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PROTECIVE ROLE OF VITAMIN E ON LEAD INDUCED NEUROTOXICITY IN MALE ALBINO RATS

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ABSTRACT

Lead is a pervasive environmental toxin that affects multiple organ systems, including the nervous, renal, reproductive and hematological systems. Even though lead is probably the most studied toxic metal, some of the symptoms of lead toxicity still cannot be explained by the known molecular mechanisms. Therefore, lead induced oxidative stress has recently started to gain attention. This experimental study is planned to investigate the- role of oxidative stress as a possible mechanism of sub-chronic lead induced neurotoxicity in rats and to evaluate the role of alphatocopherol (Vitamin E) as anti oxidant in reversing this effect.

In order to achieve our goal, we measured both the blood level. Morever, the enzyme activities of reduced glutathione (GSH), glutathioneperoxidase (GPx), superoxide dismutase (SOD),malondialdhyde (MDA), 8-hydrodydeoxyguanosine (8-OHdG) were determinedin brain tissues of lead acetate exposed rats in the presence or absence of Vit. E. Increases in MDA, 8- OHdG contents were observed in brain's of rats received only lead acetate but supplementation with Vit. E returned these measures to nearly pretreatment levels. The level of GSH, SOD and GPx. significantly decreased in lead acetate exposed rats but increased to about pretreatment levels in supplementation of Vit.E concomitantly to lead acetate treated rats. This study also showed that administration of lead acetate to male rats had elevated blood and brain lead level which not decreased on administration of Vit. E concomitantly. To confirm these results a histopathological examination of rats brain were done. Histopathological changes were observed in the brain of lead exposed rats in the form of sever edema, gliosis, and neuronal degeneration, but addition of Vit. E concomitantly to lead showed mild changes in the form of mild edema, and gliosis. These results suggests that Vit.E can protect against oxidative stress effect of lead inducing neurotoxicity by its antioxidant effect, but not associated with decreasing brain or blood lead level.

INTRODUCTION

Lead is an ancient metal. It is widely used by Man since prehistoric time, because of its malleability, resistance to corrosion and low mellting point. Lead is one of the most toxic and pervasive pollutant in society and is known to have toxic effects on several biological systems. Although population on exposure to lead has been declined in recent years as a result of change to lead free gasoline, lead is still the most serious environmental hazard to young children [1,2].

In Humans Lead can result in a wide range of biological effects depending upon the level and duration of exposure. The major exposure pathway in the general non smoking population is from food, water and air [3,4,5].Epidemiologic studies over the past several decades have suggested that even slightly elevated lead levels during early childhood can produce cognitive impairments and behavioral problems that endure long past the period of exposure [6].

Lead poisoning is largely a disorder of young children with a peak incidence in one to three years of age. The relatively fast growth and metabolic rates of children coupled with their small body size are in themselves predisposing factors to susceptibility to lead toxicity. Adults with occupational exposure to lead constitute another large group at risk [7,8].

Elevated concentrations of blood lead levels in children who are chronically exposed to low levels of lead may be a cause of CNS toxicity including learning disabilities, lowered intelligence Quotient (IQ) and behavioral abnormalities; in addition to lead encephalopathy [9,10,11,12,13].

Although no single mechanism for lead toxicity has yet been defined, recent studies indicate that at least some lead induced damage may occur as a consequence of lead -induced oxidative stress [14, 15, 16]. Lead- induced oxidative stress has led scientists to study the protective qualities of antioxidants against lead toxicity [17,18,16].

The aim of this study is to investigate the role of oxidative stress as a possible mechanism of sub-chronic lead toxicity induced neurotoxicity in rats and to evaluate the role of alphatocopherol Vitamin E as antioxidant in reversing that effect.

MATERIAL AND METHODS

This is an experimental study that was conducted on 50 adult male albino rats weighting 100-150 gm. Purchased from Helwan research animal Center. The animals were fed on ordinary food and housed in ordinary conditions in the animal house in

the department of forensic medicine and toxicology, faculty of medicine Tanta University. Rats were divided randomly into five groups, 10 rats each (n =10):-

Group (Group 1) Served as a negative control group and received nothing.

