Protective Role of Different Doses of Ascorbic Acid Against Harmful Effects of Lead in Liver, Kidney and Brain in Male Rats

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Abstract

Ascorbic acid (AA) is one of the most potent antioxidants that interacts directly with the oxidizing radicals and protects the cells from reactive oxygen species. Therefore, this study aimed to estimate the beneficial effect of different level of (AA) that can protect liver, kidney and brain from harmful effects of lead in male rats. Fifty male albino rats with average body weight 180 g were assigned into five equal groups; control group (received tap water only), lead group (received 0.2% lead acetate /kg BW) and the other three groups (received 500, 1000 and 1500 mg ascorbic acid along with 0.2%lead acetate /kg BW), respectively. Doses were orally administered every day for 8weeks.The results showed that lead acetate significantly ($P<0.05$), increased transaminases and Phosphatasesin plasma and decreased in liver. Lead acetate increased urea and creatinine and decreased bilirubin.Furthermore, the presence of AA with lead acetate alleviates its toxic effects.The best effect was found with the high level of AA (1500mg/kg

BW).Histopathology examination showed that; the presence of AAcaused improvement in the histopathological changes caused by lead acetate. From the present study, it can be concluded thatAA is capable to alleviate the harmful effects of lead and highly recommended increasing the daily intake of AA either from food (high source of AA) or from supplementation.

Introduction

Ascorbic acid (AA) is low molecular mass antioxidant that interacts directly with the oxidizing radicals was widely reported with the capability of protecting cells from oxidative stress ***(Patra and Swarup, 2004)*** and protect the cells from reactive oxygen species ***(Raiet al., 2009).*** It also has been shown to regenerate other antioxidants within the body, including vitamin E***(Jacop, 2002).***

A free radical may be defined as any molecule that has one or more unpaired electrons. Reactive oxygen radicals (ROS) formation in the tissue was likely to cause oxidative damage and the oxidative stress could then contribute to tissue injury in liver, brain, kidney, lung, and other organs ***(Halliwell, 1994).*** Organisms have developed many defense mechanisms to protect themselves from injuries by ROS.The small molecule antioxidants, such as vitamin E and AA are able to interact with oxidizing radicals directly ***(Jones et al., 1995).***

Lead (Pb) is a common environmental and industrial pollutant that has been detected in all phases of environment and biological system. The persistence of lead in the animals and humans and the associated health risk is a topic of current debate and concern

(Juberget al., 1997).Lead (Pb) toxicity is probably the most common form of heavy metal intoxication. It is welldocumented as one of the most dangerous and insidious poisons. Its continuous environmental and occupational exposure may contribute to renal, nervous, hepatic, hematological and reproductive disorders in man and animals ***(El-Sayed and El-Neweshy, 2009, Ashryet al., 2010).***The absorbed Pb is conjugated in the liver and passed to the kidney, where a small quantity is excreted in urine and the rest accumulates in various body organs and affects many biological activities at the molecular, cellular and intercellular levels, which may result in morphological alterations that can remain even after Pb levels have fallen ***(Flora et al., 2006).***The neurotoxic effect of lead,particularly in the developing brain is a matter of serious concern and behavioral abnormalities,learning impairment, decreased hearing and impaired cognitive functions in humans and experimentalanimals have been recorded with blood lead levels as low as 10 µg/dl ***(Bressleret al., 1999).***

Consumption of 1000 mg of Ascorbic acid (AA) a day has been shown to significantly decrease lead levels apparently more through reduced absorption rather than increased excretion. Ascorbic acid (AA) improves iron absorption if it can mix with food in the stomach (food or liquid being preferable forms), as well as increasing iron's capacity to displace lead during food absorption**(*Chunhonget al., 2007).*** Thus, this study aimed to estimate the beneficial effect of different level of (AA) towards the harmful effect of lead in male rats.

