Vitamin C in Paraquat poisoning

DR Moshiri

Vitamin C in Paraquat poisoning

- ✓ یافته های ضد نقیض در مورد اثر ویتامین ث در سمیت پار کوات

مطالب :

الف) ویتامین ث چیست

ب) اثرات سمیت پار کوات بر میزان ویتامین ث

ج) اثرات مفید ویتامین ث بر سمیت پاراکوات (مثبت گروه A)

د) یافته های منفی و یا عدم تاثیر ویتامین ث بر سمیت پار کوات (منفی گروه B)

ه) مقالت مروری و کتاب گلد فرانک (گروه C)

د) بحث و نتیجه گیری

Vitamin C in Paraquat poisoning

- ✓ روش کار
- ✓ Pubmed & scopus ??????
- ✓ Googlescholarبا کلمات کلیدی Vitamin C و Paraquat جستجو شد تا ده صفحه مقالات بررسی شد
- ✓مقالات تا حد امکان فول تکس گرفته شد (5 تا فول تکس پیدا نکردم)
- ✓مقالات مطالعه شد و خلاصه شد بر اساس اهداف ، روش کار، یافته ها و نتیجه گیری
- ✓ مقالات مروری که نکته تحلیل اضافی داشتند آورده شد و انهایی که تنها به بیان نتایج سایر مقالات پرداخته بودند حذف شد
- ✓مقالاتی که مطالعات مقطعی وگزارشات انسانی بودن که تنها اعلام شده بود که ویتامین ث جزو پروتکل درمانی ما بوده و به مقایسه اثر ویتامین ث نپرداخته بودند آورده نشد

Vitamin C

- Ascorbic acid is effective in scavenging free radicals, including hydroxyl radical, aqueous peroxyl radicals and superoxide anion.
- Ascorbic acid acts as a two-electron reducing agent and confers protection by contributing an electron to reduce free radicals → neutralizing these compounds in the extracellular aqueous environment prior to their reaction with biological molecules

- Moreover, it has ability to regenerate other **small molecule antioxidants**, such as a-tocopherol, glutathione and b-carotene

- High concentrations of ascorbic acid are found naturally in the fluid of the **lung** to protect against free radicals generated by toxic chemicals in air, such as ozone, sulfur dioxide, metal fumes and cigarette smoke

- vitamin C is regenerating vitamin E.

Biosci. Biotechnol. Biochem., 67 (5), 1130–1131, 2003

Note

Change in the Concentration of Vitamins C and E in Rat Tissues by Paraquat Administration

Kazumi IKEDA, Yumi KUMAGAI, Yuka NAGANO, Naoko MATSUZAWA, and Shosuke KOJO†

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Received September 10, 2002; Accepted December 26, 2002

Paraquat causes lung injury by oxidative stress. After 48 h of intraperitoneal administration of paraquat (50 mg/kg of body weight) to rats, the vitamin C concentration in the lungs was significantly decreased

	Control (n = 5)	12 h (n = 4)	24 h (n = 8)	48 h (n = 5)
Lungs	16.30 ± 2.13	18.02 ± 4.41	17.02 ± 2.27	8.13 ± 1.74**
Plasma	0.66 ± 0.17	0.73 ± 0.26	0.70 ± 0.25	0.60 ± 0.07
Liver	6.66 ± 0.17	7.90 ± 0.56	8.15 ± 2.77	7.39 ± 1.91
Kidneys	4.20 ± 0.35	4.11 ± 0.16	3.97 ± 0.60	4.19 ± 1.27

A 1

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Toxicology Letters 126 (2002) 51–59

Toxicology Letters

www.elsevier.com/locate/toxlet

Effect of vitamin C on plasma total antioxidant status in patients with paraquat intoxication

Sae-Yong Hong [a], Kyu-Yoon Hwang [a,*], Eun-Young Lee [a], Soo-Whon Eun [a], Suk-Ran Cho [b], Chan-Soo Han [c], Yung-Hyun Park [d], Sung-Keun Chang [e]

A1) Effect of vitamin C on plasma total antioxidant status in patients with paraquat intoxication

- Main goal:

1) Effect of vitamin C (VC) on total antioxidant status (TAS) in human plasma

2) usefulness of VC on TAS in the treatment of patients with paraquat poisoning

- type:

In vitro , pharmacokinetic , human

A1) Effect of vitamin C on plasma total antioxidant status in patients with paraquat intoxication

- Methods

1) various concentrations (1–100 mg/dl) of VC in pooled plasma from 10 volunteers → and TAS was measured.

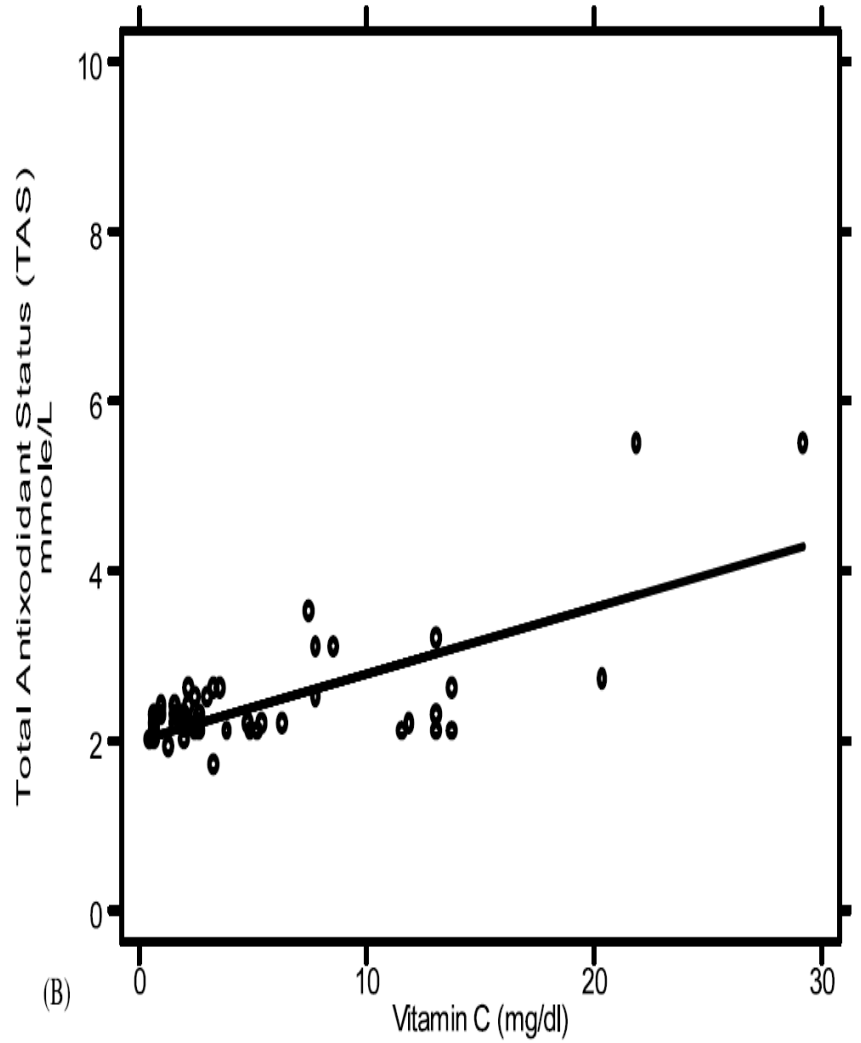
2) VC (50 mg/kg) in seven volunteers → TAC (at 0.5, 1, 2, 3, 5, 7, 9, and 11 h) and Pharmacokinetic.

3) VC (100, 500, 1000, 3000 mg/day, and 3000 mg/8 h) in 10 PQ cases for 5 days →TAS 1 h after each injection

A1) Effect of vitamin C on plasma total antioxidant status in patients with paraquat intoxication

- results

- 1) Positive correlations between vitamin C and TAS
- 2) in seven volunteers after injection of 3000 mg vitamin C → Vd= 32.0, Clearance =2.13 l/h, half life (*T*1/2)=1.0+/- 0.8 h
- 3) As the amounts of vitamin C were increased over 5 consecutive days in 10 PQ patients, TAS was increased
- All patients were recovered within mean (SD) 21.2 (5.4) admission days



A1) Effect of vitamin C on plasma total antioxidant status in patients with paraquat intoxication

- Conclusion

- VC was a significant antioxidant as TAS in human plasma and that increased TAS by high doses of VC could be useful as a free radical scavenger for paraquat poisoned patients.

