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Pathological and clinic-pathological studies on the effects of potassium bromate in selected organs of albino rat

Elmahdy M.M., Bakeer A.M.*, Gad M.G.**, And Alwazzan A.A.****

*Pathology Dept., Facult, Vet, Med., Cairo University.
**Dept. of cell and tissue, Facult, Vet, Med., Cairo University.
***PhD student from Saudi Arabia

Abstract

The present study was conducted to investigate the toxic effects of various levels of potassium bromate in male and female rats. The criteria for assessment include its effects on the pathological, and haematological alterations.

A total number of 105 albino rats of both sexes, weighing 120 g were used in this experiment. The animal used were 45 male, 45 female and 15 rats of both sexes used as control. Both male and female rats were divided into three groups. The animals were left for a week, as an adaptation period. KBrO3 dissolved in water at concentrations of 200, 400 and 600 ppm respectively and administered to male and female group rats daily till the end of the experiment. After 6, 9 and 14 months ten animals from each group (5 male and 5 female) and five from the control were sacrificed by cervical dislocation. Blood samples and tissue specimens were collected for haematological and histological examination. Haematological results revealed significant variations of most of the different estimated parameters except monocytes and eosinophil as compared with the control group.

Histological examination of lung, heart, spleen and brain revealed congestion of their blood vessels, with various degenerative, necrotic and inflammatory alterations were recorded.

Keywords: Potasium bromate, lung, heart, spleen, brain, blood parameters, histopathology
Corresponding author: *Elmahdy M.M. E-mail: Elmahdy_Elmahdy@yahoo.com*

Introduction

Potassium bromate ($KBrO_3$), is a white crystalline solid and a widely used as food additive **(WHO,1996)**, (KBrO3) is a drinking water disinfection by-product and used in food often in bakeries as flour improver yielding higher bread volume (Kurokawa *et al.*, 1990) and used as a dough conditioner for flour **(Diachenko and Warner 2002)**. Long term exposure to KBrO, has been studied in rat **(Kurokawa et al., 1983, 1986, 1986b and 1990,and Ohno 1982)**. Ozone when used as water disinfection results in the formation of hypobromous acid in water with high bromine content. The acid reacts with natural organic material to form brominated organic byproducts and bromate **(Fiessinger,1985 , Glaze, 1986 and Cavanagh 1992)**. Several researches on safety evaluation of potassium bromate were carried out and also found to be a genotoxic and carcinogenic. Potassium bromate ($KBrO_3$), a salt of the bromate ion, is nephro- and neurotoxic in humans and carcinogenic in rodents **(IARC, 1986;Kurokawa et al. 1990)**.

The international Agency for Research on Cancer (IARC) recently evaluated all of the data on KBrO3 and concluded that there is sufficient evidence for the carcinogenicity of KBrO3 in experimental animals **(IARC, 1986).**

The present investigation was conducted to investigate the toxic and carcinogenic effects of various levels of dietary potassium bromate in male and female rats. The criteria for assessment include its effects on hematological and pathological, alterations.

Material and Methods

Chemical:

Potassium bromate (KBrO3) with a purity of greater than 99.5%. It was supplied by a private chemical company at Cairo Egypt.

Animals:

Albino rats of both sexes, weighing 120 g were supplied by faculty of Veterinary medicine, Cairo University. They were kept under standard conditions and had free access to water and standard diet. The animals were left for a week, as an adaptation period.

Experimental Design:

In this experiment; a total of 105 rats were used (45 male, 45 female and 15 rats of both sexes used as control). Both male and female rats were divided into three groups. KBrO3 dissolved in water at concentrations of 200, 400 and 600 ppm respectively was administered to male and female group rats daily till the end of the experiment. The rats were observed throughout the experimental periods to record the signs and deaths occurred till the end of the experiment, After 6, 9 and 14 months ten animals from each group (5 male and 5 female) and five from the control were sacrificed by cervical dislocation.

Histopathological examination:

Tissue samples of spleen, lungs, hearts and brains were removed carefully, washed and fixed in neutral buffered formalin 10%, dehydrated in ascending grade of alcohol, cleared and embedded in paraffin, sectioned at 5 µ thickness and stained by H & E and examined microscopically (***Bancroft et al. 1996***).

Haematological methods:

Blood samples were collected by puncturing retro-orbital plexus with heparinized capillary tube into dry clean tube containing EDTA (ethylene diamine tetra-acetic-acid) as anticoagulant for haematology.

Hemoglobin (Hb) concentration, Red Blood Cell (RBC) counts, Packed Cell Volume (PCV), and White Blood Cell (WBC) counts were determined by standard methods **(Schalm *et al.*, 1975).**

Statistical Analysis:

The significance of differences between means was compared at each time point using Duncan's multiple range test after ANOVA for one-way classified data **(Snedecor and Cochran, 1989).**

Results

Haematological Results:

From table (1) it is clear that there's statistically significant decrease in the RBC , HB and PCV parameters between the Control, 200 ppm, 400 ppm, 600 ppm after 6, 9 and 14 months as P-value level less (0.01). From table (2) it is clear that after 6 , 9 and 14 months : There's statistically significant increase in the mean value of WBC between the **Control, 200 ppm, 400 ppm, 600 ppm)** as (F) value equal (9.313), (21.780) and (14.576) respectively with P-value level less (0.01). From table (3) it is clear that There's statistically

significant increase in the lymphocyte % in the treated groups (200 ppm, 400 ppm, 600 ppm) comparing with the Control group after 6, 9 and 14 months, with P-value level less (0.01). From table (4) it is clear that There's statistically significant increase in the neutrophil % in the treated groups (200 ppm, 400 ppm, 600 ppm) comparing with the Control group after 6, 9 and 14 months, with P-value level less (0.01). From the above table (5) it is clear: There's no statistically significant differences between the Control, 200 ppm, 400 ppm, 600 ppm after 6, 9 and 14 months with P-value more than (0.05). From table (6) it is clear that: There's no statistically significant differences between the Control, 200 ppm, 400 ppm, 600 ppm after 6, 9 and 14 months with P-value more than (0.05).