Materials and Methods

Experimental animals:

Male albino rats (*n:* 50) averaging 180 g of BW were obtained from the animal house of the Medical Research Institute, Alexandria University, Egypt. The local committee approved the design of the experiments and the protocol follows the guidelines of the National Institutes of Health (**NIH**). Animals received human care, and had adequate stable diet(table1) and water *ad lipitum*. Animals were acclimatized to the laboratory conditions for two weeks before being experimented.

Experimental design:

After two weeks of acclimation, animals were classified into five equal groups of ten rats each. Control group (received tap water together with the basal diet only), lead group (received 0.2% lead acetate /kg BW) and the other three groups (received 500, 1000 and 1500 mg AA along with 0.2%lead acetate/kgBW), respectively. Doses were orally administered every day for 8 weeks.

Body weight and organs weight:

Body weight of rats was recorded in the beginning and at the end of the experimental period. Animals were sacrificed by decapitation, and then liver, kidney and brain were immediately removed and weighed. Relative organ weights were calculated as g/100 g body weight. Liver, kidneys and brain were excised immediately. Half of the liver and brain and one kidney were processed immediately for biochemical investigation and the rest were stored at −20°C for wet digestion for estimation.

Blood sample:

Blood samples were collected from the sacrificed animals in heparinized tube. Plasma samples were obtained by centrifugation at 4000 rpm for 20 minutes, and then samples were stored at –20ºC until used for further analyses.

Biochemical parameters and enzyme activities:

Plasma samples were analyzed for glucose according to ***Kunst et al., (1984)*** while urea and creatinine concentrations were measured according to the method of ***Lamb et al., (2006).*** Total protein and albumin concentrations were determined according to ***Doumaset al., (1977),*** while, globulin was calculated. Total bilirubin was measured using the method of ***Wahlefeld and Bergmeyer (1972).***The activities of plasma and liver aspartate transaminase (AST) and alanine transaminase (ALT) were assayed by the method of ***Bergmeyer and Herder (1986).*** Acid Phosphatase (ACP) and Alkaline Phosphatase (ALP) activity were determined according to ***Hillmann (1971).*** All the aforementioned parameters were measured using commercial kits, [Bio systems S.A. (Spain), Diamond (Germany) and Randox (United Kingdom)].

Histological study:

Liver, kidney and brain specimen used for histological study were fixed in neutral formalin buffer for a week at room temperature, dehydrated then cleared in xylene and embedded in paraffin wax. The paraffin sections were cut at 20 microns thickness and stained with hematoxylin and eosin for histological examination using the light microscope according to ***Banchroftet al ., (1996).***

Statistical analysis:

Data were analyzed according to ***Steel and Torrie (1981).*** Statistical significance of the difference in values of the control and treated animals was calculated by F test with 5% significance level. Data of the present study were statistically analyzed by using Duncan's Multiple Range Test ***(SAS, 1999).***

Results

Table (2) showed the body weight gain and relative weight for liver, kidney and brain for different groups.No significant changes were found in body weight of all groups. Pb caused significant increase (≤0.05) in liver and kidney weight (3.2 and 0.9) than control group (2.6 and 0.7) respectively, withoutany effect on brain weight. Presence of AA could enhance relative weight of liver at 500 mg (3.1) and 1000 mg (3.1) but the high doses 1500 mg didn't have any effect. Relative weight of kidney increased at 500mg of AA (1.1) and decreased at 1000mg and 1500mg (1.0 and1.0) but it still more than Pb group (0.9),it was noticed an increase in brain weight at 1000mg of AA with Pb acetate.