- اشکالات

✓شدت مسمومیت بیماران پارا کوات مشخص نبود

✓ سایر درمان ها مشخص نبود

A2

RESEARCH ARTICLE

Beneficial effects of ascorbic acid to treat lung fibrosis induced by paraquat

Marcia Rodrigues da Silva[1], Adriana Schapochnik[1], Mayara Peres Leal[1], Janete Esteves[1], Cristina Bichels Hebeda[1], Silvana Sandri[2], Christiane Pavani[1], Anna Carolina Ratto Tempestini Horliana[1], Sandra H. P. Farsky[2], Adriana Lino-dos-Santos-Franco[1]*

aimed at investigating the role of oxidative stress in pulmonary fibrosis that was caused as the result of an acute PQ intoxication, by studying the effects of vitamin C on several parameters of lung lesions.

The data has clearly shown that oxidative stress was the main mechanism of lung fibrosis that was caused by an acute intoxication of PQ in the studied mice and that vitamin C may be a remarkable tool for treating this type of an intoxication.

Type: animal model mice

A2) Beneficial effects of ascorbic acid to treat lung fibrosis induced by paraquat

- Method:
- Seven days after the PQ or vehicle injections, the mice received vitamin C (150 mg/kg, ip, once a day) or the vehicle, over the following 7 days → bronchoalveolar lavage fluid (BALF). IL-7, SOD

- Results :

1)Vitamin C treatment reduced the number of neutrophils, macrophages and lymphocytes into the BALF of fibrotic mice

2) Vitamin C treatment reduced levels of IL-6, IL-17 and TGF-β in the lung homogenates of PQ-induced fibrosis

3) Vitamin C treatment decreased collagen deposition in the lung of fibrotic Mice

4) Vitamin C treatment increased the activity of antioxidant enzymes in the lung homogenates of fibrotic mice

5) Vitamin C treatment did not alter the maximum contractile response to methacholine in fibrotic mice

A2) Beneficial effects of ascorbic acid to treat lung fibrosis induced by paraquat

Discussion:

- The role of vitamin C on the production of the inflammatory mediators is controversial and the effects seem to be dependent on the cell type and/or the inflammatory conditions

- ایراد ها

- حجم کم نمونه

- In this study 3 sets of experiments were carried out, using 2 animals in each group, totalizing 6 animals per group

A3

Available online at www.sciencedirect.com
ScienceDirect
Toxicology in Vitro 22 (2008) 515–524
Toxicology in Vitro
www.elsevier.com/locate/toxinvit

Paraquat toxicity in a mouse embryonic stem cell model

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Aim: examined was the ability of vitamin C, at concentrations based on the RDA, to protect against paraquat injury effects

Type :
Cell culture , co-treatment

- ✓ Combining paraquat treatments with 1-, 10- or 20-fold RDA of vitamin C restored the percentages of live cells to control values (100%, 103% and 102%, respectively).
- ✓ Ascorbic acid alone resulted in percentages of live mES cells similar to the control treatment

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A4

The Comparative Effects of Vitamin E + C on the Chronic Toxicity of Paraquat in Albino Rats (*Rattus norvegicus*)

Okolonkwo, Benjamin Nnamdi [a*], Amadi, Chikadibia Fyneface [a], Chukwubike, Udoka Okeke [b] and Nyenke, Clement Ugochukwu [a]

Aim : this study, focused at evaluating the ameliorative effects of a combination of vitamin E and C therapy on liver of paraquat induced male albino rats.

Type= animal , chronic toxicity , hepatotoxicity

A4) The Comparative Effects of Vitamin E + C on the Chronic Toxicity of Paraquat in Albino Rats

Chart 1. Design grouping

Main group	Sub-group
A=no paraquat induction	A_0= without Vit E+C treatment
	A_{ve}= with Vit E+C treatment
B=0.02g of paraquat induction	B_0= without Vit E+C treatment
	B_{ve}= with Vit E+C treatment
C=0.04g of paraquat induction	C_0= without Vit E+C treatment
	C_{ve}= with Vit E+C treatment
D=0.06g of paraquat induction	D_0= without Vit E+C treatment
	D_{ve}= without Vit E+C treatment

N=50 rats per main group; N=25 rats per subgroup

500mg of vitamin E weekly oral
2000mg/l of C medicated water
one month.

A4)The Comparative Effects of Vitamin E + C on the Chronic Toxicity of Paraquat in Albino Rats

Table 1. Inter-group comparison of paraquat liver toxicity in male albino rats

Sub-group	T. Bilirubin (µmol/L)	D. Bilirubin (µmol/L)	T. Protein (g/dL)	Albumin (g/dL)	Globulin (g/dL)
A_0	0.81 ± 0.35	0.14 ± 0.03	7.52 ±0.25	3.90 ± 0.01	3.62 ± 0.03
B_0	3.53 ± 0.79[a]	1.10 ± 0.03[a]	6.05 ±0.38[a]	3.16 ± 0.01[a]	2.89 ± 0.03
C_0	9.29 ± 2.53[a]	1.08 ± 0.03[a]	6.26 ±0.57[a]	3.40 ± 0.03[a]	2.86 ± 0.03
D_0	13.56 ± 3.14[a]	1.57 ± 0.04[a]	6.54 ±0.51[a]	3.21 ± 0.04[a]	3.32 ± 0.02

Statistical significance: P ≤ 0.05

Table 2. Inter-group comparison of Vit E and C combination therapy on male albino rats

Sub-group	T. Bilirubin (µmol/L)	D. Bilirubin (µmol/L)	T. Protein (g/dL)	Albumin (g/dL)	Globulin (g/dL)
A_{VEC}	1.44 ± 0.29	0.23 ± 0.04	7.34 ±0.30	4.06 ± 0.03	3.28 ± 0.03
B_{VEC}	3.05 ± 0.62[a]	0.50 ± 0.01[a]	6.73 ±0.25[a]	3.54 ± 0.01[a]	3.19 ± 0.02
C_{VEC}	5.10 ± 0.69[a]	0.55 ± 0.02[a]	6.38 ±0.24[a]	3.32 ± 0.01[a]	3.05 ± 0.01
D_{VEC}	9.15 ± 2.29[a]	0.65 ± 0.02[a]	6.53 ±0.26[a]	3.27 ± 0.02[a]	3.26 ± 0.02

Statistical significance: P ≤ 0.05

A4) The Comparative Effects of Vitamin E + C on the Chronic Toxicity of Paraquat in Albino Rats

Table 3. Inter and Intra groups comparison of liver markers after one month treatment period.

Sub-group	T. Bilirubin (µmol/L)	D. Bilirubin (µmol/L)	T. Protein (g/dL)	Albumin (g/dL)	Globulin (g/dL)
A_0	0.81 ± 0.35	0.14 ± 0.03	7.52 ±0.25	3.90 ± 0.01	3.62 ± 0.03
A_{VEC}	1.44 ± 0.29	0.23 ± 0.04	7.34 ±0.30	4.06 ± 0.03	3.28 ± 0.03
B_0	3.53 ± 0.79^{a}	1.10 ± 0.03^{a}	6.05 ± 0.38^{a}	3.16 ± 0.01^{a}	2.89 ± 0.03
B_{VEC}	$3.05 \pm 0.62^{a,b}$	$0.50 \pm 0.01^{a,b}$	6.73 ± 0.25^{a}	3.54 ± 0.01^{a}	3.19 ± 0.02
C_0	9.29 ± 2.53^{a}	1.08 ± 0.03^{a}	6.26 ± 0.57^{a}	3.40 ± 0.03^{a}	2.86 ± 0.03
C_{VEC}	$5.10 \pm 0.69^{a,b}$	$0.55 \pm 0.02^{a,b}$	6.38 ± 0.24^{a}	3.32 ± 0.01^{a}	3.05 ± 0.01
D_0	13.56 ± 3.14^{a}	1.57 ± 0.04^{a}	6.54 ± 0.51^{a}	3.21 ± 0.04^{a}	3.32 ± 0.02
D_{VEC}	$9.15 \pm 2.29^{a,b}$	$0.65 \pm 0.02^{a,b}$	6.53 ± 0.26^{a}	3.27 ± 0.02^{a}	3.26 ± 0.02

Statistical significance: $P \leq 0.05$

- *Index (a) = represents a statistically significant difference among inter-groups such as (Ao, Bo, Co and Do) and (Ave, Bve, Cve and Dve)*
- *Index (b) = represents a statistically significant difference observed within each group (i.e. Group B: B_0Vs B_{VE})*

A4) The Comparative Effects of Vitamin E + C on the Chronic Toxicity of Paraquat in Albino Rats

CONCLUSION

Finally, this study reveals that a combination of Vitamin E + C therapy has ameliorative potency on liver excretory function than protein synthetic function on one month weekly treatment after prolong paraquat induced liver damage in male albino rats.

