

The protective effect of lycopene supplement against vancomycin-induced nephrotoxicity; a randomized double-blind placebo-controlled clinical trial

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ABSTRACT

Introduction: It has been proposed that oxidative stress plays a crucial role in vancomycin-induced nephrotoxicity (VIN).

Objectives: The present study aimed to investigate the nephroprotective effects of lycopene, as a powerful antioxidant, on VIN.

Patients and Methods: In the present study, individuals who received vancomycin (VCM) for any indication were assigned to drug (n=28) and control (n=30) groups. The individuals in the drug group received 25 mg of oral lycopene daily for 10 days started concurrently with VCM and the patients in the placebo group received placebo tablets with VCM. Serum levels of creatinine (SCr) and blood urea nitrogen (BUN) as well as creatinine clearance (CrCl) were determined and recorded before the start of interventions, every other day during therapy, and 12 hours after the last dose of VCM in 10th day of treatment for all participants. Finally, the mean values of the measured parameters were compared between the groups.

Results: The mean values of SCr were significantly lower in drug group compared to placebo at the 4th (0.85 ± 0.18 vs. 0.98 ± 0.22 , $P=0.016$) and 6th (0.83 ± 0.18 vs. 0.95 ± 0.21 , $P=0.029$) days. Also, CrCl was significantly higher in the drug group at the 4th day compared to placebo (105.82 ± 20.09 vs. 94.67 ± 20.53 , $P=0.041$). Regarding VCM-induced AKI, no case was reported in any group.

Conclusion: Lycopene has the potential for diminution of VCM-induced nephrotoxicity (VIN). However, more investigations with larger sample size are necessary to confirm this effect.

Trial Registration: Present study was registered at the Iranian website (<https://www.irct.ir/trial/46859>) for registration of clinical trials (identifier: IRCT20171030037093N37).

Implication for health policy/practice/research/medical education:

It has been proposed that oxidative stress plays a crucial role in vancomycin-induced nephrotoxicity (VIN). The present study aimed to investigate the nephroprotective effects of lycopene, as a powerful antioxidant, on VIN. Lycopene has the potential for reduction of VIN. However, more investigations with larger sample size are necessary to confirm this effect.

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Introduction

Vancomycin (VCM) is a bactericidal antibiotic with a molecular weight of 1.446 kD that stops the synthesis of cell wall in gram-positive bacteria (GPB) (1). This antibiotic is a keystone drug for the management of severe infectious conditions caused by GPBs. Prescription of VCM is effective for management of bacterial infections that triggered by *Staphylococcus epidermidis*, *Streptococcus*

pyogenes, *Streptococcus pneumoniae*, *Streptococcus viridans*, *Clostridium*, *Corynebacterium*, *Staphylococcus aureus*, and certain bacillus species (2-4). However, it is not selected as a first-line treatment because of its reported side effects (5). Renal toxicity, ototoxicity, phlebitis, chills, exanthema and fever are some of the side effects of VCM (4,6). Additionally, the dose, concentration of the infusion solution, and infusion rate are important factors for

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occurrence of the aforementioned toxicities.

The precise underlying mechanism of vancomycin-induced nephrotoxicity (VIN) is not well known; however, it has been proposed that free radicals play a crucial role in the pathogenesis of VIN (7). It has been reported that urinary levels of malondialdehyde (MDA), as an important marker of lipid peroxidation, and N-acetyl-D-glucosaminidase, as a marker of renal tubular injury, increase following VCM administration in laboratory animals and conversely, the activity of some antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) decreases in them (8-10). Due to the key role of oxidative stress in the pathogenesis of VIN, treatment with natural antioxidants is considered as a potentially useful therapeutic option.

Lycopene, a member of carotenoid family, is found plentifully in tomato and related products (11). Due to the presence of a large number of conjugated double bonds, lycopene is considered as an important natural antioxidant (12). Bae et al reported that intake of lycopene reinforces the antioxidant system and inhibits lipid peroxidation in cell membrane. They also revealed that lycopene blocks the chain of nuclear factor kappa B (NF- κ B) activation and tumor necrosis factor- α (TNF- α) generation (13).