As showed in table (3), Pb caused significant increase in plasma creatinine, urea, billirubin and glucose (1.4, 63.0,1.09 and 156.2) respectively than control group(0.9, 48.9, 0.77 and 105.3), italso caused significant decrease in total protein, albumen and globulin (34.6, 24.4 and10.1) respectively compared to control group(71.5, 41.2 and 30.3). All doses of AAimproved the levels of creatinine (1.4, 1.1 and 1.03), urea (53.4, 52.3 and 49.7) and bilirubin (0.9, 0.93 and 0.9) at (500, 1000 and 1500 mg respectively). AA also decreased glucose level (134.8, 135.3 and 122.5) at (500,

1000 and 1500 mg respectively) .Total protein, albumin and globulin levels were increased by adding AA.

Enzymes activity of liver and plasma discussed in table (4), showing that Pb affected dramatically liver function it caused depression by half amount of enzymes level AST,ALT,ALP and ACP (193.8,109.9,12.1 and 5.1) in Pbgroup respectively, compared to (324.8, 219.9, 24.1 and 10.1) in control group respectively. Presence of AA with Pb acetate enhanced the enzymes activity. The best effect was found with the high level of AA 1500 mg (288, 189.1, 21.0 and 8.5) respectively. On the other hand it was noticed that Pb caused significant increase in the level of AST, ALT, ALP and ACP in plasma (47.6, 69.2, 98.1 and 14.7) than control group (31.7, 46.7, 65.9 and 9.4) but AA decreased significantly levels of enzymes AST, ALT, ALP and ACP especially with the high dose 1500 mg (37.2, 54.3, 76.3 and 11.1).

Hematoxylin and eosin stained sections of liver; kidneys and brain were evaluated under light microscopy. The number of rats with certain types of histopathological findings and their occurrence in Pb and AA supplemented groups are summarized as follow:

Control group showed normal hepatic histology of intact portal areas and normal hepatocytes (fig.1L).In Pb group the histopathological examination of liver tissues showed congested central vein and blood sinusoids (fig.2L). While adding AA along with Pb in different dosesdecreased harmful effects of Pb. By increasing doses of AAthe improvement in liver architecture was increase (fig.3L, 4L and 5L).

The kidneys of control rats exhibited normal renal tissue, where normal glomerular vacuolations tissues were observed (fig.1K)**.** In Pb group the histopathological test of kidneys showed vacuolated glomerular tuft (fig.2K). While adding AA along with Pb in different doses decreased harmful effects of Pb. By increasing doses of AA the improvement in kidney architecture was increase (fig.3K, 4K and 5K).

Upon histopathological examination of control rats, brain tissue showed apparently normal neuronal cells and meninges (fig.1B). In Pb group brain showed massive brain edema with demylination (fig.2B).While adding AA along with Pb in different doses decreased harmful effects of Pb. By increasing doses of AA the improvement in brain architecture was increase (fig.3B, 4B and 5B).

Discussion

Nutritional factors may modify Pb absorption and/or the toxic response to Pb***(Lauwery, 1983).*** Animal studies have suggested an antagonistic effect of AA on Pb absorption and toxicity, and AA may chelate Pb***(Dalley, 1989).***

This study confirmed previous work showing that exposure to Pb caused increase in urea, criatinine, which indicate that renal affected by Pb exposure.***Odigie, 2004*** also reported that, blood urea nitrogen and serum creatinine are some of the parameters that can be used to detect the renal effects caused by occupational exposure to Pb**.**

Pbcaused significant increase in plasma billirubin and glucose; it also caused significant decrease in total protein, albumen and globulin than control group. The elevation of plasma bilirubin value under the ingestion of lead acetate may be due to the induction of hemeoxygenase. The catabolism of heme from all heme proteins is carried out in the microsomal fraction of cells by a complex enzyme system and hemeoxygenase is an enzyme which can convert heme to bilirubin ***(Seddik, 2010 and Murray, 2006),*** they reported that bilirubin formed in different tissues is transported to liver as a complex with serum bilirubin. Bilirubin is conjugated with glucuronide in the smooth endoplasmic reticulum of liver, but under the effects of lead toxicity, the conjugation of bilirubin with glucouronoid will become inactive. This may be due to the peroxidation of membrane lipids of smooth endoplasmic reticulum.