Table (1): The haematological values of rats treated orally with various levels of potassium bromated. Differences between groups of variable RBC $X10^9$

Treatment Variables	Control (1) Mean ±Std.	200ppm Mean ±Std.	400ppm Mean ±Std.	600ppm Mean ±Std.	F-test	p-value
1. RBC 6	5.92 ± 0.28	4.99 ±0.21	4.63 ±0.56	4.79 ±0.39	11.056	0.001**
2. HB 6	13.04±0.34	12.11 ±0.59	11.09 ±0.38	10.16±0.48	36.472	0.001**
3. PCV 6	35.65 ±1.24	31.88 ± 0.45	31.64 ± 0.65	30.72 ± 1.35	23.574	0.001**
1. RBC 9	5.73 ± 0.65	4.83± 0.22	4.25 ±0.59	4.59 ± 0.50	7.328	0.003**
2. HB 9	13.12± 0.49	12.48 ± 0.54	11.03± 0.77	10.26± 0.58	23.065	0.001**
3. PCV 9	34.67 ± 094	31.99 ± 0.77	31.19 ± 0.68	30.44 ± 0.94	23.801	0.001**
1. RBC 14	5.66 ±0.23	4.88 ± 0.21	4.15 ± 0.35	4.35 ± 0.44	21.445	0.001**
2. HB 14	13.08± 0.40	12.28 ± 0.56	10.96± 0.64	10.61± 0.52	25.799	0.001**
3. PCV 14	34.91± 0.50	31.99 ±0.77	31.95± 0.55	30.62± 0.77	36.859	0.001**

**Significant at the (.01) level *Significant at the (.05) level

Table (2): Differences between (WBC) in the control and KBrO3 treated groups.

Treatment Variables	Control (1) Mean ±Std.	200ppm Mean ±Std	400ppm Mean ±Std	600ppm Mean ±Std	F-test	p-value
1. WBC E6	7.06 ±0.60	8.38± 1.24	9.18 ±0.71	10.05± 1.01	9.313	0.001**
2. WBC 9	7.56 ±0.64	8.00 ±1.05	11.41 ±0.96	10.39± 0.84	21.780	0.001**
3. WBC 14	7.91 ±1.32	9.97 ±1.40	12.10 ±1.07	12.66 ±1.25	14.576	0.001**

**Significant at the (.01) level *Significant at the (.05) level

Table (3): Differences between (Lymphocyte %) in the control and treated groups by KBrO3 by using One way ANOVA (F test).

Treatment Variables	Control (1) Mean ±Std.	200ppm Mean ±Std	400ppm Mean ±Std	600ppm Mean ±Std	F-test	p-value
1. Lymphocyte 6	0.44 ±0.03	0.62 ± 0.01	0.66 ±0.04	0.69 ±0.04	44.396	0.001**
2. Lymphocyte 9	0.42± 0.03	0.69 ±0.03	0.71 ±0.02	0.72± 0.03	92.190	0.001**
3. Lymphocyte 14	0.47 ±0.05	0.65 ±0.04	0.736± 0.04	0.738± 0.04	38.757	0.001**

**Significant at the (.01) level *Significant at the (.05) level

Table(4): Differences between (NEUTEROPHIL%) in the control and treated groups by KBrO3 by using One way ANOVA (F test).

Treatment / Variables	Control (1) Mean ±Std.	200ppm Mean ±Std.	400ppm Mean ±Std.	600ppm Mean ±Std.	F-test	p-value
1.NEUTEROPHIL% 6	0.218 .±0.03	0.214 .±0.01	0.238 .±003	0.288 .±0.03	5.866	0.007**
2.NEUTEROPHIL% 9	0.206 ±0.02	0.208 0.±008	0.27 0±.02	0.24 0.±02	9.514	0.001**
3. NEUTEROPHIL%14	0.22 .±0.03	0.21 .±0.02	0.27.6± 0.02	0.274 .±0.01	7.390	0.003**

**Significant at the (.01) level *Significant at the (.05) level

Table (5)Differences between (Monocyte) in the control and treated groups by KBrO3 by using One way ANOVA (F test)

Treatment / Variables	Control (1) Mean ±Std.	200ppm Mean ±Std.	400ppm Mean ±Std.	600ppm Mean ±Std.	F-test	p-value
1. Monocyte 6	0.35 ±0.08	0.30 ±0.10	33 ±0.12	0.36 ±0.07	0.363	0.78
2. Monocyte 9	0.37 ±0.13	0.35 ±0.08	0.46 ±0.13	0.35 ±0.06	1.142	0.36
3. Monocyte 14	0.38± 0.25	0.57± 0.36	0.41± 0.09	0.34 ±0.06	0.980	0.42

**Significant at the (.01) level *Significant at the (.05) level

Table (6) Differences between (Eosinophil) in the control and treated groups by KBrO3by using One way ANOVA (F test)

Treatment / Variables	Control (1) Mean ±Std.	200ppm Mean ±Std.	400ppm Mean ±Std.	600ppm Mean ±Std.	F-test	p-value
1. Monocyte 6	0.31 ±0.03	0.29 ±0.04	0.28 ±0.06	0.31 ±0.03	0.554	0.65
2. Monocyte 9	0.32± 0.03	0.29 ±0.05	0.30 ±0.06	0.29 ±0.04	0.421	0.74
3. Monocyte 14	0.28± 0.06	0.32 ±0.04	0.27± 0.05	0.31 ±0.03	1.048	0.39

**Significant at the (.01) level *Significant at the (.05) level

Clinical signs:

Clinical signs of some rats due to the effects of pot. bromate included dullness, ataxia and lose their appetite, sometimes circling with paddling movements and hyper-excitability were also recorded in some animals.

