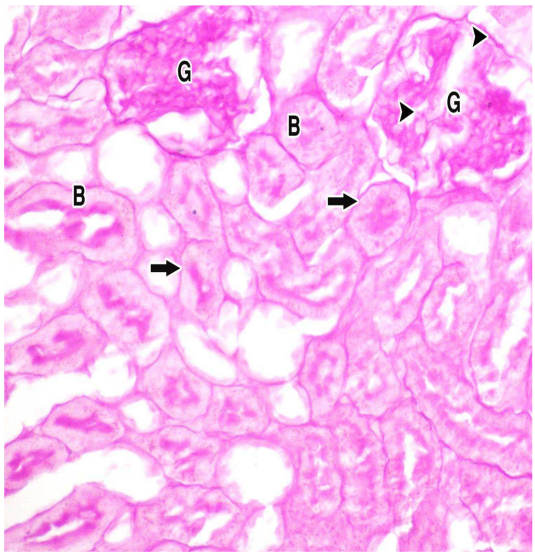


Fig. (17): A photomicrograph of a section in the kidney of a control adult male albino rat showing glomerulus (G) with condensed capillaries (arrow head). Thick intact basement membrane (arrow) with strongly stained brush border (B) is observed.
(PAS X400).

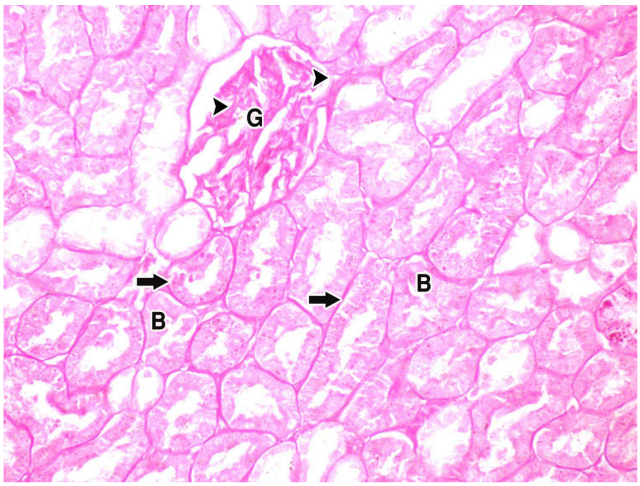


Fig. (18): Photomicrographs of a section in the kidney of adult male albino rat of enflurane exposed group showing glomerulus (G) with less condensed capilaries (arrow head). Thin interrupted basement membrane (arrow) with weakly stained brush border (B) is observed**.**
(PAS X400).

DISSCUSION

Since the initiation of administration of halogenated inhalational anesthetics, their possible negative effects on parenchyma organs have been discussed. Histopathological changes in kidneys of enflurane exposed group were glomerular congestion and widespread proximal and distal tubular necrosis with desquamated necrotic epithelial cells in the lumen. This is in agreement with of [9] who assessed changes in kidney by the modified scoring criteria (0-3), 0-No histopathological change, 1-minimal; glomerular mesangial proliferation and congestion, 2-moderate; thicking in basal membrane, intratubular mass and interstitial cell infiltration 3-severe; thicking in basal membrane and widespread tubular nephrosis.

Vitamin E supplemented group were glomerulus with minimal congestion. Structure of cortical renal tubules was preserved with few tubules that contain intra luminal cell debris**.** Corticomedullary tubules of same group preserved its shape and lined with cuboidal epithelium. Some tubules contained intraluminal hyaline casts**.** This is in accordance with[10] who estimate level of live vitamin E level and recorded that vitamin E level in vitamin E supplemented group is low in anesthetic group and high in vitamin E supplemented group

Histopathological changes in the liver of enflurane exposed group showed congested liver sinusoids, dilated central vein with dilated blood sinusoids. Large vacuoles in the liver cells and shedding in central vein endothelium were observed. This is in agreement with [11] who has modified scoring criteria of, 0- no histopathological changes 1-minimal degenerative changes, 2-moderate centrilobular degnerative and necrotic changes, 3-serious centrilobular cellular changes 4-centrilobular and moderate midzonal cellular changes, 5-severe centrilobular and midzonal cellular changes, 6-widespread and severe degenerative and necrotic changes**.**

Histopathological changes in the liver of vitamin E supplemented group showed central vein that surrounded with preserved liver cells with rounded nuclei. Congested central vein was observed. This is in accordance with[10].