Ibrahim etal., 2012 also found that total soluble protein and albumin contents of plasma were significantly decreased, while the content of globulin was changed by the Pb treatments, while plasma glucose level was elevated as a result of lead acetate intoxication. The variation in total protein of plasma was correlated with the changes in albumin value. The reduction in plasma total soluble protein and albumin levels may be due to inhibition of protein biosynthesis through the specific enzymes in cell processes and low significant excretion of hormones which can regulate protein biosynthesis. Heavy metals including lead can precipitate soluble protein and albumin in plasma is used as carrier for poison lead ***(Murray, 2006).*** The elevations in blood glucose levels may be due to the increases in the rate of glucose transport from the tissues to blood, glycogenolysis and gluconeogenesis or decreased rate

removal of glucose from the blood to tissues ***(Yousif and Ahmed 2009).***

Adding AA along with lead caused an improvement in the levels of glucose, bilirubin, total protein, albumin and globulin. By increasing the level of AA, the improvement was increase. Using AA supplementation can be considered as a useful harmless, economical and convenient prophylactic agent for Pb-exposed population**(*Shahrabi, 2006).***

Liver is a major organ where the particles are deposited and inducing damage ***(Ahamedet al., 2010; Roy et al., 2014).***When liver is damaged a variety of enzymes located normally in cytosol is released into the blood, thereby causing increased enzyme level in the serum. The estimation of enzymes in the serum is a useful quantitative marker of the extent and types of hepatocellular damage**(*Jadonet al., 2007).***

There is evidence that some nutrients, especially AA, exhibit some protective effects against Pb intoxication ***(Houston and Johnson, 2000).*** Herein, the beneficial role of co-administration of a low dose of AA with Pb is shown in the main target organs; liver, kidneys and brain and expressed as histopathological scores.

Autopsy studies of Pb exposure cases indicate that liver tissue is the main organ affected among the soft tissues, followed by the kidney cortex and medulla ***(Patrick, 2006).***In the recent study it was noticed a congested central vein and blood sinusoids**.** ***Hamir and Sullivan, 2008*** reported that Pb-induced hepatic damage with

portal cellular infiltration, cholestasis and biliary hyperplasia is well-documented.

Another histological indication of Pb toxicity in the rat kidney is the vacuolated glomerular tuft, interstitial and glomerular damage are also characteristic renal lesions due to Pb toxicity as the same in our study.Tubular changes occur earlier than glomerular and interstitial changes, including development of pathognomonic intranuclear inclusions in the renal tubular epithelium ***(McGavin and Zachary, 2007).*** It was found massive brain edema with demyelination, and congested blood vessel in our study. ***Blood and Hinchcliff, 2000*** also found that Pb is a well-known neurotoxin resulting in varying degrees of edema of the brain,Herein, the histological portrait of the brain in Pb-intoxicated rats showed clear structural damage of the central nervous system, characterized by edema of cerebellar white matter, neuronal degeneration. This may be attributed to oxidative damage associated with chronic Pb intoxication in the rat brain ***(Adonayloet al., 1999).*** In contrast, rats treated with Pb plus AA exhibited mild neuronal degeneration with scant tissue reactions. Neither cerebellar edema nor cerebral encephalomalacia were noted.It can be concluded that AA is capable to alleviate the harmful effects of lead and highly recommended increasing the daily intake of AA either from food (high source of AA) or from supplementation.Five servings of fruits and vegetables per day may be beneficial in preventing from many diseases and reduce blood lead level .This study could be used in nutrition education programs for consuming Ascorbic acid rich food.

Table (1): Compound of standard commercial laboratory diet

Contents	Percent
Corn	56.8
Soya beanmeal (44%)	28.08
Corn gluten (60%)	7.2
Soya oil	3.6
Lime stone powder	1.7
Di calcium phosphate	1.5
Salt	0.4
Vitamins and minerals mixer	0.3
L.lysine hydro chloride	0.25
D.L.Methionine	0.17

Table (2): Changes in body weight gain (g) and relative weight of organs g/100 g BW in the control and different group treatment.

