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Prophylactic Effect of Vitamin C on Cyclosporine A-induced Liver Toxicity

Maryam Mohsenikia [1], Babak Hajipour [2*], Mohammad Hossein Somi [3], Ali Khodadadi [4], Mehran Noori [5,6]

[1] Young Researchers Club, Tehran Medical Branch, Islamic Azad University, Tehran, IR Iran
[2] Young Researchers Club, Tabriz Branch, Islamic Azad University, Tabriz, IR Iran
[3] Gasteroenterology and Liver Research Center, Tabriz University of Medical Sciences, Tabriz, IR Iran
[4] Islamic Azad University, Science and Research Branch, Tehran, IR Iran
[5] Student Research Committee, Tehran Medical Branch, Islamic Azad University, Tehran, IR Iran
[6] Amiralmomenin Hospital Research Center, Tehran Medical Branch, Islamic Azad University, Tehran, IR Iran

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ABSTRACT

Background: Cyclosporine A (CsA) is an important immunosuppressive agent; however, its clinical use is limited by several side effects such as hepatotoxicity. Vitamin C (ascorbic acid) is a very important and powerful antioxidant and protects membranes against oxidation.
Objectives: The aim of this study was to study protective role of vitamin C against CSA-induced hepatotoxicity.
Materials and Methods: Thirty male Wister strain rats weighting 230-260g were randomly divided into 3 groups (n = 10): group A was the control group and received placebo (Normal Saline), group B was the CSA-treated group and received 15mg/kg/day CsA for 21 days, group C was the CsA + vitamin C group and was received 200mg/kg/day vitamin C orally 3 hours before receiving 15mg/kg/day CsA. On 22th day rats serum obtained for measuring biochemical factors including bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglyceride, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH), total protein, and albumin.
Results: Bilirubin, ALT, AST, triglyceride, ALP, and LDH levels were lower in CsA + ascorbic acid group than that of CsA group ($P < 0.05$) while plasma total protein and albumin were significantly higher in CsA + ascorbic acid group than that of CsA group ($P < 0.05$).
Conclusions: In conclusion, we have shown that vitamin C administration provides protection against CSA-induced injury in rat liver function and may have hepatoprotective role in the patients experiencing CSA treatment.

Implication for health policy/practice/research/medical education:
To reduce CsA-induced hepatotoxicity.

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* *Corresponding author:* Babak Hajipour, Young researchers club -Islamic Azad University, Tabriz Medical Branch, Post box: 51385-3633, Tabriz, IR Iran. Tel: +98-9141075936, Fax: +98-41147811496, *E-mail*: hajipourb@yahoo.com

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1. Background

Cyclosporine A (CsA) is an important immunosuppressive agent which is an essential part of drug regimen in transplant patients and in the treatment of diseases involving immune system (1). However, its clinical and experimental use is limited by several side effects such

as nephrotoxicity, cardiotoxicity, hypertension and hepatotoxicity (2). Different authors suggest that reactive oxygen species (ROS) production, oxidative stress, depletion of hepatic antioxidant system, and increase in malondialdehyde (MDA) be possible mechanisms of CsA hepatotoxicity (3-6). Fortunately, there are several antioxidant mechanisms that can neutralize free radicals in living organisms. Antioxidant defense mechanisms can be grouped by enzymatic antioxidants (mainly superoxide dismutase, glutathione peroxidase and catalase) and non-enzymatic antioxidants (e.g. tocopherols, carotenoids, ascorbic acid and others) that can neutralize free radicals (7). From non-enzymatic antioxidants, vitamin C (ascorbic acid) is a very important, and powerful, antioxidant, and protects membranes against oxidation. (8). Recent in vitro and ex-vivo studies have revealed that Vitamin C in plasma increases dose-dependent resistance to lipid peroxidation (9). Majority of in vivo studies have showed reduction in markers of oxidative DNA, lipid and protein damage after supplementation with vitamin C (10).

2. Objectives

The aim of this study was to study protective role of vitamin C against CsA-induced hepatotoxicity through studying changes in some plasma biochemical factors.

3. Materials and Methods

Thirty male Wister strain rats weighting 230-260g were randomly divided in to 3 groups (n=10); besides, they were kept in accordance with the "Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals". They had free access to commercial rat food and water. The CsA (Sigma-Aldrich Corp. St. Louis, MO, U.S.A.) oral solution (100 mg/mL15mg/kg/day) was delivered by oral gavage. Vitamin C (Osveh, Tehran, IR Iran) (100mg/mL, 200mg/kg/day) solution was given orally by gavage to CsA + Vitamin C group. Group A was the control group and received placebo (Normal Saline), group B was CsA-treated group and received 15mg/kg/day CsA for 21 days. Furthermore, group C was CsA + vitamin C group and was received 200mg/kg/day vitamin C orally by gavage 3 hours before receiving 15mg/kg/day CsA. treatment of oral vitamin C was started since 3 days before initiation of CsA therapy and continued during CsA treatment. Blood samples were obtained on day 22th under light ether anesthesia to study changes of bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglyceride, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) on commercial kits (Pars Azmoon, Karaj , IR Iran) by auto analyzer.

