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Prevention of Acute Kidney Injury Related (AKI) related by vancomycin; A Randomized Clinical Trial

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ABSTRACT

Introduction:
Acute kidney injury (AKI) is one of the potential side effects of vancomycin in children with systemic infections. We aimed to evaluate the effect of selenium on the prevention of Vancomycin-associated AKI (VA-AKI)

Materials and Methods:
This study is a parallel randomized controlled trial in Heshmatieh Hospital, Sabzevar, Iran. According to the simple random sampling method, thirty patients between 1 month and 18 years old with systemic infections were randomly assigned to two groups**.** The intervention and control groups were treated with vancomycin plus selenium and vancomycin alone, respectively. Urine and blood samples were obtained from patients at the beginning and seven days after the treatment to evaluate AKI among patients.

Results:
We found no significant difference between baseline BUN, creatinine, and microalbumin in the two groups (P>0.05). There was a significant difference between the two groups post-treatment urine microalbumin (P= 0.045). The frequency of AKI in the intervention group [5(33.3%)] was lower than the control group [11(73.3%)] (P = 0.02). There were few changes between the mean difference baseline and post-treatment Cr (0.1mg/dl) and BUN (2.9mg/dl). Drug efficacy was 66%, and the number needed to treat (NNT) was equal to 2.

Conclusion:
In the present study, we concluded that selenium could prevent vancomycin-induced AKI. Future investigations on the higher numbers of patients are needed.

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Introduction

Vancomycin is an antibiotic for treating methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant Staphylococcus epidermis infections.

It also plays a bactericidal role against Streptococcus sp, Enterococcus sp, Actinomyces sp, Clostridium sp, and EU bacterium sp (1). One of the empirical treatments of meningitis is vancomycin. However, in complicated pyelonephritis and other infections, treatment can be started if the antibiogram and cultures show sensitivity to vancomycin (1). However, there are concerns about its adverse effects on various organs due to the nephrotoxic Antimicrobial Agent. Animal models demonstrated that in the presence of vancomycin, histopathologic damage occurs in the proximal tubules, which is further supported by elevations of the novel biomarkers kidney injury molecule-1 (KIM-1), beta2microglobulin, and Neutrophil Gelatinase Associated Lipocalin(NGAL) (1,2). Improvements in the drug formulation coupled with drug monitoring (drug-level testing) have reduced the risk of limiting excessive drug exposure. Numerous potential risk factors have been ascertained for Acute Kidney Injury (AKI) development in receiving parenteral vancomycin therapy. Some factors directly relate to vancomycin exposure, including total daily dose, treatment duration, and administration method (3). Others are patient-related factors, obesity markers, preexisting kidney disease, the severity of illness, and receipt of concurrent nephrotoxins (4,5). AKI is one of the potential side effects of this drug, caused by the production of free radicals and reactive oxygen species (6). Therefore, knowing the pathophysiology of drug-induced AKI is necessary to know methods that reduce side effects (7,8). Some animal and human studies have assessed the effect of antioxidants on vancomycin-induced AKI by inhibiting the production of free radicals (9-11). However, there have not been any comprehensive human studies on the effect of selenium on vancomycin-induced AKI. This study aimed to assess the effect of selenium in reducing vancomycin-induced AKI.

Materials and Methods

We performed a parallel randomized controlled trial in the Pediatric Department, Heshmatieh Hospital, Sabzevar, Iran.

Population /patients

The sample size was calculated using the formula of comparing two means [1.16 (standard deviation = 0.24) and 1.5 (standard deviation = 0.29)] and considering beta 0.2 and alpha 0.05. The sampling method was convenience samples (easy access). Inclusion criteria were patients aged one month to 18 years and body mass index between 25-95 percentile. Patients with severe dehydration, chronic liver and kidney disease, history of underlying disease, for example, cystic fibrosis malignancy, congestive heart failure, and the concomitant use of another nephrotoxic drug were excluded. So, thirty children with systemic infections such as meningitis, complicated pyelonephritis, and sepsis were enrolled in the study. The selection of patients is shown in the flowchart (Figure 1).