انتقاد

مقاله ضعیف نوشته شده بود

مسمومیت مزمن تنها در کبد بررسی شده بود

در مورد سمیت مزمن کار میکرد نه حاد

جداگانه ویتامین ها بررسی نشده بود و رژیم توام بود

معلوم نیست اثرات مربوط به کدامیک از ویتامین ها است

Advances in Research

23(3): 32-37, 2022; Article no.AIR.86825
ISSN: 2348-0394, NLM ID: 101166096

A5

Synergistic Effect of Vitamin E and C Treatment on Paraquat Induced Haemotoxicity in *Rattus norvegicus*

Okolonkwo, Benjamin Nnamdi [a*], Jonathan, Nyebuchi [b], Adjekuko, Ohwonigho Collins [c] and Zebedee, Loveday Udu [d]

Sub-group	Hb(g/dL)	PCV (%)	T-WBC	Neutrophil	Lymphocytes
A_0	22.42 ± 0.46	66.50 ± 1.36	9.05 ± 0.35	40.0 ± 2.1	60.0 ± 2.1
A_{VEC}	21.70 ± 1.86	64.67 ± 5.19	9.70 ± 0.72	37.2 ± 2.6	62.8 ± 2.6
B_0	16.78 ± 2.71[a]	51.17 ± 7.37[a]	10.32 ± 0.69	39.3 ± 1.6	60.7 ± 1.6
B_{VEC}	18.92 ± 1.71[a,b]	57.50 ± 4.33[a,b]	8.65 ± 0.51	40.2 ± 1.9	59.8 ± 1.9
C_0	15.12 ± 2.21[a]	47.33 ± 5.78[a]	10.10 ± 0.66	46.3 ± 2.4	53.7 ± 2.4
C_{VEC}	19.68 ± 1.26[a,b]	59.00 ± 3.52[a,b]	9.80 ± 0.56	43.7 ± 2.5	56.3 ± 2.5
D_0	14.07 ± 2.23[a]	44.00 ± 5.87[a]	9.50 ± 1.01	38.8 ± 2.3	61.2 ± 2.3
D_{VEC}	17.43 ± 1.99[a,b]	53.33 ± 5.28[a,b]	8.02 ± 0.87	33.8 ± 2.6	66.2 ± 2.6

Statistical significance: $P \leq 0.05$

A6

Paraquat 중독에서 Vitamin C의 항산화성 효과에 관한 연구

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김성혜 · 정중식 · 권운용 · 이중의 · 서길준 · 정성은* · 윤여규

= Abstract =

The Antioxidant Effect of Vitamin C on the Paraquat Poisoning

Sung Hye Kim, M.D., Jung Sik Jeung M.D., Wun Yong Kwon M.D.,
Joong Eui Rhee M.D., Gil Joon Suh M.D., Sung Eun Jung M.D., Yeo Kyu Youn M.D.*
Department of Emergency Medicine, Department of Pediatric Surgery,*
College of Medicine, Seoul National University

Methods : 24 rats were divided to 6 groups after paraquat injection(20mg/kg), and each group has 4 rats. In 2 control groups we only observed until 6hours and 24hours. And Vitamin C of 10 mg per kilogram body weight on the low dose group and 100 mg per kilogram body weight on the high dose group were injected simultaneously. And in 6hours group, after 6hours of paraquat and vitamin C injection biochemical levels of malondialdehyde, superoxide dismutase and catalase were measured in liver and lung. And in 24 hours group after 24 hours the same mea-

Simultaneously , low dos and high does

Conclusion : High dose Vitamin C suppresses lipid peroxidation, increases catalase activity and superoxide dismutase activity in paraquat intoxiation. It is thought to by antioxidant effect of vitamin C but it's effect is observed only in 24hours after intoxication.

A7

cells

MDPI

Article

Topical Ascorbic Acid Ameliorates Oxidative Stress-Induced Corneal Endothelial Damage via Suppression of Apoptosis and Autophagic Flux Blockage

Yi-Jen Hsueh [1,2], Yaa-Jyuhn James Meir [2,3], Lung-Kun Yeh [1,4], Tze-Kai Wang [1,2], Chieh-Cheng Huang [2,5], Tsai-Te Lu [2,5], Chao-Min Cheng [2,5], Wei-Chi Wu [1,3] and Hung-Chi Chen [1,2,3,*]

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we aim to investigate the protective effect of ascorbic acid against oxidative stress in HCEC.

Type: Cell culture , pretreatment
animal (rabbit) model

A7) Topical Ascorbic Acid Ameliorates Oxidative Stress-Induced Corneal Endothelial Damage via Suppression of Apoptosis and Autophagic Flux Blockage

- Cell lines :

1) The human retinal pigment epithelium cell line ARPE-19
2) human corneal endothelial cell line B4G12
3) rabbit corneal endothelial cells (CECs)

Study: paraquat-induced cell damage model, + pretreatment by ascorbic acid

- Results:

1) Ascorbic Acid Attenuates Oxidative Stress-Induced Cell Injury
2) Ascorbic Acid Ameliorates Paraquat-Induced ROS and Oxidative Stress-Induced Apoptosis and Autophagic Flux Blockage in B4G12 and ARPE-19 Cells

A7) Topical Ascorbic Acid Ameliorates Oxidative Stress-Induced Corneal Endothelial Damage via Suppression of Apoptosis and Autophagic Flux Blockage

- In Vivo Rabbit Corneal Damage Model
- Rabbits received administration of 5% ascorbic acid (284 mmol/L in BSS solution) to the cornea three times a day for two days. Subsequently, 25 mM paraquat (diluted in BSS, total 20 mL) injected into the anterior chamber

✓**Afterwards**, the topical administration of ascorbic acid three times a day was continued for two days.5 mM paraquat (diluted in BSS, total 20 mL)

- Results:
- Topical Ascorbic Acid Ameliorates Oxidative Stress-Induced Corneal Endothelial Damage in Rabbits

- ایراد

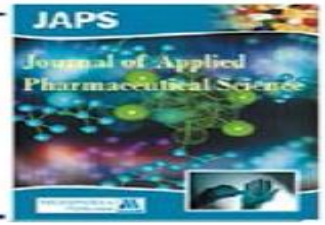
- پیش درمان

A8

Journal of Applied Pharmaceutical Science 01 (06); 2011: 85-91

Journal of Applied Pharmaceutical Science

Available online at www.japsonline.com



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Supplementation of vitamins C, E and its combination on paraquat-intoxicated rats: effects on some biochemical and markers of oxidative stress parameters

Akinloye O.A., Adamson I., Ademuyiwa.O and Arowolo T.A

this study was therefore carried out to investigate ameliorating effect of antioxidant vitamins (vitamins C and E) and its combination in both pre- and post-treatments against PQ toxicity.