Group (Group 2) Served as a positive control group and received intraperitoneal injection of sodium acetate in dose of 1mg/kg/day for four weeks.

Group (Group 3) Served as a positive control group and received olive oil orally in dose of 54 mg/kg/day for four weeks.

Group (Group 4) Received intra peritoneal injection of lead acetate in dose of 1mg/kg b.w. /day for four weeks[19].

Group (Group 5) Received the same dose for the same period of lead acetate in dose of 1mg/kg b.w. /day for four weeks in addition to Vit . E orally in a dose of 54 mg/ Kg/day dissolved in olive oil[20].

A pilot study had been done to compare the results of all positive control groups. The study included sodium acetate as a positive control of lead acetate, de-ionized water and olive oil as a solvent for lead acetate and Vit . E. respectively. The duration of this experiment was 4 weeks. Lead acetate and sodium acetate were obtained from Aldrich, chemical company, Germany. Vitamin E was purchased from Sigma chemical Company. St. Louis, USA. At the end of the experimental period, the rats were sacrificed by cervical dislocation, blood samples were collected by heart puncture into clear sterile tubes, and then the whole brain were excised and washed from extraneous materials. How it kept?

Metal analysis: whole blood and brain tissue lead levels were determined by atomic absorption spectrophotometer Model 2380 Perkin-Elmer[21].

Determination of reduced glutathione: Reduced glutathione was determined in brain tissue using double beam spectrophotometer, according to method described by Richardson and Murphy, 1975[22]. Results were obtained from standard curve and expressed in nmol /gm tissue.

Determination of Glutathione peroxidase activity: Glutathione peroxidase activity was determined in animal's brain tissue using double beam spectrophotometer, according to method described by Urisini et al.,1995[23].

Determination of Supernatant protein contents: Protein contents of supernatant was measured colorimetrically using double beam spectrophotometer, according to method described by Lowery et al.,1951[24].

Determination of Super oxide dismutase activity:- Sper oxide dismutase was determined in animal's brain tissue using double beam spectrophotometer, as described by Arther and Boyne,1985[25]. Using Ransod kit (Randox laboratories limited).

Determination of Lipid per oxidation: Lipid per oxidation was determined in animal's brain tissue using double beam spectrophotometer, Using thiobarbituric acid method according to method described by Uchiyama and Mihara, 1978[26]. Result were obtained from standard curve and expressed in nmol /gm tissue.

Determination of 8-Hydroxy deoxyguanosine (8-OHdG): 8-hydroxy deoxyguanosine (8-OHdG) contents in the animal's brain were determined after enzymatic digestion of DNA, followed by HPLC detection, as described by Shigenaga et al., 1990[27].

Histopathological examination of brain sections of all groups: Immediately after sacrificing the animals, sections from the brain were removed and immediately fixed in buffered formalin 10%, 0.5 thickness slices were cut and processed, paraffin embedded, then paraffin embedded sections were cut and stained with H&E stain to be studied with light microscope. All sections were evaluated without prior knowledge of the animal treatment groups by the examiner.

Statistical Analysis

Statistical presentation and analysis of the present study was conducted, using the mean, Standard Deviation [SD], t. test analysis of variance [ANOVA] test. p. value significant less than 0.05 ($p < 0.05$)

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RESULTS

The pilot study showed non significant changes between all control groups and sodium acetate treated group as well as olive oil treated group were used as a represented group.