Pathologic results:

Macroscopic results:

The examined organs appeared to be hyperemic, the spleen of most of the potassium bromate treated animals were moderately to severely enlarged and firm (splenomegaly), while in some cases the spleen was pale and slightly shrunken. The lungs of most cases were congested with focal swollen and depressed areas. The brain of some cases showed congestion of the meningeal blood vessels.

Histopathological findings:

Spleen: The histopathological examinations of the spleen of Pot, bromate treated rats (6 months) showed marked lymphoid depletion, congestion and presence of brown hemosiderin pigment either free or inside the macrophages in the splenic red pulp (Fig.1A), it was occasionally associated with severe hemorrhages. The splenic blood vessels were severely dilated and congested. Necrosis was observed in some follicles which typically characterized by apoptosis and necrosis of lymphocytes. Edema and hemorrhage in the red pulp were also observed in some cases.

After 9 and 12 months the lesions of the spleen appeared to be more severe as we found that congestion and hemorrhage in the red pulp

were more pronounced (Fig.1B), and hemosiderin pigments either free or engulfed by macrophages were more pronounced. The splenic follicles showed areas of severe necrosis in the lymphoid cells (Fig.1C). Increase in the number of tingible body macrophages which in the germinal centers of the lymphoid follicles, characterized by the appearance of clear spaces of large cells filled with cellular debris and nuclear remnants of apoptotic and necrotic lymphoid cells (Fig.1D).

Lung: The microscopic pictures of male and female lungs of rats treated with different doses of potassium bromate revealed several pathological changes and its severity varies according to the given doses. Most of the pulmonary blood vessels were congested and surrounded by large number of mononuclear inflammatory cells mainly lymphocytes and macrophages. Some of the congested blood vessels showed thickening of its wall and surrounded by edema and few inflammatory cells. Thickening of the alveolar walls by dilated perialveolar blood capillaries, edema, proliferating pneumocytes and mononuclear inflammatory cells mainly lymphocytes. Marked peribronchiolar and perivascular edema and hemorrhage with congested and thickened blood vessel wall. In some cases there were focal areas of mononuclear inflammatory cells aggregation containing golden yellow hemosiderin pigments engulfed by macrophages. Perivascular and interstitial edema and hemorrhage with mononuclear inflammatory cells infiltration was seen in some areas.

After 9 and 14 months post treatment by potassium bromate there were perialveolar and interstitial edema with perivascular cuffing by mononuclear cells mainly lymphocytes and the blood vessel wall was thickened (Fig.2A). Vasculitis and thrombus formation, with infiltration of the blood vessel wall by mononuclear cells and polymorphnuclear leukocytes were seen (Fig.2B). Hyperplasia of the peribronchial lymphoid follicles with hyperplasia of bronchial and bronchiolar epithelial cells lining with sloughing of some lining cells (Fig.2C), in most cases the blood vessels showed marked hypertrophy of their muscle wall. The wall of some blood vessels were severely destructed with edema and separation of the muscle wall (Fig.2D).

Heart: The cardiac blood vessels and capillaries were dilated and engorged with blood in most of the examined cases. Perivascular edema and hemorrhage (Fig.3A) with slight mononuclear inflammatory cells aggregation were observed. In few cases, cardiac hemorrhages in the interstitial tissue in between cardiac muscle bundles was seen (Fig.3B). Some sections showed degenerative and necrobiotic changes (Fig.3C) of cardiac muscle fibers, on the other side few cases revealed myocardial atrophy. In two cases after 12 months post treatment the muscle fibers were degenerated, atrophied and the area infiltrated by mononuclear cells (Fig.3D).

Brain: Microscopic examinations of the brain tissue of male and female rats administered by potassium bromate revealed nearly the same pathological pictures in all groups, but the severity varies according to the dose and time of administration. Mild to moderate congestion of the meningeal, cerebral and cerebellar blood vessels, and marked perivascular edema manifested by dilatations of the Virchow Robin space together with glia cells vacuolation were observed. Many neurons in the cerebral cortex and the purkinje cells of cerebellum showed degenerative changes in the form of chromatolysis in some, and some neurons showed chromatolysis with shrunken deeply basophilic stained and pyknotic nuclei were also seen (Fig.4A) and others were shrunken, deeply basophilic stained and their nuclei were pyknotic (Fig.4B). Neuronophagia and satellitosis with multiple large focal and diffuse areas of gliosis

were seen here and there in both cerebrum and cerebellum(Fig.4C). Meningitis with meningeal hemorrhages were observed in some cases characterized by marked edema and hemorrhage together with mononuclear cells aggregation especially in the subarachnoid space (Fig.4D).
Severe subcapsular edema and vacuolation of the brain tissue together with mononuclear cells aggregations and congested blood capillaries were observed in some cases after 9 and 14months post treatment (Fig. 5A).

After 9 and 14 months post treatment there were marked subcapsular mononuclear cells aggregations of the cerebrum in some cases and perivascular mononuclear cells cuffing (Fig.5B). Vacuolation of the white mater and glia cells (edema) and diffuse gliosis of the mid brain were observed. In a dead cases large area of malacia and hemorrhage of the cerebral white mater was observed, severe demyelination (Fig.5C) with hemorrhage especially after 14 months post treatment (Fig.5D).

