Protective Effects of Vitamin E in Some Physiological and Biochemical Parameters Changes in Rabbits Exposed to Cytosar

Saif Al-Jammas[1], Sinan Th. Abdullah[2]*, Ghada AbdAlrhman Taqa[3]
[1, 2, 3]Dental Basic Sciences Department, College of Dentistry. University of Mosul, Iraq
Email: sinantag2016@uomosul.edu.iq

Abstract
The objectives of the present study were to examine the side-effects of Cytosar on some physiological and biochemical parameters in rabbits and evaluate the protective effect of Vitamin E in rabbits administered Cytosar. Twenty-seven white New Zealand healthy male adult rabbits weighing 1.5-2.0 kg were randomly divided into 3 experimental groups including (i) control group; treated with 1mL distilled water intra-peritoneal (IP), (ii) Cytosar group; treated with 1 mL Cytosar (50 mg/kg) IP, and (iii) Cytosar-vitamin E group; administered vitamin E orally (800 IU) 4 hours before the Cytosar injection (50 mg/kgIP). All groups were treated daily for 5 days. On day 5, all rabbits were sacrificed, and blood samples were collected. Results showed that the concentrations of GOT, GPT, ALP were significantly increased in Cytosar group compared to control and Cytosar-vitamin E groups. No differences were observed between control and Cytosar-vitamin E groups. Calcium and phosphorus concentrations were not different between study groups. In conclusion, Cytosar has a direct toxic effect of the liver in rabbits; however, administration of vitamin E before Cytosar can have a protective effect.
Keywords: Cytosar, Vitamin E, liver, toxicity

1. Introduction

Cytosar is a brand name for the chemotherapeutic drug Cytarabine, which is also known as cytosine arabinoside (ARA-C). It has been used for treatment of acute myeloid leukemia (AML) for about 40 years (1). Cytosar inhibits DNA polymerase in competition with deoxycytidine 5-triphosphated-CTP (d-CTP) which is an essential component of DNA and induces d-CTP deficiency preventing DNA synthesis and cell division (2).

Cytosar is considered toxic to tumor cells as a function of increase of cellular oxidative stress that can be potentially abrogated by antioxidants (3). Vitamin E (alpha-tocopherol), on the other hand, is one of the most fat-soluble antioxidants protects cells from oxidative processes and neutralizes cell-damaging free radicals (4). All forms of vitamin E act as a chain-breaker prevents oxidation by trapping free hydroxyl radicals (5). Vitamin E maintains living cell membrane stability by giving an electron to those cells affected by oxidative damage (6).

Administration of vitamin E before Cytosar dose could have a protective effect against the oxidative damage of Cytosar. However, this protective effect is still not examined. Therefore, the objectives of the study conducted here were to examine the side-effects of Cytosar on some physiological and biochemical parameters in rabbits and to evaluate the protective effect of Vitamin E in rabbits treated with Cytosar.

2. Materials and Methods

Ethical approval

This study was approved by the Institutional Animal Care and Use Committee (IACUC), College of Veterinary Medicine, University of Mosul, UM.VET.2021.059 on July 1st, 2021.

Study Animals

Twenty-seven white New Zealand healthy male adult rabbits with age 3-months old and weight 1.5-2.0 kg were included in this study. The rabbits were kept in cages under standard condition housing at 25 ±2°Cwith 12 hrs. Light/dark cycle at the animal house belongs to the College of Dentistry, University of Mosul. Study rabbits were given standard diet of wheat and fresh vegetables with freely tap water. The rabbits were allowed to adapt the laboratory environment one week before the experiment.