Parameters	Experimental groups				
	Control	Pb	500 mg AA	1000 mg AA	1500 mgAA
Initial weight	178.5 ± 5.3 [a]	183.0 ± 6. 7a	181.7 ± 5.9a	185.7 ± 7. 2[a]	185.8 ± 9.4[a]
Final weight	215.5 ± 6.9[a]	215.4 ± 14.7[a]	210.0 ± 11.0[a]	207.1 ±13.3 [a]	211.7 ± 14.7[a]
Body weight gain	37.0 ± 6.4[a]	32.4 ± 6.8[a]	28.3 ± 7.1[a]	21.4 ± 10.6 [a]	25.8 ± 10.1[a]
Liver	2.6 ± 0.05[b]	3.2 ± 0.1[a]	3.1 ± 0.04[a]	3.1 ± 0.06 [a]	3.2 ± 0.1[a]
Kidney	0.7 ± 0.01[c]	0.9 ± 0.03[b]	1.1 ± 0.0 5[a]	1.0 ± 0.02[ab]	1.0 ± 0.06[ab]
Brain	0.7 ± 0.04[a]	0.7 ± 0.05[a]	0.7 ± 0.03[a]	0.8± 0.05[a]	0.6 ± 10.05[a]

Results are expressed as mean ±SE; Means with different letters in the same row imply significant differences at P≤0.05.

Table (3): Effect of ascorbic acid with different doses and lead acetate on biochemical parameters

Parameters	Experimental groups				
	Control	Pb	500 mg AA	1000 mg AA	1500 mg AA
Creatinine (mg/dl)	0.9 ± 0. 3^{c}	1.4 ± 0.07^{a}	1.4 ± 0.04^{b}	1.1 ± 0.02^{b}	1.03 ± 0.02^{b}
Urea (mg/dl)	48.9 ± 2.5^{c}	63.0 ± 2.7^{a}	53.4 ± 2.9^{b}	52.3 ± 3.1^{b}	49.7± 3.1^{bc}
T. bilirubin(mg/dl)	0.77 ± 0.02^{c}	1.09 ± 0.03^{a}	0.9 ± 0.02^{b}	0.93 ± 0.02^{b}	0.9 ± 0.05^{b}
T. protein(g/dl)	71.5 ± 2.3^{a}	34.6 ± 1.1^{d}	54.6 ± 1.6^{c}	54.1 ± 1.0^{c}	60.5 ± 1.4^{b}
Albumen(g/dl)	41.2 ± 1.3^{a}	24.4 ± 0.7^{d}	30.5 ± 0. 7^{c}	31.2 ± 1.1^{c}	34.9 ± 1.3^{b}
Globulin(g/dl)	30.3 ± 2.1^{a}	10.1 ± 0.6^{c}	24.1 ± 1.2^{b}	22.9± 1.5^{b}	25.6 ± 1.0^{b}
Glucose(mg/dL)	105.3 ±2.5^{d}	156.2± 5.8^{a}	134.8 ± 1.0^{b}	135.3 ± 1.4^{b}	122.5 ±2.9^{c}

Results are expressed as mean ±SE; Means with different letters in the same row imply significant differences at P≤0.05.