Oxidative status:-

The rate brain tissues levels of reduced glutathione (GSH) in animals [treated with 1mg/kg b.w. /day for four weeks group (4)] were significantly lower than those observed in control groups P<0.05. Treatment with Vitamin E in a dose of 54 mg/ Kg/day concomitantly with lead [group (5)] enhanced significantly increase in GSH in animals brain tissues in comparison to group (4) p<0.05. as shown in Table (1). The activities of glutathione peroxidase GPx and superoxide dismutase SOD in rat brain tissues of lead treated group (group 4) were significantly decreased (in comparison to the control groups p<0.05. However, a significant increase in GPx and SOD activity were detected in lead & Vit . E treated group (group5) in comparison to group (4) p<0.05. as shown in table (2, 3) respectively. As regard to the contents of malonaldhyde (MDA) as an end product of lipid perxidation nerve cells membrane as measured by double beam spectrophotometer) and 8- Hydroxy deoxyguanosine (8- OHdG) of rat brain contents as measured by HPLC are shown in table (4, 5) respectively. The activities of MDA and 8-OHdG contents of rat brain tissues in the lead only treated group (group 4) were significantly increased (in comparison to the control groups. p<0.05. However, a significant decrease in MDA and 8- OHdG contents of the brain tissues were measured in lead & Vit . E treated group (group5) in comparison to group (4) p<0.05. On the other hand the mean values of blood and brain lead level among different studied groups. were significantly higher in intraperitoneal injection of lead acetate with or without oral administration of vitamin E (group 4&5) compared to lead unexposed groups (control groups). There is no reduction in blood and brain lead level on administration of Vitamin E. There was no significant difference between + ve & - ve control groups as shown in Table (6).

The histopathological findings

The histopathological study confirmed the previous results. Photomicrograph (1) showed the brain contained normal amount of glial cells without pathological changes in controle group.On there hand, in studying sections from group (4) that received intraperitoneal injection of lead acetate (1mg/kg/day) for 4 weeks, Brain sections from all studied rats showed Extensive gliosis ,oedema and Subpial mononuclear cellular infiltration (Photomicrograph 2).While Photomicrograph 3 showed mild oedema and gliosis in sections from group (5) that received lead acetate (1mg/kg/day) intraperitoneally concomitantly with vit E orally in dose (54mg/kg/dy) for 4 weeks.

DISCUSSION

Lead is an abundant toxic metal that primarily affects the peripheral and central systems, red blood cells and calcium metabolism (28). Exposure to environmental lead is particularly neurotoxic to the developing nervous system of children's. Neurotoxic effects of lead exposure include memory impairment, lowering of IQ and increased reaction time. [29,30, 31, 32, 33].

One of the major concepts on the mechanism of heavy metals toxicity is attributed to its ability to generate reactive oxygen species (ROS) which causes peroxidation of membrane lipids and DNA degeneration. ROS formation in the tissue was likely to cause oxidative damage and oxidative stress which could be contributed to tissue injury in liver, brain, kidney and other organs [34,35]. Usually the deleterious effects of the oxidative stress are counteracted by natural cellular defense mechanisms that involve enzymatic and non enzymatic scavengers of free radicals[36].

Recent studies reported that lipids peroxidation in neuronal cells was accentuated following lead exposure, also the antioxidant capacity of the neuronal

cells was diminished. So they suggested that lead may exert its neurotoxic effects via per oxidative damage to the membrane [37].

Based on the above considerations this study was carried out to investigate the role of oxidative stress in lead induced neurotoxicity and to study the possible protective effect of vit . E against lead induced oxidative stress in rat's brain.

The present study revealed significant reduction of the measured antioxidant scavenger such as reduced glutathione (GSH) and glutathione peroxidase (GPx) and super oxide dismutase (SOD) enzymes, following exposure to lead acetate. These finding are consistent with the finding of others who reported that lead decrease GSH level in brain, which has been proposed as a sensitive indicator of oxidative stress [38,39,40]. Other workers have also reported a decrease in GPx activity in brain of lead exposed rats which might attribute to exhaustion or inactivation of the GPx enzyme by lead induced ROS [23,40]. Similar results were reported as a decrease in SOD activity in brain of rats received lead acetate [41, 40, 42].

In this study; vit. E was found to have a protective effect against lead induced reduction in GSH, GPx, SOD such effect was observed in rats received vit .E concurrently with lead acetate which show significant elevation in the previous parameters in brain of treated animals as compared to lead acetated treated rats. Possible mechanisms were postulated for these activities, which could be explained by the antioxidant capability of vit . E.[37].