Since, the initiation of administration of halogenated inhalational anesthetics, their possible negative effects on parenchymatus organs have been discussed. While, halothane comes to the forefront in discussions, the negative effects of its alternatives have widely been discussed [12-14]**.** The new alternatives bring forward the effects of them on personnel and environment[13]. A study by [15] on dogs stated observed that as a result of the change in the oxygen balance of hepatic blood flow and hepatic drug metabolism, there were negative effects**.** [16] stated that enflurane, isoflurane and sevoflurane have less effect on protein synthesis than halothane in similar concentrations in isolated rat livers. It has been reported that the degree of metabolism of a volatile anaesthetic depends on, among other factors, the amount of the anaesthetic absorbed by the organism and therefore, the metabolism correlates with the solubility in blood and other tissues[4] **.** It has been assessed that there is a relationship between metabolism rates of halogen containing inhalation agents and hepatic and renal injury. When, the enflurane is used as alternative of halothane, it is metabolized with a rate of 2% [14,16]**.** The fact that inhalation agents are more metabolized in rats than humans[1,6] is the reason for usage of rats in the present study. It was reported that the liver and the kidneys are the major organs affected by inhalational anaesthetic toxicity[4]**.** Observed histopathological changes in liver and kidneys are formed with reactive metabolites due to enflurane biotransformation[3,4]**.** Although, some researches[17,18] reported deaths in accordance with enflurane exposure period and personal sensitivity, it has been claimed that as seen in this study, severe hepatic

injury duo to enflurane does not generally occur[3]. In the present study, of the 10 rats administered with enflurane for 2 h, in 2 cases no findings was observed in liver, 6 cases had minimal histopathological changes (score 1) and 2 cases had moderate histopathological changes (score 2).

Enflurane has nephrotoxic effects as well as hepatotoxic effects and it has been reported that the reason of renal injury duo to enflurane is the inorganic fluoride in blood circulation[6,19,20]. In this study, degenerative and necrotic changes in kidneys of experimental groups were seen. These changes were minimal in six cases (score 1) and moderate in four cases (score 2). When, the number of cases and histopathological changes are taken into consideration, it is obvious that kidneys are more affected than liver.

PAS staining, liver of anesthetic group showed less staining liver cells. These in agreement with[10,21] that relate this changes with minimal collagen content due to necrotic cells. PAS staining, kidney of anesthetic group showed less staining glomeruli and tubules. These changes in agreement with[22] that relate these changes to destructed basement membrane of renal tubules and glomeruli.

Consequently, the present study assessed the histopathological effects of 2% enflurane in terms of hepatic and renal toxicity. Enflurane caused significant changes in liver and kidneys. It was suggested that renal function should be taken into consideration while using this anesthetic agent.

[10,21] reported that liver vitamin E level was slightly lower in the anesthesia group than in control group. However was significantly increased in vitamin E supplemented group. In general, plasma levels of alanine aminotransferase, creatin kinase, total bilirubin, urea, red blood cell counts, packet cell volume, and hemoglobulin values were significantly ($p < 0.05$ and $p < 0.001$) increased during the anesthesia and returned to near control values after the vitamin E. Plasma levels of some enzymes and metabolites were significantly increased in the enflurane anesthesia of rats, whereas the liver vitamin E levels were slightly decreased. Therefore, we observed that vitamin E have a protective effect against anesthesia complication.

Enflurane metabolites are reasonable to widespread toxicity due to generation of reactive oxygen species (ROS). So, vitamin E as antioxidants overcome enflurane induced oxidative stress[21].

CONCLUSION

Volatile anesthetics may exert toxic effects, especially at high doses and in chronic exposure. Shortly speaking, patients receiving single exposure do not suffer because of side effects of anesthesiology. Contrary, a prolonged occupational exposure can be followed by serious health effects described above. In

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تاثير الانفلوران على الهيكل النسيجي للكبد والكلى في ذكور الجرزان البيضاء البالغة ودور مكملات فيتامين هـ

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قسم الهستولوجيا- كلية الطب -جامعة الزقازيق
قسم التخدير - كلية الطب -جامعة الزقازيق

مقدمة:
يعتبر الانفلوران مخدر لة كثير من الاضرار على انسجة الكبد و الكلى ولهذا أجريت هذه الدراسة لإلقاء مزيد من الضوء علي التغيرات الهستولوجية التي يحدثها هذا المخدر في كبد و كلى ذكور الجرذان البيضاء ودراسة دور اعطاء فيتامين ه على سلامة هذة الانسجة.