Study Groups

The study rabbits were randomly divided into 3 experimental groups. Each group included 9 rabbits and treated as in the following: (i) control group, which was treated with 1 mL distilled water intra-peritoneal (IP), (ii) Cytosar group, which was treated with 1 mL Cytosar IP at dose 50 mg/kg IP; Cytosar was manually prepared as previously described by (3), and (iii) Cytosar-vitamin E group, which was orally administrated vitamin E at dose (800 IU) 4 hours before the treatment of Cytosar at dose 50 mg/kg IP. All groups were treated daily for 5 days. On day 5, all rabbits were sacrificed, and blood samples were collected from the jugular vein. Blood samples were centrifuged at 3000 R/min for 10 min in order to collect the serum for laboratory examinations.

Outcome of interest

Serum concentrations of glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and alkaline Phosphatase (ALP), in addition to

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calcium and phosphorus ions were used to evaluate the oxidative damage of Cytosar and potential protective effect of vitamin E. The reflectance photometry was performed for estimating the outcome of interest (7) using Reflotron plus 2011 (Roche, Germany).

3. Statistical Analyses

One way analysis of variance (ANOVA) was used to examine the differences of investigated parameters among study groups. Duncan's multiple range test was used for pair wise comparisons between study groups. A value of P ≤0.05 was considered statistically significant. All statistical analyses were performed using SPSS 18.

Results

The results showed the concentrations of GOT, GPT and ALP were significantly increased in the rabbits treated with Cytosar 50 mg/kg IP compared to control group, whereas significantly decreased in rabbits administered vitamin E orally (800 IU) 4 hours before the Cytosar injection (Fig. 1, 2, and 3). On the other hand, no significant difference was observed between Cytosar-vitamin E group compared to control group (Fig. 1, 2, and 3). Although calcium concentration increased in both Cytosar and Vitamin E + Cytosar groups compared to control group, the difference was not significant (P = 0.92; Fig. 4). In contrast, phosphorus concentration was decreased in Cytosar group and increased in Vitamin E + Cytosar groups compared to control group; however, the difference was also not significant (P = 0.79; Fig. 5).

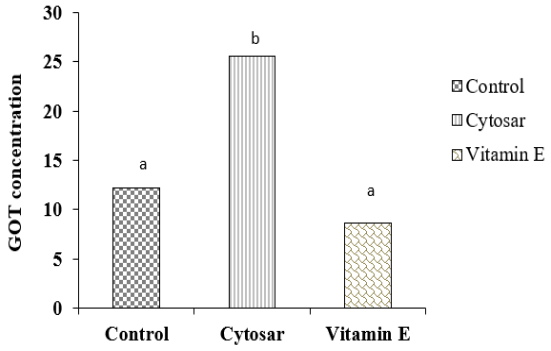

Figure 1. Changes in GOT concentration between control, Cytosar and Vitamin E + Cytosar groups after 5 days of treatment. Different letters mean statistical difference at P ≤ 0.05.

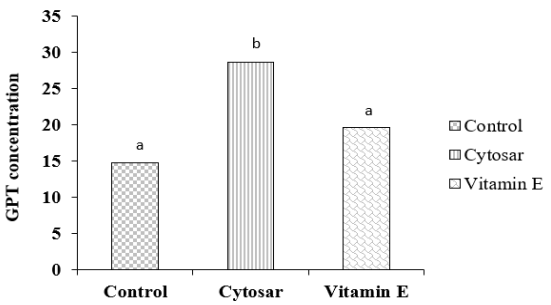

Figure 2. Changes in GPT concentration between control, Cytosar and Vitamin E + Cytosar groups after 5 days of treatment. Different letters means statistical difference at P ≤ 0.05.

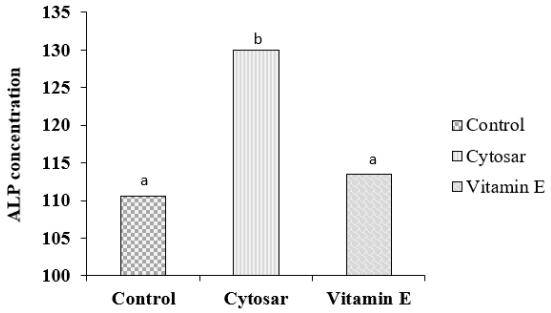

Figure 3. Changes in ALP concentration between control, Cytosar and Vitamin E + Cytosar groups after 5 days of treatment. Different letters mean statistical difference at P ≤ 0.05.