Type: animal , pre and post-treatment

A8) Supplementation of vitamins C, E and its combination on paraquat-intoxicated rats: effects on some biochemical and markers of oxidative stress parameters

- method

groups:

1) Normal saline gavage
2) PQ (150mg /kg)
3) PQ (150mg /kg) post treated VIT C (1000mg/Kg)
4) PQ (150mg /kg) post treated VIT E (300mg/Kg)
5) PQ (150mg /kg) post treated Vit c +Vit E
6) PQ (150mg /kg) pretreated VIT C (1000mg/Kg)
7) PQ (150mg /kg) pretreated VIT E (300mg/Kg)
8) PQ (150mg /kg) pretreated Vit c +Vit E

A8) Supplementation of vitamins C, E and its combination on paraquat-intoxicated rats: effects on some biochemical and markers of oxidative stress parameters

Pretreatment with vitamins C → 40%
Pretreatment E → 20%
Pretreatment C+E → 20%

posttreatment with vitamins C → 80%
posttreatment E → 20%
posttreatment C+E → 20%

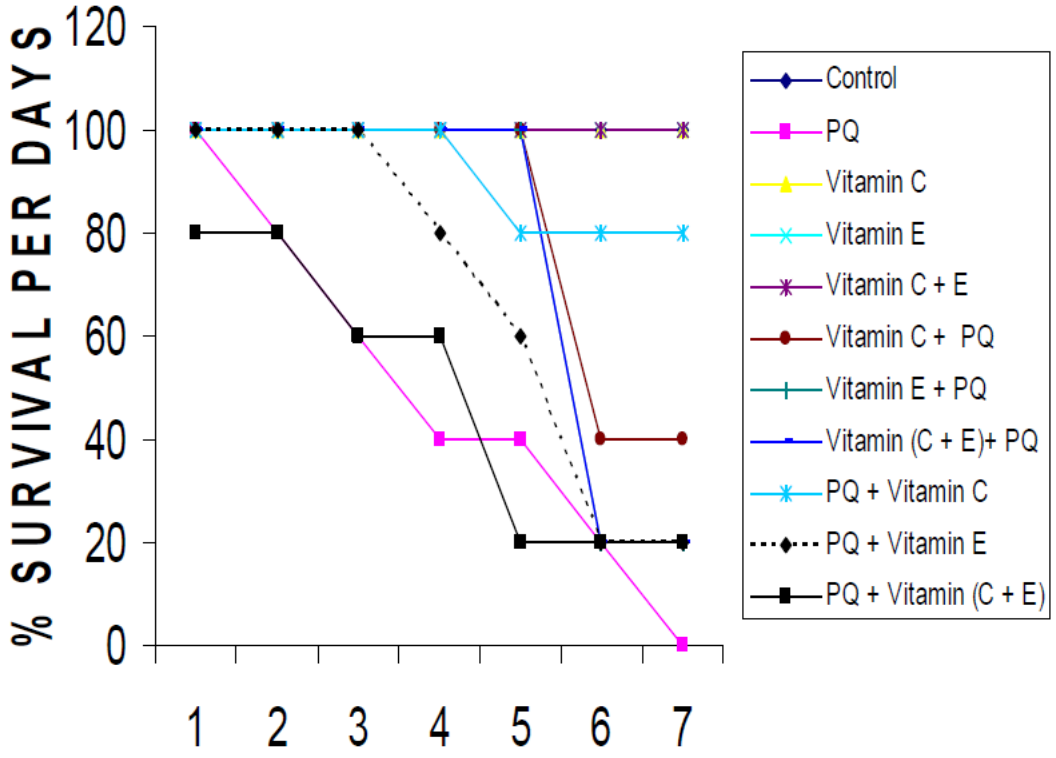

FIG. 1: Effects of treatments of the survival rate of rats given lethal dose (150mg/Kg) of paraquat.

A8) Supplementation of vitamins C, E and its combination on paraquat-intoxicated rats: effects on some biochemical and markers of oxidative stress parameters

- method

groups seconds :

1) Normal saline gavage
2) PQ (70 mg /kg)
3) PQ (70 mg /kg) post treated VIT C (1000mg/Kg)
4) PQ (70 mg /kg) post treated VIT E (300mg/Kg)
5) PQ (70 mg /kg) post treated Vit c +Vit E
6) PQ (70 mg /kg) + VIT C (1000mg/Kg)pretreated (for seven days before PQ)
7) PQ (70 mg /kg) VIT E (300mg/Kg) pretreated (for seven days before PQ)
8) PQ (70 mg /kg) pretreated Vit c +Vit E
9) PQ (70 mg /kg) pre and post treated VIT C
10) PQ (70 mg /kg) pre and post treated VIT E
11) PQ (70 mg /kg) pre and post treated VIT C+E

A8) Supplementation of vitamins C, E and its combination on paraquat-intoxicated rats: effects on some biochemical and markers of oxidative stress parameters

ایراد ها

1) گروه ها وروش درمان خیلی واضح نبود (چقدر قبل ، چقدر بعد)
2) نوشته که 24 ساعت بعد از دریافت اخرین دوز حیوانات خونگیری و کشته میشند ولی از طرفی درصد میزان بقا را تا 7 روز نشان میدهد
3) گروه های 70 میلی گرم پار کوات را با 150 مقایسه می کند
4) نتایج و جداول غیر قابل استفاده بود
5) مطالعه خوب طراحی شده بود وبسیار بد نوشته شده بود

A9 and B1

Original Article

In Vivo Dual Effects of Vitamin C on Paraquat-Induced Lung Damage: Dependence on Released Metals from the Damaged Tissue

Soon Ahkang, Yeon Jin Jang & Hyoungsuf' Park

Pages 93-107 | Received 23 May 1997, Accepted 01 Aug 1997, Published online: 07 Jul 2009

Download citation https://doi.org/10.3109/10715769809097880

Free Radical Research
Volume 28, 1998 - Issue 1

An pro-oxidant role of vitamin C has been suggested, but direct evidence for it is scant. Here, we report the dual role of vitamin C on paraquat-induced lung injury, which appears to depend on the metal ions released from damaged cells.

Vitamin C (10 mg/kg) given at the time when the extensive tissue damage was in progress aggravated the oxidative damage, while it protected against the damage when given before the initiation of the damage.

Deferoxamine, given intraperitoneally as a bolus dose of 50 mg/ **kg,** completely blocked the aggravation of oxidative damage by vitamin C. Moreover, deferoxamine unmasked the antioxidant effect of vitamin C.

A9 &B 1) In Vivo Dual Effects of Vitamin C on Paraquat-Induced Lung Damage: Dependence on Released Metals from The Damaged Tissue

- vitamin C accelerates the generation of hydroxyl radicals upto several hundred times by accelerating the redox cycling of **Fe+++F/ e++** when it exists with free transition metal ions in the aqueous phase

- ✓ Our hypothesis is that vitamin C given before paraquat would protect the lung by quenching radicals as soon as they are produced.
- ✓ When vitamin C is given to ongoing tissue damage, it would aggravate the damage by interacting with free metal ions released from damaged cells to accelerate the hydroxyl radical production.

A9 &B 1) In Vivo Dual Effects of Vitamin C on Paraquat-Induced Lung Damage: Dependence on Released Metals from The Damaged Tissue

- Intravenous administration of 10 mg/kg vitamin C 5 minutes before the paraquat injection ('pretreatment of vitamin *C')* reduced ethane production by 60.2 +/- 5.4%.
- vitamin C given 1 hour after the paraquat injection ('post-treatment of vitamin C') increased the paraquat-induced ethane production by 44.2 +/- 3.5%.