Table (4): Effect of ascorbic acid with different doses and lead acetate on Liver and Plasma enzymes

Parameters	Experimental groups				
	Control	Pb	500 mg AA	1000 mg AA	1500 mg AA
Liver					
AST (U/l)	324.8 ±2. 2a	193.8 ±2.0d	252.0 ± 7.6c	255.2 ± 8.1^{c}	288.0±4.1^{b}
ALT (U/l)	219.9 ±4.1a	109.9 ± 2.0e	162.7 ± 3.0d	169.3±3.1^{c}	189.1±3.5^{b}
ALP (U/l)	24.1 ± 0.5^{a}	12.1 ± 0.3^{e}	17.6 ±0.4d	18.3 ±0.4^{c}	21.0 ± 0.5^{b}
ACP (U/l)	10.1 ± 0.5^{a}	5.1 ±0.2^{d}	7.3 ±0.2^{c}	7.4 ± 0.2^{c}	8.5 ± 0.1^{b}
Plasma					
AST (U/l)	31.7±1.2^{c}	47.6±2.5^{a}	39.7±0.8^{b}	39.1±1.7^{b}	37.2±0.9^{ab}
ALT (U/l)	46.7 ±1.9^{c}	69.2 ± 1.2^{a}	59.6± 1.6^{b}	57.7 ± 1.7^{b}	54.3± 3.2^{ab}
ALP (U/l)	65.9 ± 1.8^{c}	98.1 ± 1.5^{a}	81.9± 1.9^{b}	80.3 ± 1.8^{b}	76.3± 2.6^{ab}
ACP (U/l)	9.4 ± 0.2^{ab}	14.7 ± 0.8^{a}	12.2 ± 0.9^{b}	11.6 ± 0.7^{b}	11.1± 0.5^{b}

Results are expressed as mean ±SE; Means with different letters in the same row imply significant differences at P≤0.05.

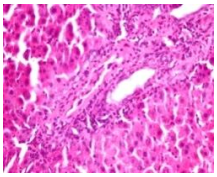

Fig. (1L) Liver of control group showed portal tract infiltration with mononuclear cells (arrow) (H&E X 400).

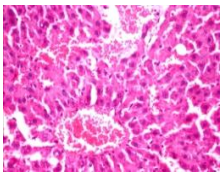

Fig. (2L) Liver of Pb group showed congested central vein (arrow), and blood sinusoids (arrow head) (H&E X 400)

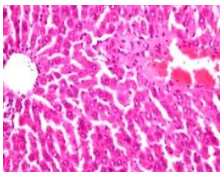

Fig. (3L) Liver of 500 AA mg showedperihepatic edema (arrow) with congested blood sinusoids (arrow head)

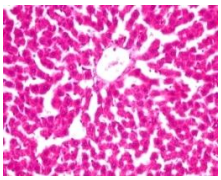

Fig.(4L) Liver of 1000mg AA showed widening and dilatation of blood sinusoids (arrow).

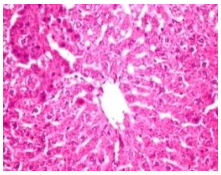

Fig. (5L) Liver of 1500mg AA group showed hepatocytic swelling and granulation (arrows) (H&E X 400).

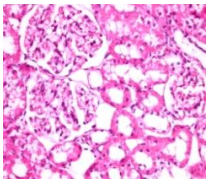

Fig. (1K) Kidneys of control group showed glomerular vacuolations (arrow) (H&E X 400).

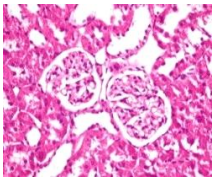

Fig.(2K) Kidneys of Pb group showed vacuolated glomerular tuft (arrow) (H&E X 400).

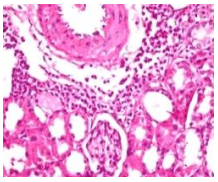

Fig.(3K) Kidneys of 500 mg AA showed dilated blood vessel with thick wall and perivascular eiosinophilic cells infiltration

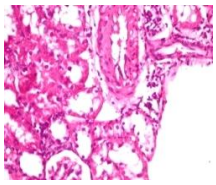

Fig.(4K) Kidneys of 1000mg AA showed dilated thick walled blood vessel and focal areas of mononuclear cells infiltrations