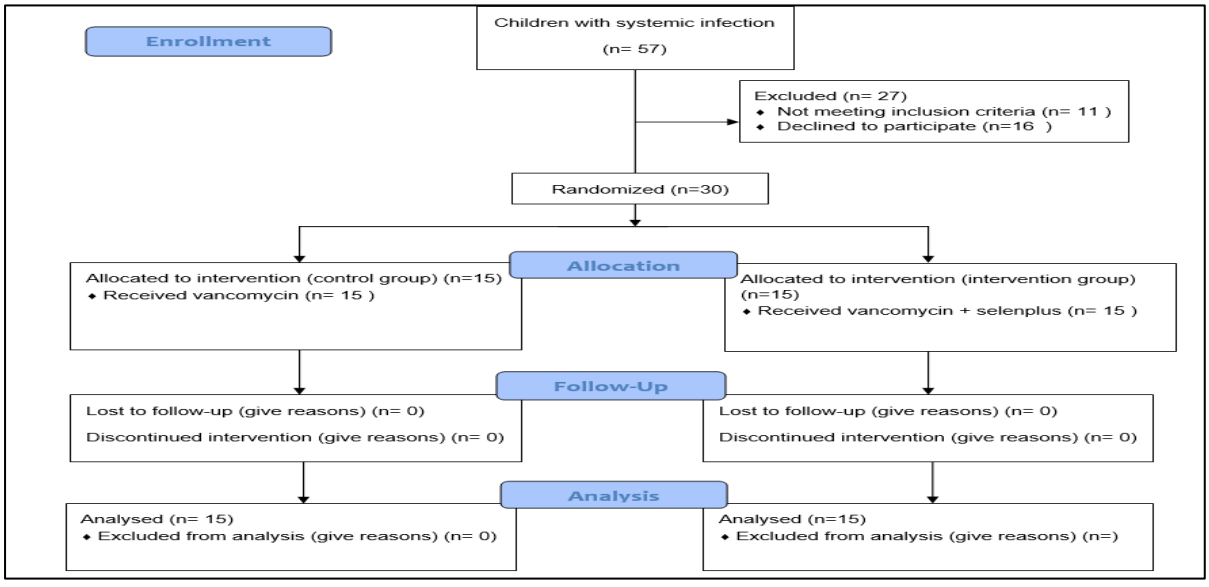

Figure 1. Consort Flowchart

Randomization

Random allocation was performed to block randomization. This method was used to balance the number of patients in each group. A block size of 4 was considered because two groups participated in the study. After block size has been determined, all possible balanced combinations of assignment within the block. In this method, (A) who is placed in the intervention group and (B) who is placed in the control group A blocking method with fixed blocks is used. Blocks of four were used, two of which were assigned to the intervention group and two to the control group.

Intervention

The patients were randomly divided into two groups after obtaining inclusion criteria and informed consent from the parents /guardians. This research was conducted as a double-blind trial, as allocation concealment was conducted to coded packages, where the person allocating treatment was not informed of its contents. Also, the treatment assessor and statistics consultant were blind about the type of treatment assigned to each group.The control group was treated with 60 mg/kg of vancomycin daily every six hours, and the intervention group was treated with the same dose of vancomycin and a selenium supplement. Selenium supplements contain the daily recommended amount of selenium for children under three years old: 15 to 20 micrograms; for 4 to 13 years old: 30 to 40 micrograms; and for 14 to 18 years old: 55 micrograms. The primary outcome measurements included bilirubin (BUN), creatinine (Cr), and urine microalbumin, which were considered in both groups at the onset and after seven days of treatment. Since BUN and Cr are not highly sensitive and increase with a delay in acute kidney injury, we used urine microalbumin to detect AKI. We examined urine microalbumin, and a value between 0 and 3 mcg/ml was considered normal. Blood urea nitrogen was normal and abnormal between 10 - 40 and above 40 mg/ dl. In the creatinine assessment in children, the values at less than five years, 5 to 12 years, and above 15 years were considered to be 0.2-0.4, 0.3-0.6, and 0.4-0.8 mg/dl, respectively. Spot urine microalbumin was examined, and a value less than 20 mg/L was considered normal, and between 20 and 200 mg/L was considered microalbuminuria.