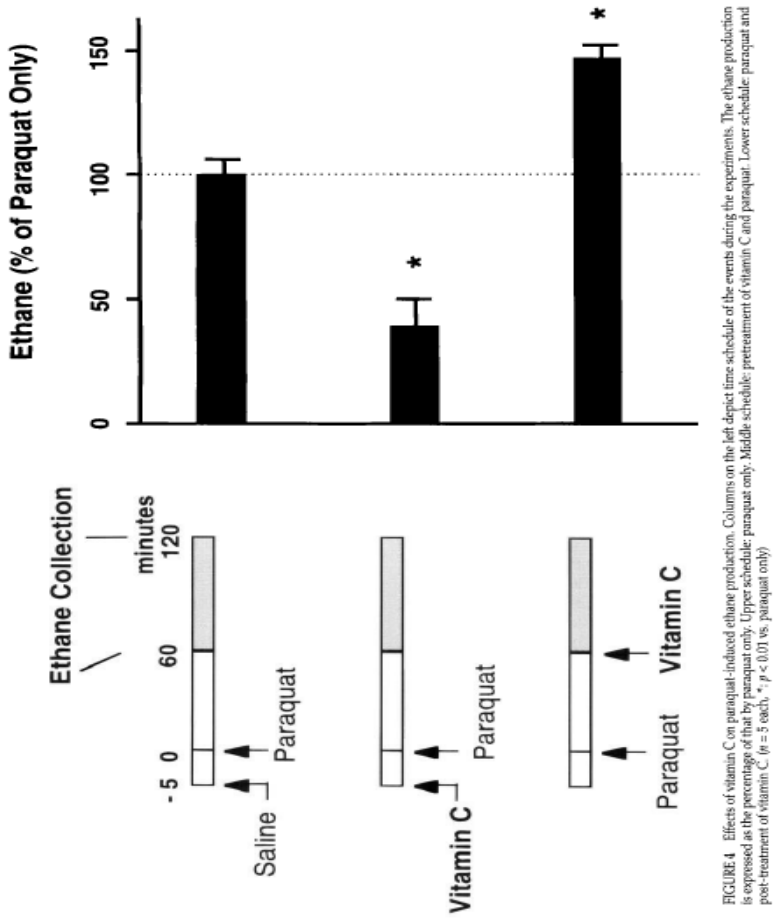

FIGURE 4 Effects of vitamin C on paraquat-induced ethane production. Columns on the left depict time schedule of the events during the experiments. The ethane production is expressed as the percentage of that by paraquat only. Upper schedule: paraquat only. Middle schedule: pretreatment of vitamin C and paraquat. Lower schedule: paraquat and post-treatment of vitamin C. ($n = 5$ each, * $p < 0.01$ vs. paraquat only)

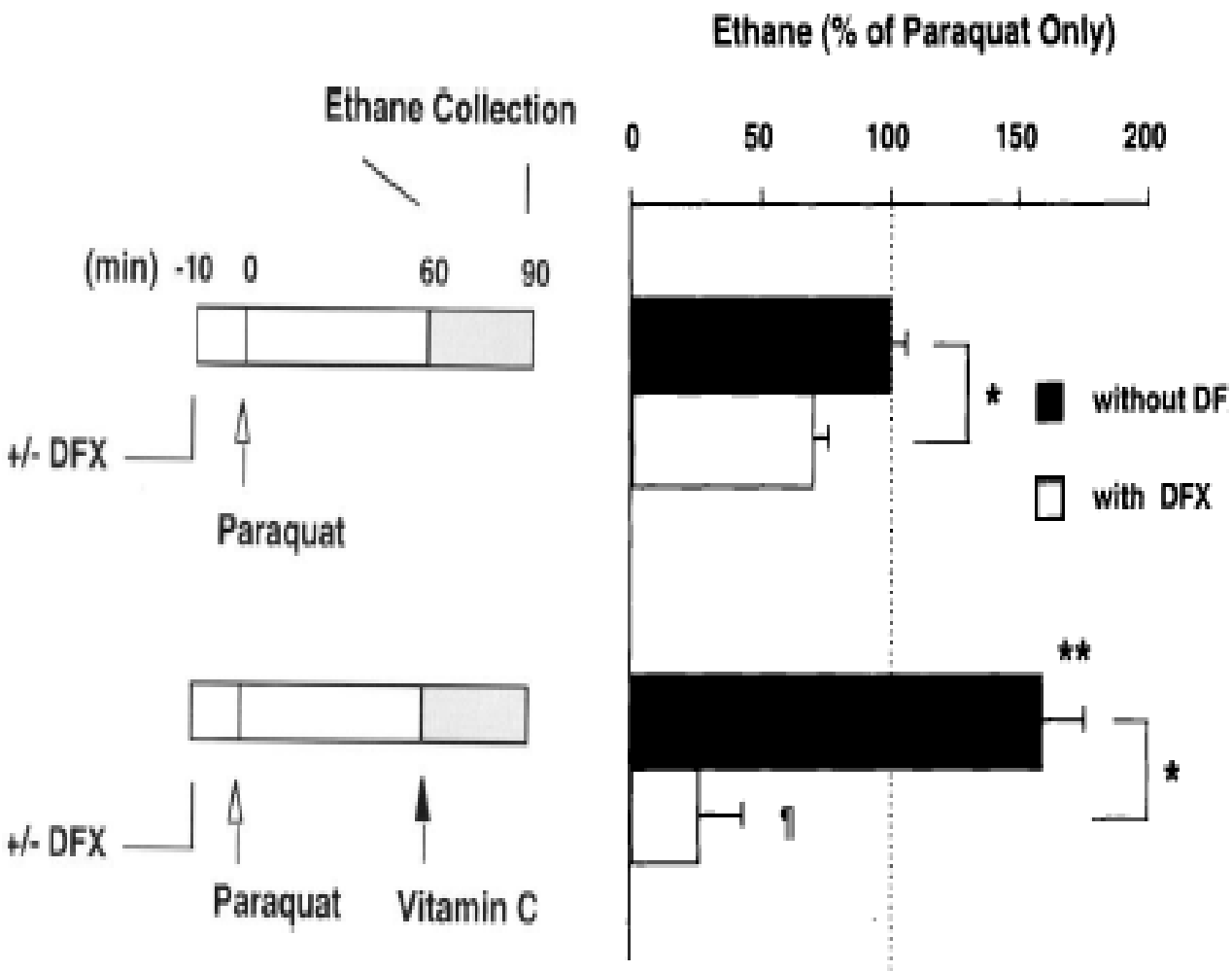

FIGURE 5 Effect of deferoxamine on expiratory ethane. Upper schedule: paraquat with/without deferoxamine (DFX; 10 mg/kg in saline). Lower schedule: paraquat plus pre treatment of vitamin C with/without deferoxamine ($n = 5$ each, *: $p < 0.01$ between with and without deferoxamine, **: $p < 0.01$ vs. paraquat only without deferoxamir ¶: $p < 0.05$ vs. deroxamine only on paraquat)

A10 & B2

Human and Experimental Toxicology
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SAGE

The efficacy of high doses of vitamin C in patients with paraquat poisoning

Jeong Mi Moon and Byeong Jo Chun

The purpose of this study was to assess the effect of high doses of vitamin C in combination with anti-inflammatory and immunosuppressant therapy in patients with PQ poisoning.

Type:
Human , retrospective , comparing two group

A10 &B2) The efficacy of high doses of vitamin C in patients with paraquat poisoning

- hospital medical record system
- The patient selection criteria were as follows:

✓age > 18 Y

✓24 hours after exposure to PQ between

- A total of 229 patients were identified.
- 18 underlying disease
- 11 missing data or not dithionate test
- 15 unknown amount of ingested PQ
- 10 unknown time of exposure
- 32 referred to other hospital
- 9 non oral

A10 &B2) The efficacy of high doses of vitamin C in patients with paraquat poisoning

- A total of 134 patients were finally identified.

- ✓ **57 patients**
- ✓ **January 2004 and September 2005**
- ✓ **gastric lavage**
- ✓ **12.5 g of Fuller's earth was given through a nasogastic tube every 2 hours five times.**
- ✓ **infusion of 10 mg of dexamethasone q8h for 14 days. 1 g of cyclophosphamide in 200 ml of 5% dextrose saline (DS) given for 2 days,**
- ✓ **1 g of methylprednisolone in 200 ml of 5% DS infused for 3 days.**
- ✓ **morphine for pain .**
- ✓ **furosemide + fluid → urine output → 1ml/kg/h**

- ✓ 77 patients
- ✓ Between October 2005 and January 2008 r
- ✓ received the same treatment plus a high-dose regimen of vitamin C for 14 days after admission.
- ✓ One gram of vitamin C in 500 ml of 5% DS was infused as a loading dose, and then 4 g of vitamin C was infused daily for 14 days.

To keep the vitamin C from being exposed to light, the vinyl bag and the line of the vitamin C were wrapped in a dark bag.