الهدف من هذه الدراسة : هو تقييم التغيرات التشريحية المرضية المحتملة الكبد والكلى في الفئران بعد التعرض للانفلوران الذي يزال يستخدم للتخدير والدور المحتمل من اعطاء فيتامين ه

المواد و الطرق: واستخدمت "مواد وأساليب" ٣٠من الفئران كان عمره ٤ أشهر ووزنه حوالي ٣٥٠-٤٠٠ جرام. تم الاحتفاظ بها في درجة الحرارة ٢١±٢ درجة مئوية مع رطوبة ٥٠±٩% على الفئران وغذيت مع اتباع نظام غذائي قياسي لمدة ١٠ أيام. تعرض الحيوانات لنظام البرق اليومية الضوء ح ١٢ تليها ١٢ ح الظلام. تلقت الفئران تشاو الجرذان القياسية وصنفت الفئران عشوائياً إلى ٣ مجموعات متساوية كالمجموعة الضابطة والمجموعة المعرضة للمخدر و المجموعة المعطاة فيتامين (ه). السيطرة على المجموعة تدار بالهواء الجاف الأكسجين % ٥٠-٥٠ ح ٢ في ٥٠ × ٥٠ × ٤٠ سم زجاج إليه استخدام جهاز تخدير .على الفئران في المجموعة المعرضة للمخدر ٢% استنشاق انفلوراني والجاف ٥٠-٥٠% دل-ألفا-)أكسجين الهواء ح ٢ مع نفس الآلية. تم تخديره الفئران في مجموعة فيتامين (ه)التي تديرها نفس مثل المجموعة (توكوفيريل اسيتات، ١٠٠ مغ/كغ من وزن الجسم)

النتائج: التغيرات التشريحية المرضية في كلية المجموعة المعرضة للانفلوران الازدحام الكبيبي وشغل بسبب الازدحام، كبسولة بومان الشعبية، نخر أنبوبي الدانية والبعيدة على نطاق واسع. ولوحظت خلايا في التجويف التعديلات للأنابيب في منطقة كورتيكوميدولاري لنفس المجموعة التي تحتوي على مخلفات الحطام الخلوية. وكانت حالات النزيف وتأثرت الكلي أكثر مقارنة بالكبد .في المجموعة المعطاة فيتامين (ه) كانت الكبيبة مع الحد الأدنى من الازدحام. تم الاحتفاظ ببنية من القشرية الكلوية مع قليل من الأنابيب التي تحتوي على خلية لومينال داخل الحطام تحتوي على الحطام الأنابيب كورتيكوميدولاري لنفس المجموعة الاحتفاظ بشكله ومبطنة بظهارة كوبويدال. ويتضمن داخل الخلية لومينال وأظهرت الكبد في المجموعة عنصر التحكم الوريد وسط الجدار رقيقة محاطة بخلايا الكبد مع بعض الأنابيب يلقي هيلين نويات جولة وقد لوحظت الكبدية الكبد مع لومن ضيقة التغيرات التشريحية المرضية في كبد المجموعة انفلوراني مكشوف كبيرة في خلايا الكبد وذرف ولوحظت الكبدية الكبد المزدحمة، وأظهرت المتوسعة وسط الوريد مع الدم المتوسعة الكبدية التغيرات التشريحية المرضية في الكبد من فيتامين (ه) تستكمل المجموعة أظهرت وسط الوريد في بطانة الوريد المركزي .(التي حاصرت مع الحفاظ على خلايا الكبد مع نويات مستدير الزوايا. ولوحظ ازدحام الوريد المركزي

الخلاصة:
المواد التى تستخدم فى التخدير قد تمارس تأثيرات سامة، خاصة في الجرعات العالية وفي التعرض المزمن يعاني المرضى الذين يتلقون التعرض مرة واحدة لا بسبب الآثار الجانبية للتخدير. العكس من ذلك، يمكن اتباعها تعرض المهني لفترة طويلة بآثار صحية خطيرة الموصوفة أعلاه