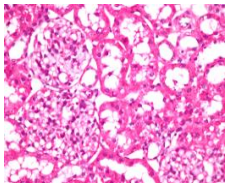

Fig. (5K) Kidneys of 1500mg AA group showed vacuolated glomerular tufts (arrows)

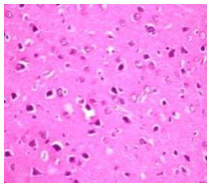

Fig. (1B) Brian of control group showed apparently normal neuronal cells and meninges

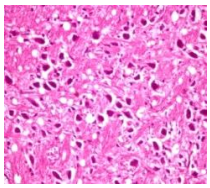

Fig.(2B) Brain of Pb group showed massive edema (arrows) with demyelination (arrow head)

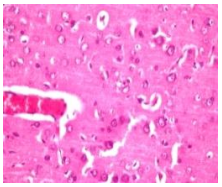

Fig.(3B) Brian of 500 mg AA group showed congested blood vessel (arrow)

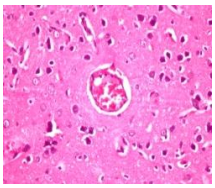

Fig. (4B) Brian of 1000 mg AA group showed congested blood vessel (arrow)

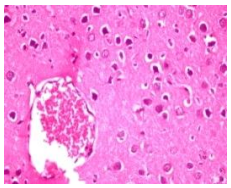

Fig. (5B)Brian of 1500 mg AA group showed severly dilated and congested blood vessel (arrow)

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الدور الوقائي لمستويات مختلفه من حمض الاسكوربيك ضد التاثيرات الضاره للرصاص في ذكور الجرذان

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الملخص العربي

حمض الاسكوربيك هو واحد من أقوى مضادات الأكسدة التي تتفاعل مباشرة مع الشوارد الحرة ويحمي الخلايا من اثار التاكسد المختلفه. لذلك، تم إجراء هذه الدراسة لتقييم الآثار الوقائية المحتملة لمستويات مختلفه من حامض الاسكوربيك التي يمكن أن تحمي الكبد والكلى والمخ من السمية التي يسببها الرصاص في ذكور الجرذان. تم استخدام خمسون من ذكور الجرذان متوسط اوزانها 180 جم إلى خمس مجموعات متساوية. المجموعة الضابطة (حصلت علي ماء الصنبور فقط)، مجموعة الرصاص (حصلت علي 0.2٪ من خلات الرصاص / كجم من وزن الجسم) بينما المجموعات الثلاث الاخرى (حصلت على 500 و 1000 و 1500 ملجم حمض الاسكوربيك بالاضافه الى 0.2٪ من خلات الرصاص /كجم من وزن الجسم)، على التوالي . كانت الجرعات تعطى عن طريق الفم كل يوم لمدة شهرين.وأظهرت النتائج أن خلات الرصاص تسببت في حدوث ارتفاع معنوي (عند مستوى معنويه <0.5) في مستوي انزيمات الترانس امينيز والفوسفاتيز في البلازما وانخفاضها في الكبد. كما تسببت خلات الرصاص في ارتفاع كلا من اليوريا والكرياتينين وانخفاض البيليروبين .ومن ناحيه اخرى، فإن وجود حمض الأسكوربيك مع خلات الرصاص يخفف من تلك الآثار الضاره، وقد اوضحت الدراسه ان أفضل النتائج كانت مع المستوى المرتفع من حمض الاسكوربيك (1500ملجم) .كما اظهرت الفحوصات الهستولوجيه ان وجود حمض الأسكوربيك ادى الى تحسن في البنيه النسيجيه المرضية الناجمة عن خلات الرصاص. ومن هذه الدراسه نستنتج أن حمض الاسكوربيك قادر على التخفيف من الآثار الضارة للرصاص . لذلك توصي الدراسه بزيادة المتناول اليومي من حمض الاسكوربيك إما من المواد الغذائية (مصادر عالية من حمض الاسكوربيك) أو من المكملات الغذائيه.