The efficacy of high doses of vitamin C in patients with paraquat poisoning

Table 1. The characteristics of two groups with paraquat poisoning

	Group 1 ($N = 57$)	Group 2 ($N = 77$)	p Value
Age (yr)	52.0 ± 15.8	52.0 ± 17.9	0.980
Male	36 (63.2%)	42 (54.5%)	0.377
Cardiovascular disease	3 (5.3%)	11 (14.3%)	0.091
Diabetes mellitus	1 (1.8%)	3 (3.9%)	0.744
Time interval (min)[a]	208.7 ± 121.7	232.0 ± 195.2	0.429
Amount of PQ ingested (mL)	131.5 ± 101.4	136.3 ± 144.5	0.847
Gastric lavage within 2 hours[b]	43 (75.4%)	56 (72.7%)	0.724
Administration of Fullers' earth	57 (100.0%)	77 (100.0%)	1.000
Serum paraquat concentration (μg/mL)	25.2 ± 43.2	34.9 ± 47.0	0.224
Sodium dithionite urine test[c]	7 L,5 N,45 D	14 L, 4 N, 59 D	0.503
Severity index of PQ poisoning			0.094
<10; survival	29 (50.9%)	25 (32.5%)	
10–50; death from lung fibrosis	6 (10.5%)	13 (16.9%)	
>50; death from circulatory failure	39 (50.6%)	22 (38.6%)	
Systolic blood pressure (mmHg)	134.9 ± 27.7	137.9 ± 22.1	0.482
pH	7.38 ± 0.08	7.37 ± 0.008	0.792
$PaCO_2$ (mmHg)	28.2 ± 8.2	29.5 ± 7.6	0.360
PaO_2 (mmHg)	95.8 ± 23.5	96.3 ± 29.4	0.919
Base deficit (mmol/L)	−7.8 ± 7.0	−7.7 ± 6.5	0.957
HCO_3− (mEq/L)	16.3 ± 6.0	17.5 ± 5.4	0.251
WBC (/mm^3)	14,107 ± 7581	15,668 ± 9635	0.316
BUN (mg/dL)	15.0 ± 5.0	13.5 ± 5.5	0.108
Cr (mg/dL)	1.4 ± 0.7	1.1 ± 0.5	0.087
K (mEq/L)	3.1 ± 0.6	3.0 ± 0.6	0.617
ALT (U/L)	30.3 ± 58.0	33.7 ± 31.9	0.662

Abbreviations: PQ: paraquat, WBC: white blood cells, BUN: blood urea nitrogen, ALT: alanine aminotransferase.

NS

A10 &B2) The efficacy of high doses of vitamin C in patients with paraquat poisoning

Table 2. The outcome of paraquat poisoning in both groups

	Group 1 (N = 57)	Group 2 (N = 77)	p Value
Mortality	45 (78.9%)	54 (70.1%)	0.321
Duration of survival (hours)[a]	36.62 ± 32.2	39.3 ± 41.2	0.740
Complication			
Acute kidney injury	36 (63.2%)	32 (41.6%)	0.013
Peak serum Cr (mg/dL)	3.2 (1.6–7.3)	4.0 (2.1–5.9)	0.527
Hepatitis	20 (35.1%)	16 (21.1%)	0.071
Peak serum ALT (U/L)	142 (77–676)	241 (74–677)	0.654
Hypoxia	16 (28.1%)	26 (33.8%)	0.482
Lowest PaO_2 (mmHg)	59.7 (44.0–66.0)	57.2 (33.1–69.4)	0.665

Abbreviation: ALT: alanine aminotransferase.

[a]Duration of survival (hours): the survival time among patients who eventually died after PQ poisoning.

The peak levels of Cr and ALT and the lowest PaO_2 were expressed as the median with range.

- ✓ No significant difference in mortality
- ✓ No significant difference in the survival time
- ✓ No significant difference in the hepatitis and hypoxia

- ✓ The most common complication was acute kidney injury followed by hypoxia.

- ✓ **It is interesting to note that, although there were no differences in the serum peak level of Cr, the incidence of acute kidney injury was higher in group 1 than in group 2(VIT C).**

A10 &B2) The efficacy of high doses of vitamin C in patients with paraquat poisoning

- ✓ High-dose vitamin C treatment was significantly associated with an increase of the survival of patients with PQ poisoning,

- ✓ serum PQ concentration and the amount ingested showed a negative correlation with survival

Table 3. Independent predictors identified by multivariate analysis

Variable	β	OR	p Value	95% CI
High dose of vitamin C	−2.689	0.068	0.026	0.006–0.726
Amount ingested	0.056	1.051	0.019	1.008–1.096
Serum pararquat concentration (μg/mL)	0.457	1.576	0.027	1.054–2.365

Abbreviations: OR: odds ratios, CI: confidence interval

A10 &B2) The efficacy of high doses of vitamin C in patients with paraquat poisoning

- no convincing evidence for toxicity Vit C
- It is well known that vitamin C is a precursor of oxalate, liable to produce hyperoxaluria and renal failure related to hyperoxaluria, especially in the presence of
- ✓ previous renal insufficiency,
- ✓ Dehydration
- ✓ metabolic acidosis
- ✓ diarrhea
- ✓ oxalate-rich diet.

- McAllister et al. reported → that acute oxalate nephropathy occurred after the administration of a single 2.5 g dose of intravenous vitamin C in patients with previous renal injury.

- High doses of vitamin C → insulin effectiveness and glucose homeostasis in normoglycemic and diabetic adults.
- Intravascular hemolysis was reported in patients with glucose-6-phosphate dehydrogenase deficiency.

- Because of retrospective nature of this study → unable to determine urinary oxalate levels or other signs related to the toxic effects of high doses of vitamin

A10 &B2) The efficacy of high doses of vitamin C in patients with paraquat poisoning

- Limitations

1) retrospective nature
2) the optimal dosage and duration of administration of vitamin C need to be investigated in future studies.
3) Complications of Vit C
4) Because PQ can affect the excretion of vitamin C because of renal failure, the optimal dosage has to be decided based on pharmacokinetic data obtained by checking the serum level of vitamin C and dose-related side effects and responses in patients with PQ exposure.
5) The two treatments were not performed simultaneously.

In conclusion, addition of high-dose vitamin C to the treatment was effective in preventing acute kidney injury and it might be well tolerated by patients with PQ poisoning. It also might improve the outcome of patients with PQ poisoning

B3

Tropical Journal of Pharmaceutical Research February 2011; 10 (1): 27-31

Available online at http://www.tjpr.org

Research Article

Effect of Antioxidants on the Outcome of Therapy in Paraquat-intoxicated Patients

Nastaran Eizadi-Mood[1], Ali Mohammad Sabzghabaee[2*], Ahmad Yaraghi[1], Kamran Montazeri[1], Mojgan Golabi[3], Alireza Sharifian[3] and Shirinsadat Badri[2]

Table 1: Frequency distribution (%) of sex, age group and mortality rate in paraquat-poisoned patients for two study periods

Study period	Total	Sex		Age group (years)			Mortality rate (%)
		Male	Female	<19	19-34	>34	
First (1985-2001)	157	108(69%)	49 (31%)	54(34.5%)	63(40%)	40(25.5%)	(31%)
Second (2001-2005)	29	21(72.4%)	8(27.6%)	8(27.6%)	14(48.3%)	7(24.1%)	(55.2%)

ایراد
فاکتور ها مختلف موثر مثل دوز مصرفی مدت
مراجعه بعد از تماس ازمایشات کلیوی و کبدی
مدت درمان دیالیز و ... بررسی نشده است
آنالیز اماری مقایسه مرگ ومیر ها هم نبود

- ✓ group 1) conventional treatment protocol consisting of fluid replacement, oral absorbents, haemodialysis,
- ✓ group 2) daily 100 - 200 mg of vitamin E IM + 2400 – 3600 mg of vitamin C IV infusion for 3 - 5 days.