Values were expressed as mean ± SD. Statistical evaluation of significant difference between means was performed with one-way ANOVA test followed by Tukey post hoc test ($P < 0.05$ was considered significant) .

4. Results

The results are shown in *Table 1*. Bilirubin Level was significantly higher in the group B (0.179 ± 0.0144 mg/dL) than those of the group A (0.120 ± 0.008) and the group C (0.154 ± 0.014, $P < 0.05$). Also, there was a significant difference between the group B and the group C ($P < 0.05$). Alkaline phosphatase level in the group B (183.740±6.361 IU/L) was significantly higher than those of the group A (109.690 ± 7.018) and the group C (160.360 ± 6.565, $P < 0.05$). Also, there was a significant difference between group B and group C ($P < 0.05$). AST level in group B (131.690 ± 5.466 IU/L) was significantly higher than those of the group A (73.920 ± 5.463) and the group C (107.200 ± 4.885, $P < 0.05$). Furthermore, there was a significant difference between the group B and the group C ($P < 0.05$). ALT level in the group B (43.770 ± 3.391 IU/L) was significantly higher than those of the group A (25.460 ± 3.312) and the group C (33.523 ± 3.046, $P < 0.05$). Also, there was a significant difference between the group B and the group C ($P < 0.05$). Lactate Dehysrogenase level in the group B (1750.00 ± 37.392 IU/L) was significantly higher than those of the group A (1156.700 ± 27.252) and the group C (1521.200 ± 33.891, $P < 0.05$). Besides, there was a significant difference between the group B and the group C ($P < 0.05$). Total protein level in the group B (5.334 ± 254

Table1. Serum levels of bilirubin, Total protein, Albumin, ALT, AST, Triglyceride, ALP, and LDM in control, CsA and CsA + Vit C groups . Results expressed as mean ± SD.

	Control	CsA[a]	CsA + Vit C
bilirubin(mg/dL)	0.120 ± 0.008	0.179 ± 0.144	0.154 ± 0.014
ALP [a](IU/L)	109.690 ± 7.018	183.740 ± 6.361	160.360 ±6.565
LDH [a] (IU/L)	1156.700 ± 27.252	1750.00 ± 37.392	1521.20 ± 33.891
ALT [a] (IU/L)	25.460 ± 3.312	43.770 ± 3.391	33.523 ± 3.046
AST [a] (IU/L)	73.920 ± 5.463	131.690 ± 5.466	107.200 ± 4.885
Total proteina (g/dL)	7.114 ± 0.154	5.334 ± 0.254	5.930 ± 0.201
Albumina (g/dL)	4.264 ± 0.251	3.012 ± 0.181	3.546 ± 0.234
Triglyceridea (mg/dL)	71.314 ± 4.516	119.900 ± 6.279	91.266 ± 5.046

[a] Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; CsA, Cyclosporine A; LDH, Lactate Dehydrogenase

g/dL) was significantly lower than those of the group A (7.114 ± 154) and the group C (5.930 ± 201, $P < 0.05$). Also there was a significant difference between the group B and the group C ($P < 0.05$). Albumin level in the group B (3.012 ± 0.181 g/dL) was significantly lower than those of the group A (4.264 ± 0.251) and the group C (3.546 ± 234, $P < 0.05$). Moreover, there was a significant difference between the group B and the group C ($P < 0.05$). Triglyceride level in the group B (119.900 ± 6.279 mg/dL) was significantly higher than those of the group A (71.314 ± 4.516) and the group C (91.266 ± 5.046, $P < 0.05$). Also, there was a significant difference between the group B and the group C ($P < 0.05$).

5. Discussion

The process of CsA-induced hepatotoxicity begins with degradation of arachidonic acid, synthesis of eicosanoids and release of free radicals (as hydroxyl radical) that initiate lipid peroxidation and the secondary activation of physiologic antioxidant defenses. In prior studies, changes in the activities of antioxidant enzymes (lowered SOD, and increased CAT activities) and observed increase in peroxidation products in the liver tissues from cyclosporine-treated rabbits have been established (11).

Our study shows that there were significant increases in ALT, AST, bilirubin, LDM, ALP and triglyceride levels in plasma, and significant decrease in total protein and albumin level of the plasma in the group B and the group C but the amount of increase between group B and C was also significant. Vitamin C treatment significantly decreased liver toxicity against CsA-induced plasma biochemical changes. The results in this experiment recommend that vitamin C be effective in decreasing the CsA-induced hepatotoxicity; however, level of ALT, AST, bilirubin, LDM, ALP and triglyceride in the group C was higher than that of the group A and the level of total protein and Albumin was lower than that of the group A significantly.

Our results approve the results of Benito B (12) report in which studied effect of vitamin C in liver protein pattern of CsA-treated rats. Although this study shows the beneficial effect of vitamin C in decreasing CsA-induced liver toxicity it has been suggested that antioxidant supplementation is beneficial only when elevated oxidative stress is present (13) because some studies show that the co-administration of antioxidants like vitamin C may decrease CsA dose in the body and interfere with the aim of using CsA regimen in patients (14). In conclusion, we have shown that vitamin C administration provides protection against CsA-induced injury in rat liver function and it may have hepatoprotective role in patients experiencing CSA treatment.

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