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Research Article

# The Impact of Vitamin E on Acute Kidney Injury Prevention in Leukemia Patients Treated With Vincristine: A Randomized Clinical Trial

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## ABSTRACT

**Background and Aim:** Chemotherapy plays an essential role in the treatment of hematologic cancers. Vincristine is commonly used to treat leukemia in children. However, this drug has many side effects, including acute kidney injury (AKI). Adjuvant therapy with antioxidant agents, such as vitamin E, can be administered to reduce this complication

**Methods:** A randomized clinical trial of leukemia patients receiving vincristine was conducted at Amir Kabir Arak Hospital. The patients were randomly divided into an intervention group (400 mg vitamin E for ten days) and a control group. Creatinine levels, glomerular filtration rate (GFR), and acute kidney injury were measured at baseline, 48 h, and seven days later. Independent t-test and chi-square were used to compare data.

Objectives: This study aims to investigate the potential effect of vitamin E supplementation in reducing acute kidney injury associated with vincristine treatment in patients with leukemia.

**Results:** Thirty-six children with leukemia, 47.2% of whom were girls, were equally divided into intervention and control groups. The essential characteristics of the two groups were not significantly different. The creatinine level at baseline (0.60±0.08 vs. 0.61±0.12 mg/dl), 48 hours (0.60±0.09 vs. 0.61±0.10 mg/dl), and seven days (0.66±0.16 vs. 0.66±0.13 mg/dl) were lower for the intervention group than the control group, but this difference was not statistically significant (P>0.05). In contrast, the GFR at baseline (92.96±17.87 vs. 91.53±13.46 ml/min/1.73 $m^2$), 48-hour (92.82±18.27 vs. 85.35±15.25 ml/min/1.73 $m^2$), and seven days (90.86±17.84 vs. 85.05±14.41 ml/min/1.73 $m^2$) were higher in the intervention group than in the control group. However, this was not significant. Finally, only one patient in the control group developed AKI, while no cases of AKI were observed in the intervention group.

**Conclusion:** Vitamin E's impact on AKI reduction in patients with leukemia was not statistically significant. However, it positively affected creatinine and GFR levels in the intervention group. In addition, no AKI cases were observed in the intervention group.

**Keywords:** Vitamin E, Acute kidney injury, Leukemia, Chemotherapy, Vincristine

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## Introduction

Based on the statistics released in 2020 by the global cancer observatory (GLOBOCAN), approximately 2.5% of all new cancer cases and 3.1% of cancer-related fatalities are allocated to leukemia [1]. Although chemotherapy plays an essential role in treating leukemia, due to significant side effects and low patient compliance, its clinical use is limited [2-4].

Vincristine (VCR), an herbal alkaloid used to treat many cancers, is also considered for the leukemia treatment. The mechanism of its function is to intervene in microtubule polymerization during mitosis and cell growth [5, 6]. Despite its anti-cancer activity, its cytotoxic effects on non-tumoral cells limit its application [7]. Acute kidney injury (AKI) is an essential and undeniable adverse effect of Vina Alkaloids, such as VCR, which occurs due to the syndrome of inappropriate antidiuretic hormone release (SIADH), causing hyponatremia and drug-induced thrombotic microangiopathy (DITMA) [8].

To decrease the adverse effects of VCR, this study aims to assess the impact of vitamin E on preventing renal failure induced by this drug. Vitamin E (α-tocopherol) is one of the top antioxidants. The primary function of vitamin E is the breaking domino effect of lipid peroxidation. Previous studies have shown its beneficial effects in preventing nephrotoxicity caused by some substances and drugs, such as mercuric chloride, gentamicin, cisplatin, and vancomycin [9-15]. Although there have been many investigations on the antioxidant effects of vitamin E and its preventive role of nephrotoxicity induced by some medications, little information is available about its impact after VCR treatment. (Perhaps due to most biliary excretion of VCR), only 10% of VCR is excreted in the urine. Therefore, the present study was designed to evaluate the preventive effects of vitamin E on acute renal failure in patients with leukemia receiving VCR as their medication.

## Materials and Methods

This study was a randomized controlled clinical trial conducted at Amir Kabir Arak Hospital. Patients with leukemia who needed to receive VCR were included in the study.

### Study design

Available or easy methods were used to select the samples. The patients were then randomly placed in one of the two intervention or control groups. The randomization method was performed in blocks of four. Patients' allocation was performed through sealed opaque envelopes. After enrolling the patients, their group was revealed by opening the envelope in order. In this study, blinding was not performed and the researchers and patients were aware of the study group.

### Intervention

All patients received a routine VCR drug of 1.4 mg/m$^2$. In addition, one 400 mg vitamin E tablet (made in Iran) was prescribed daily for one month to the patients in the intervention group, concomitant with the initiation of VCR.

In contrast, the control group did not receive any additional medication.

### Outcome

This study's primary outcome was evaluating kidney function by calculating the glomerular filtration rate (GFR), which was calculated using the Equation 1.