Clinical Toxicology (2012), **50**: 754–758

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DOI: 10.3109/15563650.2012.718783

B4

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RESEARCH ARTICLE

Effect of pirfenidone on pulmonary fibrosis due to paraquat poisoning in rats

method :(single PQ + 4 days treatment)

Five groups of ten rats

1) PQ IP 15 mg/kg + normal saline
2) PQ IP 15 mg/kg + VIT C (500 mg/kg, IP), Vit E (200 mg/kg, IP) and NAC (250 mg/kg, IV);
3) PQ IP 15 mg/kg + pirfenidone (200 mg/kg, IV)
4) Normal saline
5) pirfenidone (200 mg/kg, IV)

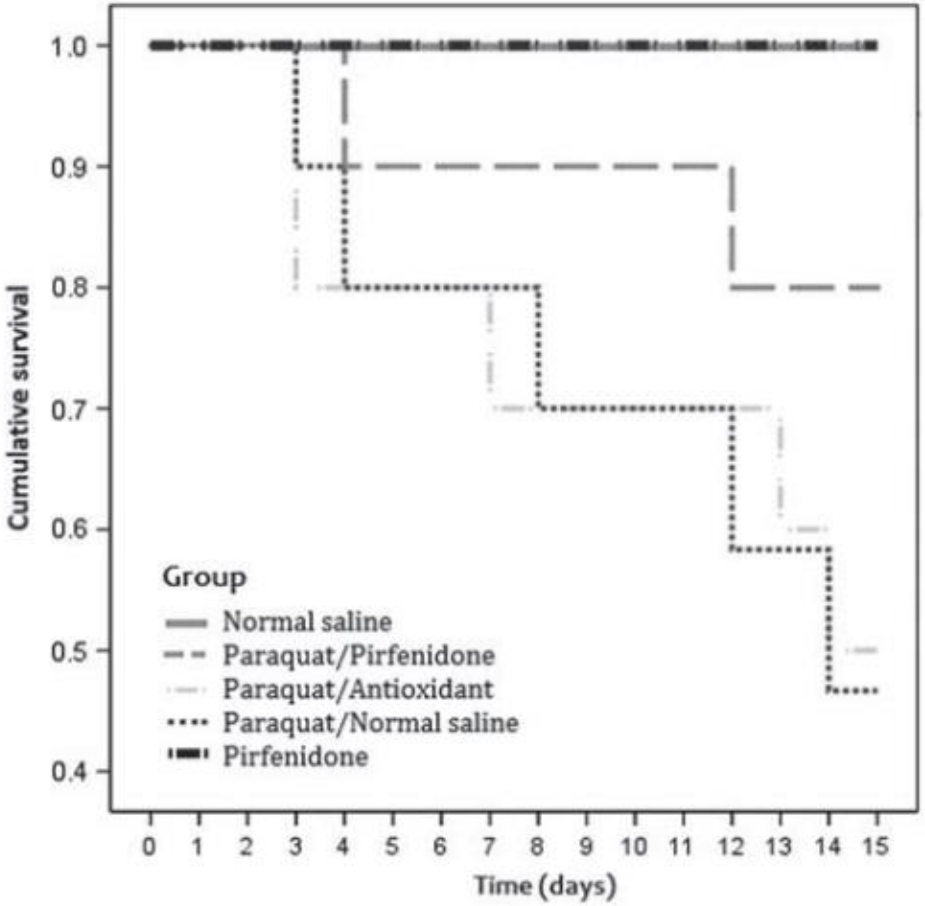

Fig. 2. Cumulative survivals of five different groups.

- ✓ Antioxidant-vitamin therapy in our study did not improve the survival of poisoned rats, which is not in accordance with the results of a number of previously published studies.
- ✓ Administration of higher doses and probably repeated boosters could be more efficient and could increase the survival of rats in the vitamin treatment group

Buendía et al. BMC Res Notes (2019) 12:584
https://doi.org/10.1186/s13104-019-4598-0

B5

BMC Research Notes

RESEARCH NOTE

Open Access

Comparison of four pharmacological strategies aimed to prevent the lung inflammation and paraquat-induced alveolar damage

Jefferson Antonio Buendía[1*], José Armando Justinico Castro[2], Laura Joanna Tapia Vela[2], Denis Sinisterra[1], Juana Patricia Sánchez Villamil[3] and Andrés Felipe Zuluaga Salazar[1]

Our objective was to compare the in vivo effect of five pharmacological options on inflammation, alveolar damage, and pulmonary fibrosis induced by PQ.

Type: animal model Rat

B5) Comparison of four pharmacological strategies aimed to prevent the lung inflammation and paraquat-induced alveolar damage

- Method:
- After 2 h post-intoxication with paraquat ion, groups of 9 animals were randomly assigned to (21 days) :

(1) cyclophosphamide plus dexamethasone

(2) low molecular weight heparin

(3) Unfractionated heparin

(4) vitamin C every 24 h (20, 40 or 60 mg/kg)

(5) atorvastatin

(6) placebo with intraperitoneal saline

B5) Comparison of four pharmacological strategies aimed to prevent the lung inflammation and paraquat-induced alveolar damage

Table 1 Number of rats by lung histopathological findings between treatments

Variable	Severity	Cicl/Dex n=9	Ator n=9	Vit C n=9	HepSC n=9	HepIT n=9	PQ n=9	p
Alveolar injury	Absent/mild	4	3	1	2	2	1	0.5275
	Moderate/severe	5	6	8	7	7	8	
Lung inflammation	Absent/mild	1	4	0	1	4	0	0.2699
	Moderate/severe	8	5	9	8	5	9	
Interstitial fibrosis	Absent/mild	7	9	9	7	8	9	0.2699
	Moderate/severe	2	0	0	2	1	0	

Cicl/Dex cyclophosphamide–dexamethasone, *Ator* atorvastatin, *Vit C* vitamin C, *HepSC* low molecular weight heparin, *HepIT* unfractionated heparin intratracheal, *PQ* paraquat

B5) Comparison of four pharmacological strategies aimed to prevent the lung inflammation and paraquat-induced alveolar damage

Table 2 Number of rats by liver and renal histopathological findings between treatments

Variable	Severity	Cicl/Dex n = 5	Ator n = 5	Vit C n = 4	HepSC n = 6	HepIT n = 4	PQ n = 8	p
Hepatocyte damage	Absent	0	1	3	4	3	2	0.057
	Present	5	4	1	2	1	6	
Hepatic regeneration	Mild	1	4	0	5	1	3	*0.009*
	Moderate	2	0	4	1	3	1	
	Severe	2	1	0	0	0	4	
Acute tubular necrosis	Absent	2	2	2	4	2	3	0.493
	Present	3	0	1	2	3	6	
Kidney congestion	Absent	5	2	3	6	4	5	0.067
	Present	0	0	0	0	0	4	

Cicl/Dex cyclophosphamide–dexamethasone, *Ator* atorvastatin, *Vit C* vitamin C, *HepSC* low molecular weight heparin, *HepIT* unfractionated heparin intratracheal, *PQ* paraquat

Hepatocyte damage = 0.222 , Hepatic regeneration=0.0150 , Acute tubular necrosis=0527, Kidney congestion=0.490

B5) Comparison of four pharmacological strategies aimed to prevent the lung inflammation and paraquat-induced alveolar damage

- Limitation:

✓ the small samples of sizes

✓use of semi-quantitative scales for pathology

✓No biochemical and qualitative test

B6

Free Radical Research ›
Volume 47, 2013 - Issue 12

Original Article

Treatment of acute paraquat intoxication using recommended megadose of vitamin C: A reappraisal

J.-B. Chang, C.-C. Lin, J.-F. Chiou, S.-Y. Mau, T.-Z. Liu & C.-H. Chen

Pages 991-1001 | Received 28 Mar 2013, Accepted 22 Aug 2013, Accepted author version posted online: 02 Sep 2013, Published online: 24 Sep 2013

B6)Treatment of acute paraquat intoxication using recommended mega dose of vitamin C: A reappraisal

- Main goal:
- vitamin C can promote aggravated production of hydroxyl radical (OH) via interacting with preexisting PQ/HO system in a nonmetal-catalyzed manner

- Type: cell culture
- method: cell culture (canine kidney (MDCK)cell) treated by PQ or PQ+Mega dose of vitamin C (MVC)

- Result: the severity of apoptotic killing was further exacerbated as (PQ+MVC) a nearly 7-fold increase

A New Treatment Approach for Acute Paraquat Poisoning

C1

Article *in* Journal of Research in Pharmacy Practice · April 2018
DOI: 10.4103/jrpp.JRPP_18_13

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The main components of our proposed new approach for the treatment of PQ poisoning are the utilization of hemodialysis, N-acetylcysteine, Vitamins C and E, silymarin, curcuma, pirfenidone, selenium, methylprednisolone, and pantoprazole.