Malonadialdehyde (MDA) is an end product of the lipid peroxidation process, which can be defined as oxidative deterioration of poly unsaturated lipid. [43]. It was reported that oxidative stress may cause several types of DNA lesions. 8-hydroxy deoxyguanosine (8-OHdG) is one of the most formed oxidative DNA lesions, that can be detected in both urine and tissues after oxidative stress [44].

In the current study, a significant elevation was observed in brain MDA level as well as 8-OHdG in brain DNA of the lead acetate exposed rats . This is in agreement with A charya and Acharya 1997 [45] & Patra et al., 2001[19].Who found an increase in lipid peroxidation in brain tissues of rats exposed to lead acetate, these results in agreement with the previous findings of many authors who found an increase in level of 8HdG in liver, kidney, lung and sperm. [46,47]

Results of the present investigation showed that Vit . E decreased the MDA levels as well as 8-OHdG level significantly in rat's brain, when administrated concomitantly with lead as compared to rats of group(4). The previous results may be attributed to the effect of vit. E, which is a major lipid soluble, chain breaking antioxidant that is known to protect biological membranes and lipoproteins from peroxidative damage [48,8]. It scavenges O_2, OH, lipid peroxyl radicals, and other ROS generated during the univalent reduction of molecular oxygen and during normal activity of oxidative enzymes[49]. Vit.E was found to inhibit DNA oxidative damage in many studies. So the observed reduction of the elevated 8-OHdG levels in vit.E treated rats, could be attributed to the anti- oxidant effect of vit. E.[49,50].

In the present study, blood lead level showed non significant change in lead acetate treated rats, compared with lead and vit. E treated rats. This denotes that the protective effect of vit . E as an antioxidant inhibiting lead related oxidative stress was not associated with reduction of blood lead level. These results were supported by Hsu et al., 1998[50].Who studied the effects of Vit .E and /or Vit .C on reactive oxygen oxygen species related lead toxicity in rat's sperms. They stated that the protective effect of Vit. E or C was not accompanied by decreasing lead blood level in animals.

A confirmatory study of the effects of lead and Vit, E has been performed, through a histopathological examination of the brain. In this study, histopathological changes were observed in brain of lead exposed rats, including edema, gliosis and neuronal degeneration. Such alterations in the brain tissues could be induced through a direct action of lead on astroglaial cells and membranes lipid peroxidation

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of brain capillaries. These observation were in agreement with previous studies, that indicated capillary damage, neuronal degeneration, astroglaial and proliferation in the brain of lead exposed rats as, lead was first localized in capillary endothelial cells and then in astrocytes [51, 52,53,54].

In the current study brain tissues of rats received Vit E concomitantly with lead showed lower damage in the form of mild edema, and mild gliosis. This could be explained by the antioxidant effect of Vit, E.[8,19,40].

According to the obtained results, Vit.E by its antioxidant ability might be suggested to protect against oxidative stress effect of lead inducing neurotoxicity. However, this protective effect is not associated with decreasing brain or blood lead level. Therefore, it is advisable to give Vit.E as anti oxidant to protect against lead inducing neurotoxicity, especially to children, and enforce all protective measures against lead environmental pollution.

Table (1): Effect of lead acetate (I P) with or without oral administration of vitamin E on Reduced glutathione (GSH) contents in rat's brain.

	Treatment				
	-ve control	Sodium acetate	Olive oil	Lead acetate	Lead acetate + Vit. E
Brain GSH Level (nmol /g tissue) Mean ± SD	653 ± 16	650 ± 12	654 ± 14	530 ± 11.6[a]	648 ± 10[b]

(a) mean significant difference as compared to control groups $p < 0.05$.

(b) mean significant difference as compared to lead acetate treated group. $p < 0.05$.

Table (2): Effect of lead acetate (I P) with or without vitamin E on glutathione Peroxidas (GPx) activity in rat's brain.