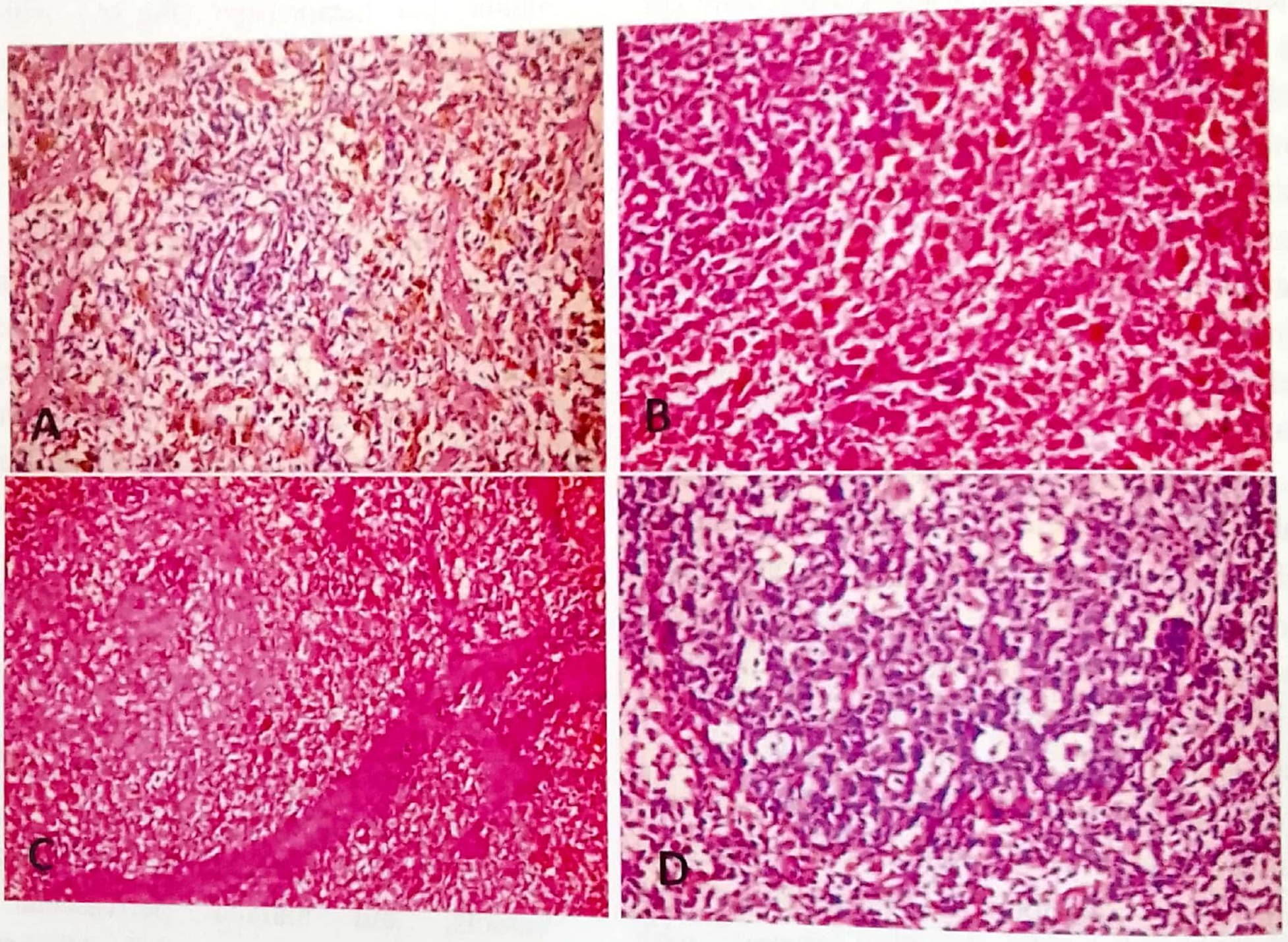

Fig. (1): H&E stained sections of rat's spleen administered with KBrO3:
A) female rat's spleen 6 months showing, marked lymphoid depletion, and presence of large number of macrophages containing brown hemosiderin pigment deposition in the splenic red pulp, Original magnification X 400.
B) male rat spleen G2 for 9 months showing congestion and hemorrhage in the red pulp., Original magnification X400.
C) male rat's spleen G3 for 12 months showing ,necrosis of the lymphoid cells in the splenic follicles. Stain Original magnification X200.
D) male rat's spleen 12 months showing tingible body macrophages in the splenic follicles. Original magnification X400.