1. $eGFR=0.413\times height\ (cm)/Scr(mg\ dL)$

In addition, AKI was investigated as a secondary outcome of the study. For this purpose, the patients' creatinine levels and urine volumes were measured upon admission, 48 h later, and one week later. An increase in creatinine level of more than 0.3 times the baseline after 48 hours, an increase in creatinine level of more than 1.5 times the baseline after one week, or a urine volume of <0.5 cc/kg/h for 6 h was considered AKI.

### Statistical analysis

Quantitative variables were analyzed using Mean±SD, while qualitative variables were analyzed using numbers and percentages. An independent t-test was used to compare quantitative variables. In contrast, chi-square, Fisher, and McNemar's tests were used for qualitative variables. Appropriate statistical charts were used to summarize the findings. All analyses were performed using SPSS software, version 25. Moreover, the significance level was considered as $P<0.05$.

## Results

### Baseline characteristics

A total of 36 children diagnosed with leukemia and receiving VCR were included in this study. The preventive effect of vitamin E against acute renal failure was evaluated in these patients. Seventeen patients of the population were girls (47.2%), 8 in the intervention group (44.4%), and 9 in the control group (50%). The mean age of participants was 7.8±2.50 years in the population, 8.0±2.19 years in the intervention group, and 7.7±2.84 years in the control groups, respectively. The mean height of the total participants was obtained at 127.79±14.85 cm, which varied from 127.22±14.19 cm in the intervention group to 128.38±15.32 cm in the control group. No statistically significant differences were observed between the baseline characteristics of the intervention and control group (Table 1).

### Outcomes

The baseline level of creatinine in the intervention and control groups was measured at 0.60±0.08 and 0.61±0.12 mg/dl, respectively. Repeating the measurement after 48 hours and seven days in the intervention group showed 0.60±0.09 and 0.61±0.10 mg/dl in creatinine levels, respectively. In the same way, measuring creatinine levels in the control group after 48 hours and after seven days showed us the amounts of 0.66±0.16 and 0.66±0.13 mg/dl. Although the creatinine level in the intervention group was lower than in the control group, this difference was not statistically significant.

The baseline GFR in the intervention and control groups was reported to be 92.96±17.87 and 91.53±13.46 ml/min/1.73 $m^2$, respectively. It reached 92.82±18.27 ml/min/1.73 $m^2$ in the intervention group after 48 hours and 90.86±17.84 ml/min/1.73 $m^2$ after seven days. In the control group, 48 hours later and seven days later, the GFR was 85.35±15.25 and 85.05±14.41 ml/min/1.73 $m^2$, respectively. Despite the higher GFR in the intervention group, the difference between the two and the control groups was insignificant.

Finally, the incidence of AKI was checked in the patients of the two groups, and only one case of AKI was observed in the control group. None of the patients in the intervention group developed this complication. This difference was insignificant in the statistical analysis, with P=0.05 (Table 2).

## Discussion

In this clinical trial study, we investigated the impact of vitamin E administration on AKI occurrence among patients with leukemia undergoing VCR treatment. Our results did not reveal any significant protective effect of vitamin E against AKI. However, the results showed lower creatinine levels and better GFR in the intervention group. No AKI was observed in the intervention group.

Kidney involvement, including AKI, is widespread in patients with leukemia [16]. In the study of Limratchapong et al. [17], 50% of patients with leukemia suffered from AKI. The incidence of AKI in patients with leukemia can be attributed to different reasons. One of the possible etiologies is the side effects of chemotherapy drugs, such as VCR [16]. VCR is a drug that treats various types of cancers, including leukemia and lymphoma [6]. The progression of AKI leads to poor prognosis in patients with leukemia. In addition, there is no definitive cure for this condition, highlighting the importance of AKI prevention. Recently, several studies have suggested a potential effect of vitamin E on kidney damage [18-20].

Patients with leukemia can develop AKI in different ways. One of them is the infiltration of leukemic cells in kidney tissues. In Wang et al.'s study, infiltration of CLL cells into the kidney parenchyma and severe kidney failure was observed in 60% of patients. This study suggests that the production of monoclonal immunoglobulins by

**Table 1.** Baseline characteristic of participants

| Variables | | No. (%)/ Mean±SD (Range) | | | P |
|---|---|---|---|---|---|
| | | Total (n=36) | Intervention (n=18) | Control (n=18) | |
| Sex | Male | 19(52.8) | 10(55.6) | 9(50) | >0.05 |
| | Female | 17(47.2) | 8(44.4) | 9(50) | |
| Age (y) | | 7.8±2.50 (4-15) | 8.0±2.19 (4-13) | 7.7±2.84 (4-15) | >0.05 |
| Height (cm) | | 127.79±14.85 (94-156) | 127.22±14.19 (94-146) | 128.38±15.32 (98-156) | >0.05 |