	Treatment				
	-ve control	Sodium acetate	Olive oil	Llead acetate	lead acetate + Vit. E
Brain Gpx Level (µmol INDPH/min /g protein) Mean ± SD	157.73 ± 6.21	156 ± 7.10	157 ± 6.67	132 ± 8.2[a]	156 ± 7.98[b]

(a) mean significant difference as compared to control groups $p < 0.05$.

(b) mean significant difference as compared to lead acetate treated group. $p < 0.05$.

Table (3): Effect of lead acetate with or without vitamin E on Superoxide dismutase (SOD) activity in rat's brain.

	Treatment				
	-ve control	Sodium acetate	Olive oil	Lead acetate	Lead acetate + Vit. E
Brain SOD (µ/g Protein) Mean ± SD	50.30 ± 0.24	50 00 ± 0.31	50 ± 0.35	40.20 ± 0.40[a]	48.00 ± 0.60[b]

(a) mean significant difference as compared to control groups $p < 0.05$.

(b) mean significant difference as compared to lead acetate treated group. $p < 0.05$.

Table (4): Effect of lead acetate with or without vitamin E on Malonaldehyde (MDA) content in rat's brain.

	Treatment				
	-ve control	Sodium acetate	Olive oil	Lead acetate	Lead acetate + vit. E
Brain MDA (nmol/g tissue) Mean ± SD	117.60 ± 3.10	116.50 ± 3.50	117.34 ± 4.2	222.00 ± 1.80[a]	140.00 ± 2.70[b]

(a) mean significant difference as compared to control groups $p < 0.05$.

(b) mean significant difference as compared to lead acetate treated group. $p < 0.05$.

Table (5): Effect of lead acetate with or without vitamin E on 8-Hydroxydeoxyguanosine (8-OHdG) content in rat's brain.

	Treatment				
	-ve control	Sodium acetate treated)	Olive oil	Lead acetate	Lead acetate + Vit. E treated
Brain 8- OHdG (fmol/mg protein) Mean ± SD	14.1220 ± 1.30	14.2000 ± 1.60	14.001 ± 1.89	29.7500±2.50[a]	17.3600±1.71[b]

(a) mean significant difference as compared to control groups $p < 0.05$.

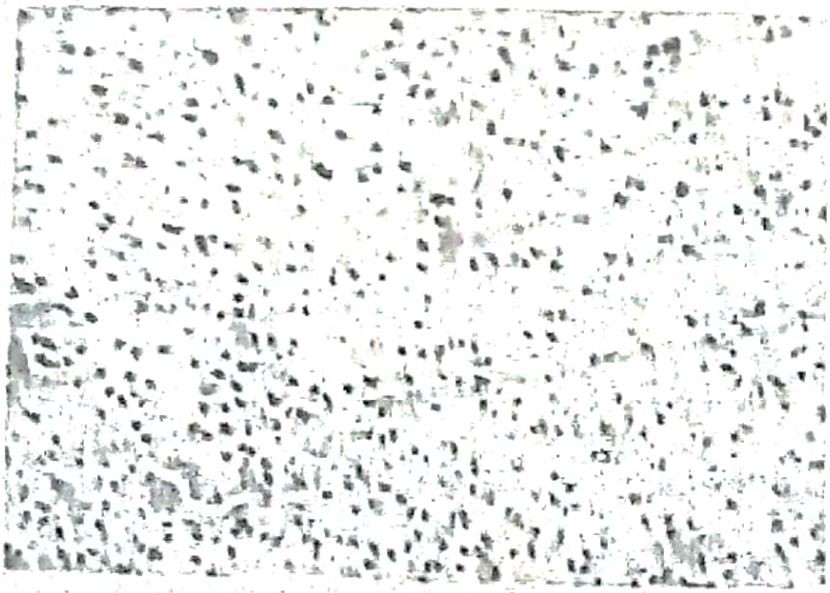
(b) mean significant difference as compared to lead acetate treated group. $p < 0.05$.

Table (6): Show changes in lead blood and brain tissues contents administration of lead acetate (I P) with or without vitamin E in rats.