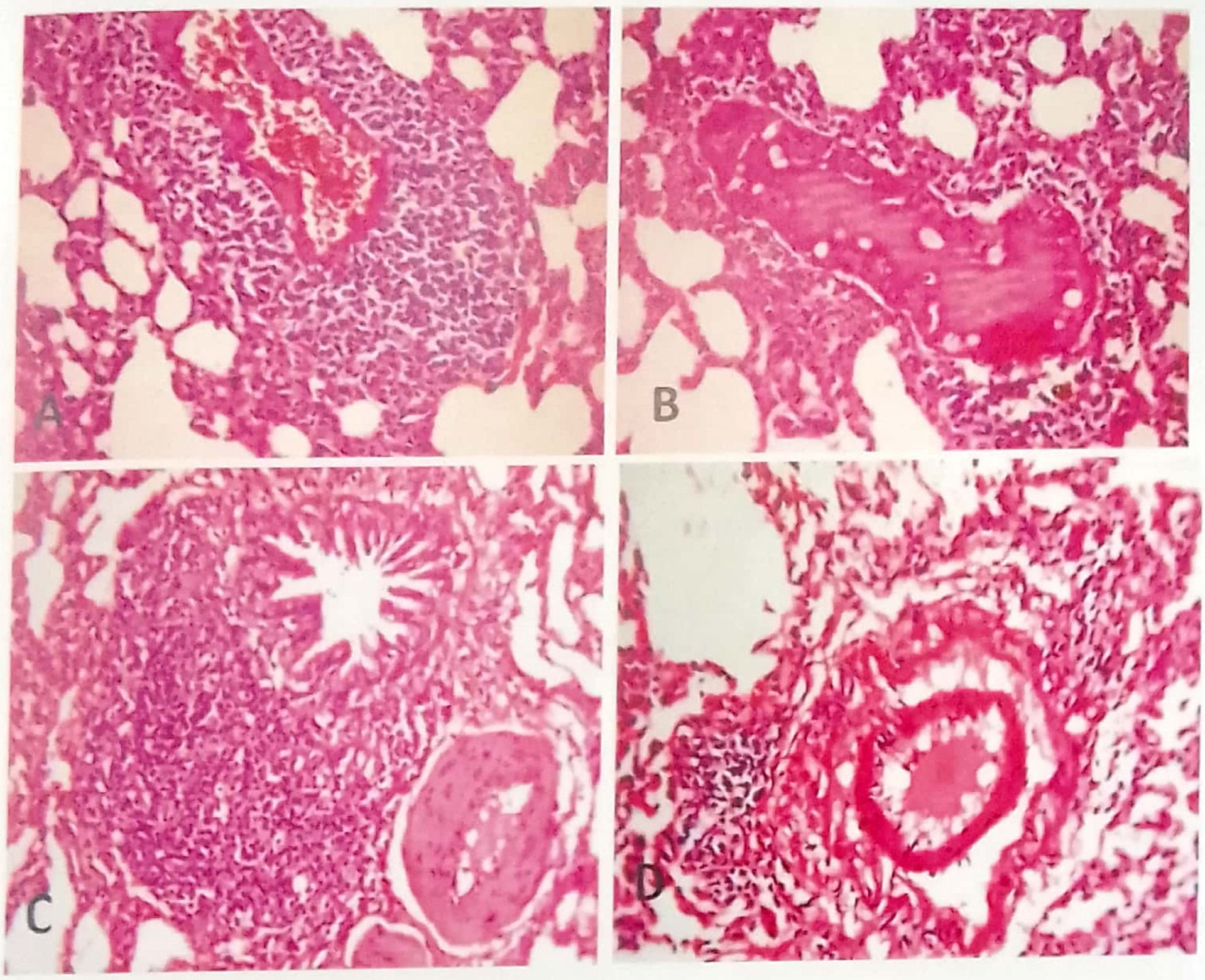

Fig. (2): H&E stained sections of rat's lung administered with KBrO3:

A) male rat's lung G2 for 14 months showing, congested blood vessel with marked perivascular cuffing by mononuclear cells and thickening of the blood vessel wall. Original magnification X 400.

B) male rat's lung G3 for 9 months showing, vasculitis and thrombus formation, with infiltration of the blood vessel wall by mononuclear cells. Original magnification X 400.

C) male rat's lung G3 for 9 months showing hyperplasia of the peribronchial lymphoid follicle with and bronchiolar epithelial wall and thickening of the blood vessel wall. Original magnificationX 200.

D) male rat lung 12 months G2, showing severe edema and destruction of the blood vessel wall with separation of the muscle layer. Original magnification X 400.