C2

ELSEVIER

Toxicology 180 (2002) 65–77

TOXICOLOGY

www.elsevier.com/locate/toxicol

Role of antioxidants in paraquat toxicity

Zacharias E. Suntres *

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C2) Role of antioxidants in paraquat toxicity

- Although **prior administration** of ascorbic acid confers protection against paraquat toxicity, the use of ascorbic acid in treating paraquat-induced tissue injuries has resulted in unfavorable consequences
- ascorbic acid can accelerate the **generation** of hydroxyl radicals by accelerating the redox cycling of free transition metal ions (i.e.Fe3/Fe2) in the aqueous phase
- during extensive cellular damage, transition metals are released into the aqueous phase
- Ascorbic acid, given at a time when the extensive tissue damage induced by paraquat is **in progress**, **aggravates** the oxidative damage
- pretreating the animals with desferoxamine → reduced the exacerbation of the oxidative damage + Vit C (In PQ poisoning)

C3

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REVIEW ARTICLE

New insights into antioxidant strategies against paraquat toxicity

T. Blanco-Ayala, A. C. Andérica-Romero & J. Pedraza-Chaverri

Department of Biology, Faculty of Chemistry, National Autonomous University of Mexico (UNAM), University City, D.F., Mexico

C3) New insights into antioxidant strategies against paraquat toxicity

Table III. Summary of the antioxidant effects against PQ-induced toxicity.

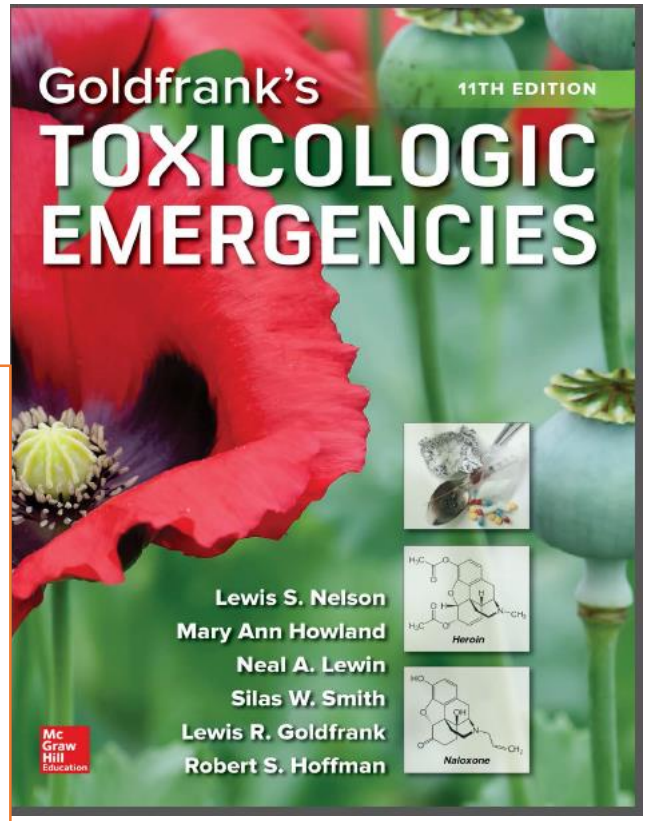
Effect on PQ-induced toxicity	Antioxidant
Inlammation markers	
↓Leukocytes nfiltration	*Naringin, LAS*
↓Neutrophils infiltration	*Naringin, BCe, LAS, Selenium*
↓TNF-α	*Naringin, Edaravone, Pirfenidone, LAS, PC, vitamin C*
↓TGF-β1	*Naringin, Pirfenidone, LAS*
↓NF-κB expression	*PC, Naringin, vitamin C*
↓IL-6	*Edaravone*
↓IL-1β	*PC*
Lung damage markers	
↓MMP-9	*Naringin, Edaravone*
↓ TIMP-1	*Naringin, Edaravone*
↓ HYP	*Naringin, LAS, PC*
↓ Cell migration to lung	*BCe, PC*
Alveolar space and density	*BCe, Selenium*
↓Haemorrhage	*BCe, LAS, Selenium*
↓Alveolar collapse	*BCe, LAS, Selenium*
CTGF	*Pirfenidone*
PDGF	*Pirfenidone*
Liver damage indicators	
↓ALT	*BCe*
↓AST	*BCe*
↓GGT	*BCe*
↓ALP	*BCe*
Redox state indicators	
↑ Nrf-2 expression	*Sylimarin, LA, Quercetin, BMe*
↑ NQO-1 activity	*Sylimarin, LA*
↑ HO-1 activity	*Sylimarin, Naringin, LA*
↑GPX activity	*Naringin, Edaravone, LA, LAS, Selenium, PC, BMe*
↑ SOD activity	*Naringin, Edaravone, BCe, LA, LAS, PC*
↑*CAT* activity	*BCe, LAS*
GSH content	*Quercetin, Selenium*
↓ ROS levels	*Sylimarin, LA, BMe, Vitamin C*
GST	*BMe*
γGCL	*BMe*
GR	*BMe*
Cellular viability markers	
Preserve plasma membrane	*Sylimarin, LA*
↓ LDH release	
Oxidative damage markers	
↓MDA, lipid proxidation	*BCe, LA, LAS, Selenium, PC*
↓ Protein carbonyl content	*BCe*
Cellular viability markers	
↑*LDH activity*	*Quercetin*
↑*MTT, XTT*	*Quercetin, BMe*
Apoptotic markers	
↓*Bax*	*LAS*
↓*Bak*	*LAS*
↑*Bcl-2*	*LAS*

C3) New insights into antioxidant strategies against paraquat toxicity

- Vit C → protecting the lung against free radicals present in the air content
- high dose of vitamin C → an antioxidant action in various clinical situations, such as renal allografts, severe burns, acute pancreatitis, and cardiovascular disease

- Although larger trials are needed to demonstrate whether high doses of vitamin C can function as a reliable therapy for PQ poisoning, this **recent evidence** points out vitamin C treatment as an alternative and efficient therapy

The choice of which interventions should be administered to a patient is made on a case-by-case basis by the treating physician in consultation with relevant resources.



Generation of reactive oxygen species is an important step in the pathogenesis of paraquat poisoning (Fig. 109–3). This leads to cytotoxicity, the extent of which depends on the concentration of paraquat and the efficiency of endogenous protective mechanisms such as vitamin C (ascorbic acid), vitamin E (α-tocopherol), and glutathione.

Administration of these vitamins and/or a glutathione donator (eg, N-acetylcysteine, S-carboxymethylcysteine, captopril) or other scavenging agents such as superoxide dismutase and amifostine and deferoxamine **is not routinely recommended because t**hey are not proven to be beneficial, and **potentially vitamin C might increase oxidative toxicity.**22

C4

22. Dinis-Oliveira RJ, et al. Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. *CRC Crit Rev Toxicol.* 2008;38:13-71.

نتیجه گیری

- ویتامین ث یک آنتی اکسیدان قوی و کم خطر است
- در مسمومیت پارکوات که اسیب ناشی از ان بدلیل سیستم استرس اکسیداتیو ایجاد می شود می تواند موثر باشد
- در صورت ادامه سمیت پار کوات و آسیب بافتی به نظر استفاده از ویتامین ث نمی تواند فایده اضافی داشته باشد و حتی ممکن است آسیب رسان باشد

سئوالات

- 1) چون ویتامین ث ترکیب قابل دیالیز است
- during hemodialysis, vitamin C is readily cleared, because it is a soluble, low-MW substance, and amounts of 50 mg or greater can be removed by a single treatment
  - آیا در بیمار پار کوات نیاز به افزایش دوز ویتامین ث در حین دیالیز نمی باشد ؟
- 2)در بیمارپاراکوات با نارسائی کلیه وکاهش کلیرانس دوز ویتامین ث تغییر کند
- 3) اگر ویتامین ث باعث افزایش آسیب بافتی می شود پس در مسمومیت قرص برنج هم ممکن است محدودت مصرف داشته باشد مخصوصا که سرعت آسیب در قرص برنج به عضله قلب خیلی زیاد است واین بافت بافتی غنی از آهن است . (Letter to editor

پیشنهادات

1) ارزیابی **total antioxidant** capacityدر بیماران پاراکوات اصفهان
2) ارزیابی میزان اتان بازدمی به عنوان شاخص آسیب ریوی در بیمارن پار کوات اصفهان
3) ارزیابی اگزالات ادراری در بیماران قرص برنج و پاراکوات که ویتامین ث می گیرند
4) کلینیکال ترایال با ویتامین ث
5) مطالعه حیوانی مناسب جهت پاسخ به سئوالت (پیش درمان ، درمان دو هفته ای درمان در هفته اول ودرمان در هفته دوم)