Objectives

The present study aimed to investigate the possible nephroprotective effects of lycopene supplementation against VIN in humans.

Patients and Methods

Study design

The present double-blind randomized placebo-controlled clinical trial was performed from September 2019 to February 2020 in infectious diseases department of Alzahra hospital, Isfahan, Iran affiliated to Isfahan University of Medical Sciences (IUMS). Demographic data of patients admitted to the department who required treatment with VCM were documented in special forms. The inclusion criteria for the participation in our study were: (1) age between 18 and 60 years; (2) receiving VCM at a dose of 1 g every 12 hours for any indication; (3) creatinine clearance (CrCl) more than 90 mL/min; (4) no positive history of acute kidney injury (AKI); (5) lack of underlying diseases causing renal impairment (e.g., diabetes mellitus and hypertension); (6) lack of any underlying kidney disorders such as glomerulonephritis, polycystic kidney disease, kidney stones, interstitial nephritis, and renal carcinoma; (7) no concurrent use of any other antioxidant supplements including vitamins C and E; and (8) no concurrent use of other nephrotoxic drugs such as aminoglycosides, amphotericin B, piperacillin/tazobactam, cyclosporine, tacrolimus, and furosemide. Development of AKI due to any reason other than VCM and allergic reaction to lycopene were considered as the exclusion criteria (Figure 1).

Subjects who met the inclusion criteria were randomly divided into two groups of drug (lycopene) and placebo. Block randomization method was used for random allocation using blocks of 4. Participants in the drug group

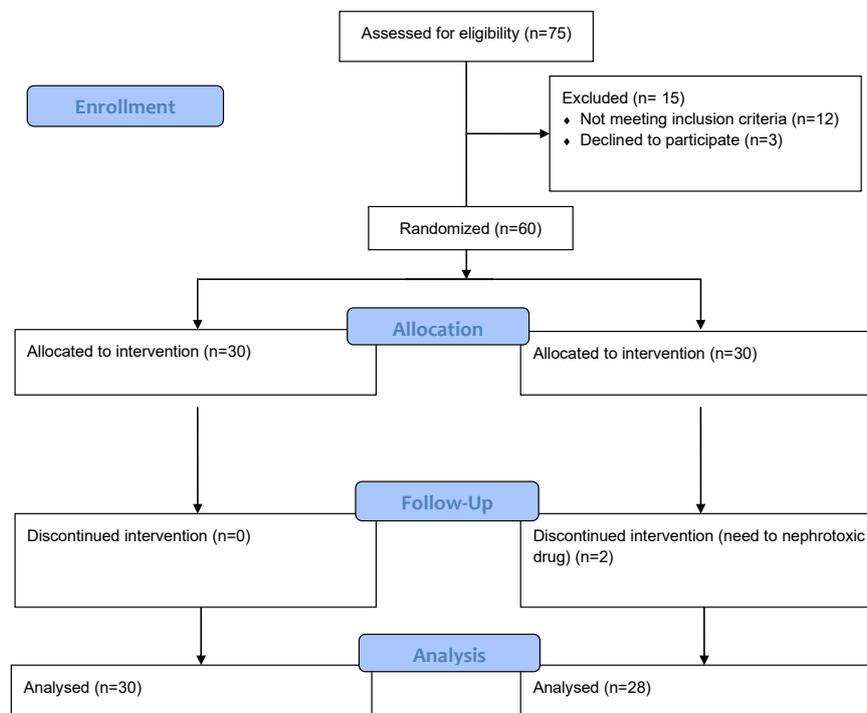


Figure 1. Flow chart of the study.

received lycopene tablets 25 mg (21st Century, U.S.A) daily for ten days started concurrently with VCM initiation. The subjects in the placebo group received placebo tablets (manufactured by the faculty of Pharmacy, IUMS, with the size, shape, and color similar to lycopene tablets) along with VCM. If VCM was discontinued earlier than ten days due to any reason except for AKI (e.g., thrombocytopenia and hypersensitivity reactions), the patient was excluded from the study.