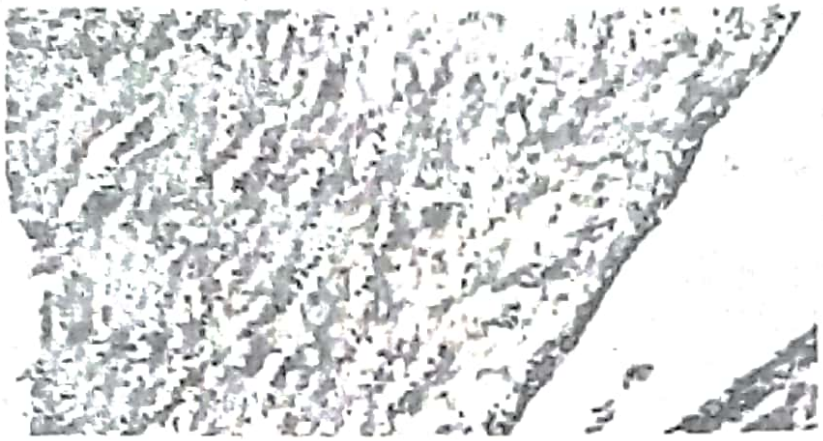
	Treatment				
	-ve control	Sodium acetate	Olive oil	Lead acetate	Lead acetate + Vit. E
Blood lead level (ppm)	7.52 ± 0.32	7.72 ± 0.24	7.58 ± 0.45	66.23 ± 0.56[a]	65.43 ± 0.76[b]
Brain lead level (ppm)	0.75 ± 0.06	0.76 ± 0.03	0.75 ± 0.07	7.6 ± 1.34[a]	7.1 ± 1.1[b]

(a) mean significant difference as compared to control groups $p < 0.05$.

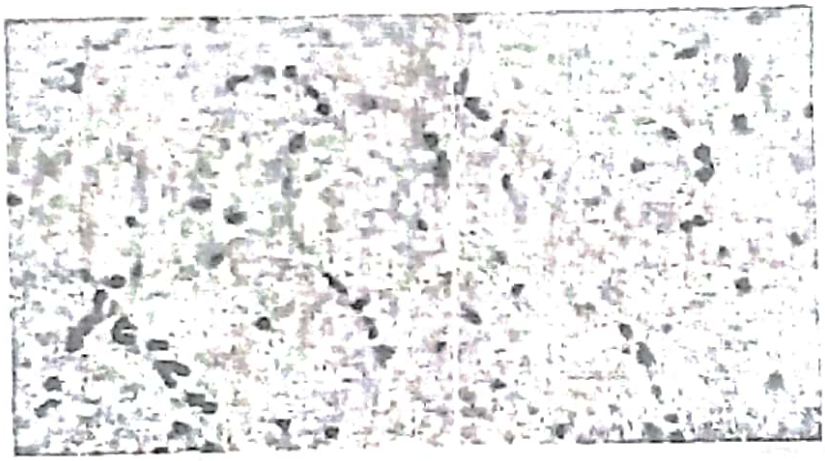
(b) mean significant difference as compared to lead acetate treated group. $p < 0.05$.



Photomicrograph (1) Brain section from control rats; showing normal cells and normal amount of glial cells. (H & E ×125)



Photomicrograph (2) Brain section from Rats received lead acetate for four weeks showing extensive gliosis (G) and oedema (E) with subpial mononuclear cellular infiltration (M). (H & E ×125)



Photomicrograph (3) Brain section from Rats received lead acetate 1mg/kg/day (IP) concomitantly with Vit. E orally in dose of (54mg/kg/day) for four weeks; showing mild gliosis (G) and oedema (E). (H & E ×125)

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دور فيتامين هـ في الوقاية من تسمم الجهاز العصبي بالرصاص في ذكور الجرذان البيضاء