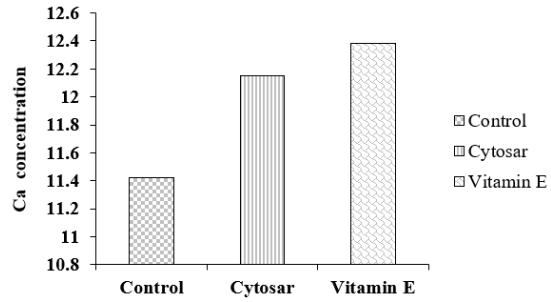

Figure 4. Changes in Calcium concentration between control, Cytosar and Vitamin E + Cytosar groups after 5 days of treatment.

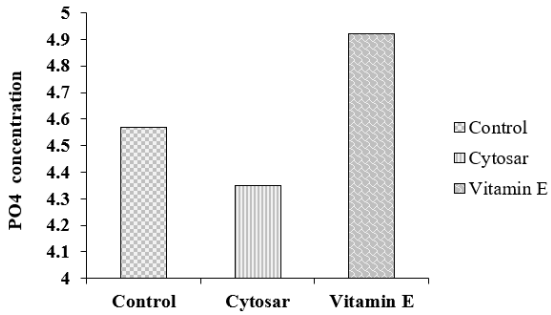

Figure 5. Changes in phosphorus concentration between control, Cytosar and Vitamin E + Cytosar groups after 5 days of treatment.

4. Discussion

The study conducted here revealed that Cytosar had negative impact on GOT, GPT, and ALP concentrations which are considered markers for hepatic injury, whereas vitamin E minimized this impact. Up to our knowledge, this is the first study indicates this effect. Further studies are required to confirm this effect in different models.

In this study, increase of GOT, GPT, and ALP concentrations in rabbits treated with Cytosar is attributed to cellular damage, particularly hepatic cells damage. That is, hepatic cells damage results in release of these enzymes into the circulation (8). Therefore, warning has to be accounted in the administration of cytotoxic drug to the patient with liver dysfunction(9). Cytosar is metabolized in the liver through the cytochrome P450 system and produce toxic or immunogenic intermediate metabolite that can trigger liver damage (10).

Fu et al., (11) mentioned that Cytosar is associated with severe hepatic damage revealed by increase of GOT, GPT, and ALP. On the other hand,

administration of vitamin E 4 hours before Cytosar injection kept GOT, GPT, and ALP concentrations in rabbits close to normal (no significant difference between vitamin E + Cytosar group and control group) indicating a protective effect of vitamin E against cellular damage. Vitamin E could have potential antioxidant activity through the removal of free radicals (12).

The results showed that the concentration of calcium and phosphorus did not significantly vary in rabbits treated with Cytosar and those administered vitamin E 4 hours before Cytosar injection compared to control group. However, some studies found that chemotherapy can alter the blood concentration of calcium and phosphorus (13, 14).

The cytotoxic effect of chemotherapy has been indicated in several animal models as a function of impact on blood vessel formation, which may affect calcium and phosphorous levels in the blood (15,16). The chemical analysis of the callus referred to the decrease of calcium and phosphorus deposition with the use of chemotherapy medications (17,18). One explanation that our study did not find significant changes in the concentration of calcium and phosphorus is the short period of the experiment. Additional reasons can be the dose of Cytosar or the animal model used in the study. More studies are important to confirm this effect as both calcium and phosphorus are important and necessary elements for the normal function of all body cells, and the use of different types of cancer treatments can cause imbalance in the natural ratio of these elements (19).

5. Conclusions

Cytosar has a direct toxic effect of the liver in rabbits; however, administration of vitamin E before Cytosar can have a protective effect.

6. Conflict of Interest

The authors declare no competing of interest.

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