Outcome variables

Outcome variables including serum levels of creatinine (SCr) and blood urea nitrogen (BUN) as well as CrCl were recorded before the start of intervention (day 0), every other day during the study (days 2, 4, 6, and 8), and 12 hours after the last dose of VCM (end of intervention; day 10) for all subjects. The estimated glomerular filtration rate (eGFR) as a magnitude of CrCl was calculated using Cockcroft-Gault equation (14). Also, the number of cases presented with AKI after VCM administration in two study groups was recorded. AKI was defined according to the KDIGO (Kidney Disease Improving Global Outcomes) definition, as an absolute increase in SCr of at least 0.3 mg/dL within 48 hours or by a 50% increase in SCr within 7 days from baseline value (15).

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The study protocol was registered in the Iranian Registry of Clinical Trials (identifier: IRCT20171030037093N37; <https://www.irct.ir/trial/46859>). Moreover, the study was approved by the ethics committee of the Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.104). Accordingly, informed consent was obtained from all patients. This study was also extracted from the residential thesis of Ali Anjomshoa at the department of infectious diseases of this university (Thesis No. 398057).

Statistical analysis

The extracted data were analyzed by statistical package for social science (SPSS) software, version 25.0 (SPSS Inc., Chicago, IL, USA). The qualitative variables were reported as percentage (%) and quantitative variables as mean \pm SD. Independent samples t test and repeated-measures ANOVA, respectively, were used for comparison of the mean values in each evaluated time point and comparison of changing trend between the groups. A *P* value <0.05 was considered as statistically significant difference.

Results

Over the study period, 112 subjects were evaluated regarding eligibility that 60 of whom met the inclusion criteria. Two patients were excluded from the drug group because of the need for another nephrotoxic drug

(piperacillin/tazobactam for one and amphotericin B for the other). Therefore, 28 and 30 individuals completed the study in drug and placebo groups, respectively. Sixteen patients in drug group (57.1%) and 23 patients in placebo group (76.7%) were male (*P* = 0.113). The mean \pm SD of patients age in drug and placebo groups was 45 \pm 12.02 and 46.5 \pm 11.98 years, respectively (*P* = 0.630).

The results of three evaluated parameters of kidney function including SCr, BUN, and CrCl are summarized in Table 1. As shown, the difference of baseline values for all variables was insignificant between the groups. Furthermore, although SCr was lower in drug group compared to placebo at all time points, the difference was statistically significant only at the 4th (*P* = 0.016) and 6th (*P* = 0.029) days of intervention. Also, the trend of changes in SCr was significantly different between the groups (*P* = 0.038).

No significant difference was found for BUN between the two groups in any evaluated time points. Furthermore, the changing trend of this parameter was not significant between the groups (*P* = 0.720).

Regarding CrCl, although the mean values were higher in the drug group compared to placebo at all evaluated times, the difference was statistically significant only at the 4th day of intervention (*P* = 0.041). Also, the trend of changes in CrCl was significantly different between the groups (*P* = 0.021). During the study, no case of AKI occurred in both groups.

Discussion

Our study showed the potential effect of lycopene for prevention of SCr rise and CrCl reduction by VCM. However, due to no occurrence of AKI in the placebo group that may be related to low dose of VCM or short duration of treatment, the judgment about this effect is difficult and needs more studies with larger sample size.

Several conditions have been recommended as the predisposing factors for VIN (14, 15). It has been stated that older subjects, those receiving a longer period of treatment, and those who are seriously ill are mainly at risk for renal toxicity induced by VCM (16-18). It has been reported that VIN occurs in 10%–20% and 30%–40% of cases receiving conventional and high doses of VCM, respectively (7).