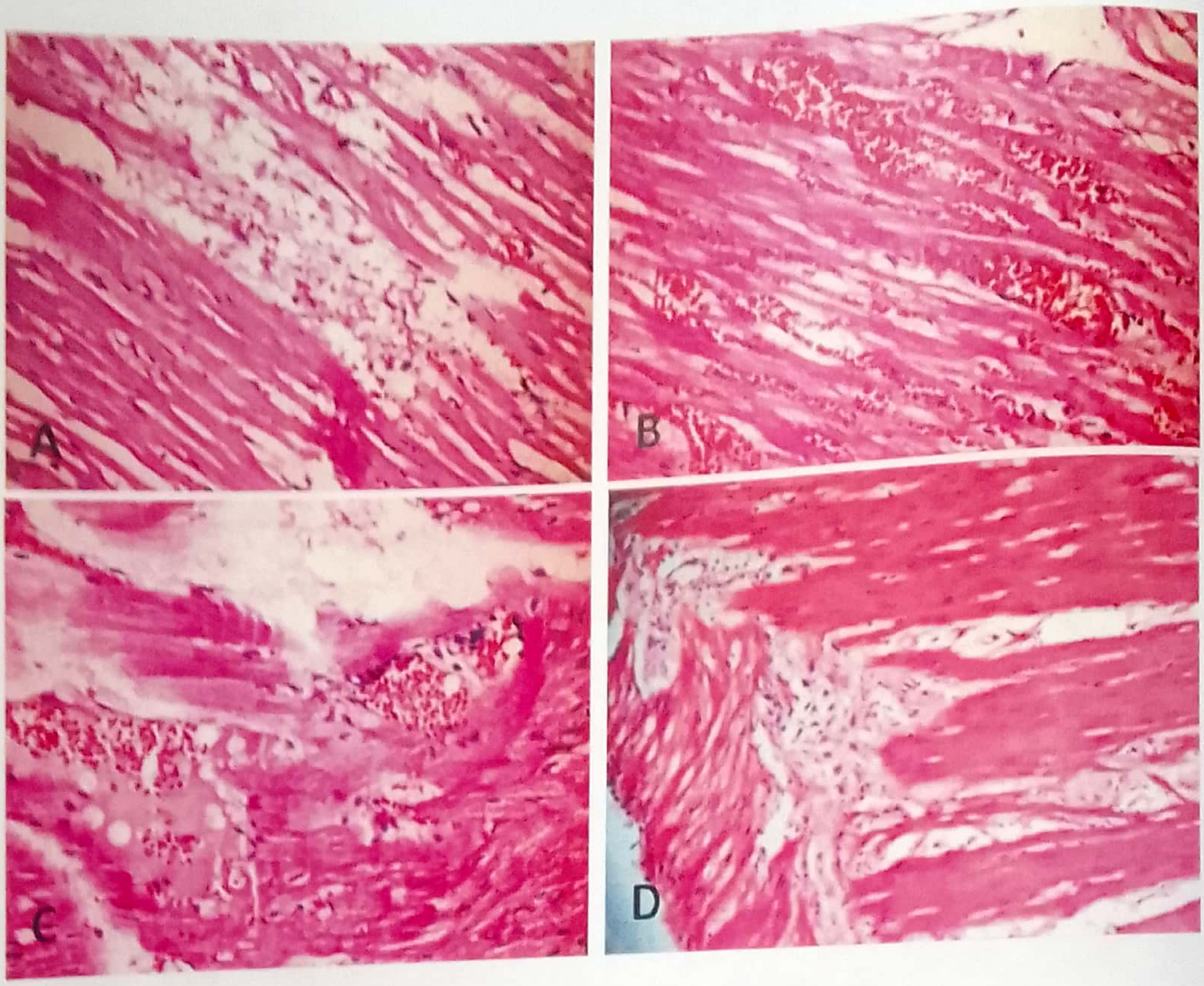

Fig. (3): H&E stained sections of rat's heart administered with KBrO3:

A) male rat's heart G2 for 6 months showing marked edema and hemorrhages between the cardiac muscle bundles.

B) male, G2, 6 months showing severe congestion of the cardiac blood vessels and capillaries.

C) male rat's heart G2 for 6 months showing degeneration and necrosis of the cardiac muscle fibers, congestion, areas of edema, and mononuclear inflammatory cell between the cardiac muscle bundles.

D)male rat's heart G1 for 9 months showing areas of necrotic muscle fibers infiltrated with mononuclear inflammatory cells, and intermuscular edema. Original magnification X 400.