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الرصاص من السموم المحدثه البيئية الشائعة والتي تؤثر على العديد من أجهزة الجسم وعلى الرغم من أن الرصاص يعتبر من المعادن السامه الشائعة في دراسته إلا أنه لا تزال هناك بعض أعراض التسمم به التي لايمكن تفسيرها بالآليات النسبيه للرصاص المعروفه بالمراجع العلميه. وعليه وفي الاونه الاخيره اتجهت الانظار لنظرية الاجهاد التأكسدي كآلية للتسمم بالرصاص. وبناء عليه فإن هذه الدراسه تهدف لتأكيد وتحديد دور الاجهاد التأكسدي للتسمم بالرصاص على أنسجة المخ بالقشران وتقييم دور فيتامين هـ لعلاج التسمم بالرصاص ولتحقيق هدفنا هذا استخدمنا اربعين من ذكور الفئران المعمليه البيضاء قسمت لأربعة مجموعات (الأولى والثانيه مجموعات ضابطه الأولى لم تحقن بشيء والثانيه حقنت بخلات الصوديوم بالتجويف البريتوني لمدة أربعة اسابيع والمجموعة الثالثة حقنت بخلات الرصاص بالتجويف البريتوني بجرعة ١ملجم/كجم/يوميا لمدة أربعة اسابيع والمجموعة الرابعة حقنت بخلات الرصاص بنفس الجرعة السابقة مع حقنها عن طريق الفم بفيتامين هـ بجرعة ١ملجم/كجم/يوميا لمدة أربعة اسابيع. و أظهرت نتائج الدراسة ما يلي:-

ارتفاع نسبة الرصاص بالدم وأنسجة المخ إرتفاعا ملحوظا ذو دلاله إحصائيه في المجموعتين الثالثة والرابعة مقارنة بالمجموعتين الضابطتين الأولى والثانية.

إنخفاض ملحوظ ذو دلالة إحصائية لمضادات الأكسدة في المجموعة الثالثة (المعرضة للتسمم بخلات الرصاص) كانزيم الجلوتاثيون المختزل ،الجلوتاثيون بيروأكسيديز والسوبر أوكسي ديسموتاز تعود هذه الانزيمات المضادة للأكسدة لمستواها الطبيعي تقريبا في المجموعة الرابعة بعد إضافة فيتامين ه كمضاد للأكسدة .

كما أظهرت النتائج إرتفاعا ملحوظا ذو دلالة إحصائية لنواتج التأكسد الفوقي للدهون وذلك بإرتفاع نسبة المالونالديهيد إرتفاعا ملحوظا كما أظهرت النتائج إرتفاعا ملحوظا ذو دلالة إحصائيه لمؤشر تحطم الحامض النووي من الإجهاد التأكسدي بإرتفاع نسبة الأيت هيدروكسيدي أوكسي جوانوزين .تعود هذه النواتج لطبيعتها مقارنة بالمجموعات الضابطة وذلك في المجموعة الرابعة التي أعطيت فيتامين هـ كمضاد للأكسدة .

وأظهرت نتائج الفحص النسجي لأنسجة المخ تغيرات باثولوجية كالأوديما وتليف بأنسجة المخ وانتشار لخلايا النهابيه لحادية النواه في المجموعة المعرضة للتسمم بالرصاص (المجموعة الثالثة) وان فيتامين هـ أدى الى تحسن هذه التغيرات الباثولوجية بأنسجة المخ بدرجه ملحوظه .

وعليه فقد استنتج من هذه الدراسة بأن فيتامين هـ كمضاد للأكسدة يضاد الإجهاد التأكسدي بأنسجة المخ الناتج عن التسمم بالرصاص .وان هذا الدور الوقائي لفيتامين هـ غير مصحوب بنقص مستوى الرصاص بالدم او انسجة المخ إنما يقتصر دوره كمضاد للأكسدة فقط ولذلك نوصي بإعطاء فيتامين هـ كمضاد للأكسدة والوقاية من مضاعفات التسمم بالرصاص وخاصة في الأطفال مع الأخذ بالإجراءات الوقائية لتقليل التلوث البيئي بالرصاص.