At the best of our knowledge, this is the first study on the preventive effect of lycopene against VIN. However, several animal and clinical studies have been performed on other nephrotoxic drugs. Mahmoodnia et al reported that consumption of lycopene supplement is related to decrease of complications due to nephrotoxicity induced by cisplatin in subjects with malignancies (19). In another study, Dai et al investigated nephroprotective effect of lycopene on colistin-induced nephrotoxicity in the experimental model (20). They proposed that co-administration of lycopene with the dose of 20 mg/kg/d

Table 1. Comparison of renal function parameters at the evaluated times

Variable	Time (day)	Group		P value ^a	P value ^b
		Drug (Lycopene) (n = 28)	Placebo (n = 30)		
SCr (mg/dL)	0	0.94 ± 0.16	0.95 ± 0.14	0.866	0.038
	2	0.89 ± 0.15	0.94 ± 0.19	0.280	
	4	0.85 ± 0.18	0.98 ± 0.22	0.016	
	6	0.83 ± 0.18	0.95 ± 0.21	0.029	
	8	0.87 ± 0.17	0.93 ± 0.19	0.242	
	10	0.88 ± 0.14	0.95 ± 0.23	0.173	
BUN (mg/dL)	0	12.93 ± 5.22	12.03 ± 4.72	0.490	0.720
	2	12.18 ± 3.61	11.87 ± 4.50	0.770	
	4	11.14 ± 4.16	11.50 ± 4.84	0.760	
	6	11.18 ± 4.58	10.47 ± 4.15	0.534	
	8	10.86 ± 2.92	10.43 ± 3.55	0.623	
	10	11.96 ± 3.08	11.00 ± 3.56	0.276	
CrCl (ml/min)	0	94.68 ± 17.02	95.63 ± 16.39	0.821	0.021
	2	100.18 ± 16.02	98.30 ± 19.66	0.699	
	4	105.82 ± 20.09	94.67 ± 20.53	0.041	
	6	108.64 ± 24.10	97.77 ± 22.01	0.078	
	8	102.57 ± 18.19	100 ± 22.84	0.633	
	10	101.43 ± 21.04	98.37 ± 23.75	0.601	

The values are mean ± SD.

sCr, serum creatinine; BUN, blood urea nitrogen; CrCl, creatinine clearance.

^aIndependent Samples t-test, between-group difference at each time point.

^bRepeated-measures ANOVA, time*group interaction (changing trend difference between the groups).

can protect against nephrotoxicity induced by colistin in animals via activation of the Nrf2/HO-1 pathway (20). Also, in the experimental study performed by Bayomy et al in 2017, the protective effects of lycopene and rosmarinic acid on gentamicin-induced renal oxidative stress were investigated. They reported that rosmarinic acid and lycopene alone or combined have useful effects against gentamicin-induced renal damage (21).

Since the most possible underlying mechanism for VIN is increased production of free radicals (22), the positive effects of lycopene observed in our and above-mentioned studies could be due to its strong antioxidant activity.

As observed in Table 1 and mentioned in the results section, the alterations in SCr and CrCl during the 10-day intervention period revealed a significant difference between the two groups, so that SCr had decreasing trend and CrCl had increasing trend until the 6th day of intervention versus relatively stable values for both parameters in the placebo group. This difference along with significantly lower SCr and higher CrCl at some time points in the drug group compared to the placebo group shows the potential ability of lycopene for improvement or preservation of renal function in the setting of VCM administration.

In the current study, we were confronted with some limitations including low sample size, short duration of the study, and lack of VCM dosing based on serum concentrations. Larger sample size could reveal the exact rate of VCM-induced AKI in our population and subsequently determine the role of lycopene in

the prevention of this adverse effect. Future studies are recommended to investigate the cellular and molecular aspects of the effects of lycopene on nephrotoxicity. Moreover, similar studies that use more specific renal biomarkers (e.g., neutrophil gelatinase-associated lipocalin) are necessary to make a definite statement about the nephroprotective effects of lycopene as these biomarkers differentiate impairment of glomerular filtration from that of tubular damage (25,26).

Conclusion

Lycopene has the potential for reduction of VIN. However, more investigations with larger sample size are needed to confirm this effect.

Limitations of the study

Low sample size, short duration of the study, and lack of VCM dosing based on serum concentrations are our limitations of the study.

Author's contribution

SH and RS were the principal investigators of the present trial study. AA, RS, and SH were included in designing the trial. AA participated in writing the initial draft of the article. AA, RS, and SH confirmed the accuracy of any part of the manuscript.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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