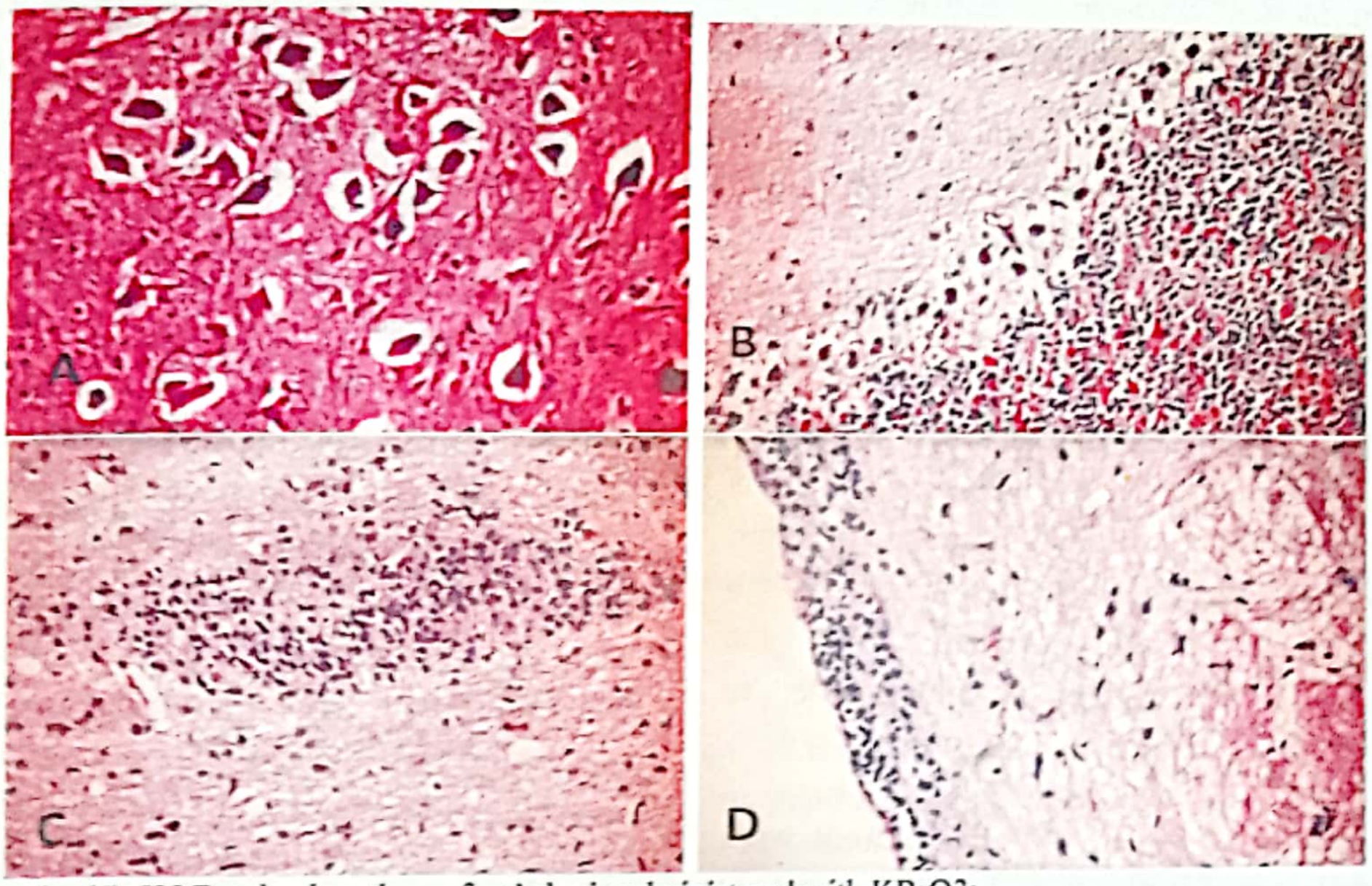

Fig. (4): H&E stained sections of rat's brain administered with KBrO3:

A) male rat brain G2 for 9 months, showing shrunken stained neurons with perineuronal vacuolation (edema)
B) Male rat brain G2 for 6 months, showing, shrunken and deeply basophilic stained purkinjee cells of cerebellum
C) male rat brain G2 for 6 months, showing, large focal gliosis
D) male rat brain G3 (dead case) for 9 months, showing, severe subcapsular mononuclear cells aggregations. Original magnification X 400.

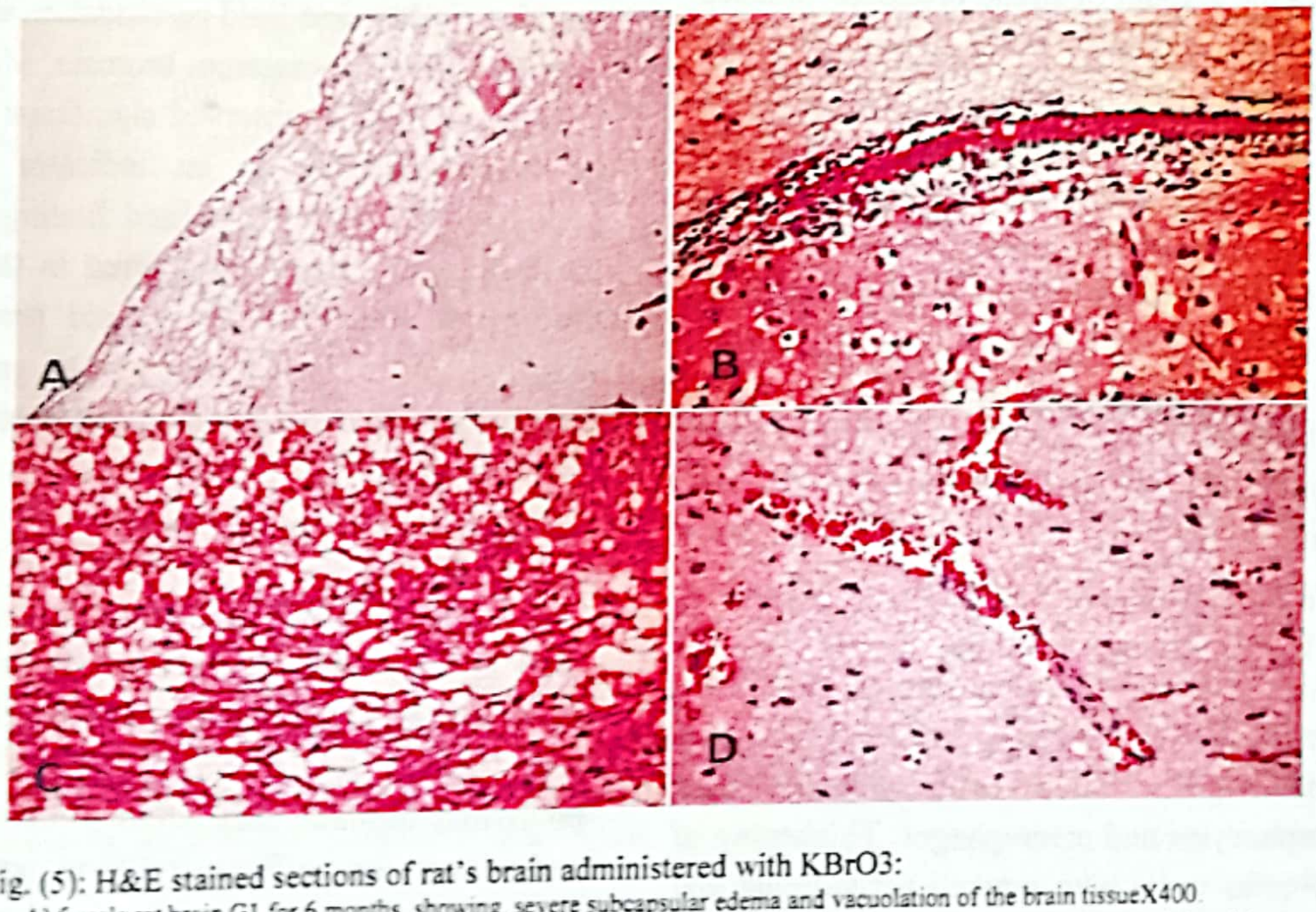

Fig. (5): H&E stained sections of rat's brain administered with KBrO3:

A) female rat brain G1 for 6 months, showing, severe subcapsular edema and vacuolation of the brain tissueX400.
B) female rat brain G2 for 14months, showing, marked perivascular mononuclear cells cuffing, vacuolation of the white mater and glia cells (edema)
C) male rat brain G2 9 months, showing severe demyelination.
D) male rat brain G3 (dead case) for 12 months, showing, congested blood vessels with severe hemorrhagic areas. Original magnification X 400)

Discussion

The long-term oral administration of KBrO3 in drinking water during the present study at doses of 200, 400, 600 ppm for 6, 9, 14 months leading to different haematological findings, degenerative and destructive effects together with generalized congestion and haemorrhages with in the examined organs.