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**Table 2.** Outcome measurements of the study

| Outcomes | | Mean±SD/ No. (%) | | | P |
|---|---|---|---|---|---|
| | | Total | Intervention | Control | |
| Creatinine (mg/dl) | Baseline | | 0.60±0.08 | 0.61±0.12 | 0.724 |
| | 48 hours | | 0.60±0.09 | 0.66±0.16 | 0.163 |
| | 7 days | | 0.61±0.10 | 0.66±0.13 | 0.271 |
| GFR (ml/min/1.73 $m^2$) | Baseline | | 92.96±17.87 | 91.53±13.46 | 0.788 |
| | 48 hours | | 92.82±18.27 | 85.35±15.25 | 0.192 |
| | 7 days | | 90.86±17.84 | 85.05±14.41 | 0.290 |
| AKI | Occurred | 1(2.8) | 0(0) | 1(5.6) | 0.55 |
| | Not occurred | 35(97.2) | 18(100) | 17(94.4) | |

GFR: Glomerular filtration rate; AKI: Acute kidney injury.

infiltrating cells and the formation of crystals are possible pathogenesiss of kidney damage in some patients. In addition, interstitial fibrosis and tubular atrophy were also observed in the pathology of patients [21].

In addition, chemotherapeutic drugs can lead to nephrotoxicity by causing inflammation, tubular damage, glomerulopathy and vascular damage [22]. Another critical underlying factor in the occurrence of AKI is tumor lysis syndrome, in which, after the start of treatment with chemotherapy drugs, the rapid destruction of tumor cells increases the levels of potassium, blood phosphorus, and uric acid levels. This disorder is primarily caused by obstruction of the tubules using uric acid crystals.

As a result, the kidney's ability to eliminate these substances is insufficient, and eventually, electrolyte disturbances and kidney damage are created [23]. Sepsis, pyelonephritis, and urinary tract infections can also cause kidney damage [24].

Recently, various studies have considered the effect of vitamin E therapy on preventing kidney damage. One of the benefits of vitamin E is its antioxidant potential. This property helps prevent of renal damage caused by chemotherapy drugs, infections, and ischemia-reperfusion events that cause oxidative stress. Vitamin E can prevent inflammation, cell damage, and AKI by neutralizing the free radicals produced under these conditions [25]. Also, vitamin E can control inflammation and reduce kidney parenchymal damage by inhibiting inflammatory pathways, including proinflammatory cytokines and interleukins [26].

Vitamin E can reduce kidney cell damage by inhibiting apoptosis and cell death. This property is attributed to its anti-inflammatory and antioxidant effects [27]. Also, as mentioned, one of the underlying causes of AKI in patients with leukemia is tumor lysis syndrome. The anti-apoptotic properties of vitamin E may play a role in reducing kidney damage by reducing the lysis rate of tumor cells. Improving the function of endothelial cells, maintaining blood flow, maintaining vascular tone, and maintaining kidney hemodynamics are other mechanisms effective in reducing kidney damage caused by vitamin E [28, 29].

A study by Ghlissi et al. (2018) on rats concluded that using vitamin E effectively prevented and protected the renal side effects caused by colistin therapy [30].

In another study, Darwish et al. showed that adding vitamin E to treatment in patients treated with cisplatin reduces the level of creatinine and blood urea, normalizes the concentration of nitrite, increases the level of glutathione, and restores the activities of superoxide dismutase and catalase in kidney tissues. Even in histopathological studies, vitamin E significantly reduced kidney damage caused by cisplatin. In addition, they observed that administering vitamin E decreased the concentration of platinum in the kidney [31]. Nasiri et al. supported the results of their research [32].

Another study by Bárány et al. proved the preventive role of vitamin E in renal hemodynamic changes caused by the administration of cyclosporin A and showed that this supplement was also effective in preventing renal fibrosis [33]. Fryer et al.'s study investigated the role of

vitamin E in patients with chronic kidney failure. In this study, the administration of this antioxidant led to a decrease in the rate of kidney function [34].

## Conclusion

In conclusion, the supplement treatment with 400 mg of vitamin E daily for ten days to prevent VCR-induced nephrotoxicity in leukemia patients was not statistically significant. However, this may have a valuable role. It is essential that among the patients in the control group, one patient developed AKI, while no cases were found in the intervention group, which was clinically significant. The observed insignificant effect could be due to the small sample size of this study.

Our study's limitations included a small sample size and a short duration of time, which need to be addressed in future studies. We also encountered limitations in the cooperation of patients and families, and it is recommended that future studies first train families and patients to overcome these limitations.

Future studies should be conducted in larger populations and with different doses and durations to achieve the best patient therapeutic regime.

## Ethical Considerations

### Compliance with ethical guidelines

The Ethics Committee of Amir Kabir Arak Hospital approved the study design (IR.ARAKMU.REC.1401.200). Also, the Iranian Registry of Clinical Trials (IRCT) has approved this study (Registry code: IRCT20190717055255N7). The patients gave written informed consent to publish this report and clinical images. The consent has been signed and collected by the journal's patient consent policy.

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### Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results, and manuscript drafting. Each author approved the submission of the final version of the manuscript.

### Conflict of interest

The Authors declared no conflict of interest.

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