Concerning haematological findings, leucocytes counts were increased in rats administered with potassium bromate in water. The increase in the leucocytes count though statistically significant and agree with the work of **(Hoffbrand et al. 2004)** due to consumption of chemicals like Bromate.

The blood picture of the present work showed increase in the lymphocyte persent in rats administered with potassium bromate, which could be due to the depletion of the intracellular GSH by diethylmaleate in lymphocytes, which decreases the amount of strand breakage induced by potassium bromate **(Parson and Chipman, 2000).** Haematological finding showed different change in the parameters of the blood. In the contrary a study in mice showed no change in blood parameters apart from transient reduction in red cell count **(Ginocchio et al, 1979).**

Spleen showed marked lymphoid depletion, congestion and presence of brown hemosiderin pigment either free or engulfed by the macrophages with severe areas of hemorrhages. The splenic follicles showed areas of severe necrosis in the lymphoid cells with increase in the number of tingible body macrophages. The lung showed congested blood vessels and surrounded by lymphocytes and macrophages. Thickening of the alveolar walls with marked perivascular and peribronchiolar edema and hemorrhage. After 9 and 14 months post treatment by potassium bromate there were vasculitis and thrombus formation, with infiltration of the blood vessel wall by mononuclear cells and polymorphnuclear leukocytes. In most cases and the blood vessels showed marked hypertrophy of their muscle wall. And some showed severe destruction and edema of its muscle wall. The heart of some cases showed degenerative and necrobiotic changes of the myocardium with congested blood vessels and inflammatory infiltrations in some areas. Concerning brain showed moderate congestion of the meningeal, cerebral and cerebellar blood vessels, and marked perivascular edema and glia cells infiltration. Different neuronal damage with neuronophagia and satellitosis and multiple large focal and diffuse areas of gliosis were seen here and there in both cerebrum and cerebellum. The present results showed that the lesions were mostly dose and time related and the severity of the lesions were more seen in groups of rats given high doses of KBrO3 in drinking water especially after 9 and 14 months post treatment. **Khan *et al.* (2003)** reported during their study a reduction of antioxidant enzymes and enhancement of xanthine oxidase and lipid peroxidation when rats were treated with potassium bromate. Meanwhile **El-Sokkary (2006)** observed significant increase in malondialdehyde as an indicator of lipid perioxidation. These mentioned findings support the histological changes occurred in the organs during the present study as lipid peroxidation play a role in tissue injury.The generalized haemorrhage and congestion may be due to the endotheliotoxic effect of potassium bromate **(Afaf Abuelgasim et al.,2008).**

The pathological changes observed in the heart in the present study were similar to those described by **Paul (1966).** The lesions in the brain during the present work indicate that potassium bromate may cross the brain barrier and exert its effects on the endothelium permeability as well as brain tissues **(Afaf Abuelgasim et al.,2008),** and they added that it may lead to neurotoxic effect. In the Contrary to

the present findings **Crofton (2006)** claimed that there were no nervous malformation caused by potassium bromated and we think that it may be due to the short duration of his study.

The results of this study thus indicated that chronic administration of potassium bromate might lead to labialization of the cell plasma membrane due to the presence of high oxygen content per molecule of potassium bromate. Such disruption of the ordered lipid bilayer of the plasma membrane has resulting in leakage of the enzymes to the extracellular fluid, the serum and this has corroborated by the histological studies. These mentioned alterations may account for the various adverse effects associated with potassium bromate administration **(Akanji et al., 2008)**.

Conclussion: Potassium bromate (KBrO3) has many dangerous effects. We have also noted its possible toxic effects on different tissues. Further studies should be encouraged in this regard. The physical properties of KBrO3 make it easy to be taken or administered as a poison to human, thus its use and handling should be highly regulated by the relevant authorities.

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وقد أجريت هذه الدراسة للتحقيق في الآثار السامة للمستويات مختلفة من برومات البوتاسيوم في الفئران الذكور والإناث. معايير التقييم تشمل آثارها على المرضية، والتعديلات المتعلقة بالدم.

تم الاستعانة بعدد من 105 الجرذان من كلا الجنسين، وتزن 120 غرام في هذه التجربة. كانت الحيوانات المستخدمة 45 من الذكور و 45 من الإناث و 15 الفئران من كلا الجنسين تستخدم السيطرة. سواء تم تقسيم الفئران الذكور والإناث إلى ثلاث مجموعات. تركت الحيوانات لمدة أسبوع، وفترة التكيف. KBrO3 الذائبة في الماء في تركيزات 200 و 400 و 600 جزء في المليون على التوالي، وتدار على الفئران مجموعة من الذكور والإناث يوميا حتى نهاية التجربة. بعد 6 و 9 و 14 أشهر عشرة حيوانات من كل مجموعة تم التضحية (5 ذكور و 5 إناث) وخمسة من سيطرة خلع عنق الرحم. تم جمع عينات الدم وعينات الأنسجة للفحص مكونات الدم والنسيجي. كشفت نتائج دموية اختلافات كبيرة من معظم المعلمات المقدرة مختلفة إلا وحيدات الحمضات بالمقارنة مع مجموعة المراقبة.

الفحص النسيجي للرئة والقلب والطحال والدماغ كشفت احتقان الأوعية الدموية لديهم، مع وسجلت في مختلف التغيرات التنكسية، نخر والتهاب.