In the investigation of AKI, urine microalbumin was considered the main indicator. An increase in urine microalbumin in both groups was considered as AKI. Also, the Number Need to Treat (NNT) is the number of patients who should be treated to prevent an adverse outcome. The present research investigated AKI, NNT, and efficacy calculation as secondary outcomes. In the investigation of AKI, urine microalbumin was considered the main indicator. An increase in the amount of urine microalbumin in both groups was considered AKI. For the calculation of NNT, the incidence of AKI in the intervention group was minus the incidence of AKI in the comparison group. Efficacy was calculated based on the incidence of AKI in the intervention group minus the incidence of AKI in the comparison group divided by the incidence of AKI in the comparison group.

Ethical considerations

This study was approved by the Local Ethics Committee of Sabzevar University of Medical Sciences under the ethical code: IR. MED SAB. REC.1399.164 and registered in IRCT.ir under IRCT number: 202104050508 57N1.

Statistical analysis

The statistical analysis was performed using the Software Package for Social Statistical Analysis (SPSS) (IBM ® SPSS ® Statistics for Windows, Version
20. Armonk, NY: IBM Corp).

The mean, standard deviation, frequency, and percentage were used to describe the variables. Chi-square and independent T-tests were used to compare differences between qualitative and quantitative variables, respectively. ANCOVA test was used to control confounding variables. A significance level of less than 0.05 was considered for statistical evaluation.

Results

In the present research, two studied groups had similar distributions of gender and age. Table 1 compares the age and gender of the studied groups. Our analysis showed no significant difference in gender and age between intervention and control groups (P>0.05).

We compared the three studied markers under two steps: within and between groups (Table 2). Our analysis showed that the two groups had similar amounts of BUN, Cr, and urine microalbumin before the study (P=0.80, P=0.09, and P=0.80).

After the treatment protocol, urine microalbumin was significantly increased in the control group compared to the intervention group (P=0.04). However, statistical analysis showed that comparisons of variations of the others, including BUN and Cr, were similar between the intervention and control groups after the study protocol (P>0.05).

In comparing the mean difference of baseline and post-treatment markers in two intervention and control groups, obvious changes in urine microalbumin in the intervention group compared to the control group; however, these changes were not clear in the Cr and BUN (Table 2).

Table 1. Comparison of age and gender of the two studied groups

Variables		Studied groups		P value
		Intervention	Control	
Gender	Male Female	7 (46.67%) 8 (53.33%)	11 (73.33%) 4 (46.67%)	0.136
Age, Month (Men±SD)		51.46±57.16	52.25±51.49	0.96
SD: Standard Deviation. Data between studied groups were compared using the chi-square test and the independent sample T-test.				

Table 2. Comparison of markers baseline and post-treatment in two groups

Variables		Studied groups		P value
		Intervention Mean± SD	Control Mean± SD	
BUN (mg/dl)	Baseline	12.8 ± 3.9	12.4 ± 5.2	0.804
	Post-treatment	9.9 ± 3.8	9.7 ± 3.9	0.927
	P-value Within- group	0.876	0.287	….
Cr (mg/dl)	baseline	0.5 ± 0.06	0.4 ± 0.08	0.097
	Post-treatment	0.4 ± 0.1	0.3 ± 0.1	0.539
	P-value Within- group	0.788	0.347	---
Urine microalbumin (mg/L)	baseline	9.09 ± 4.5	8.5 ± 7.2	0.801
	Post-treatment	7.2 ± 4.5	8.4 ± 3.2	0.045
	P-value Within- group	0.923	0.781	----
SD: Standard deviation. P-value was calculated for comparison between groups and within groups using the paired T-test and ANOVA Test. A P-value less than 0.05 was considered a significant level.				

We conducted an ANCOVA test to investigate the confounding factors. Within groups, comparisons of all three markers, including BUN, Cr, and urine microalbumin, had a normal distribution, and the Levens test was not significant for all three markers (P>0.05). Furthermore, the results showed no significant difference between the two groups after study processes (P>0.05). However, this difference was significant for urine microalbumin post-treatment processes (P-value = 0.048; Table 3).

Table 3. Investigation of confounding variables according to the Uni-variable ANCOVA Test

Uni-variable ANCOVA (Mean±SD)					
Markers	Leven test	Intervention	Control	Post-treatment marker	Baseline marker
BUN	P=0.59	9.8±1.01	9.8±1.01	P=0.98 Eta=0.0001 F=0.001	P=0.39 F=0.75
Cr	P=0.09	0.36±0.04	0.40±0.04	P=0.62 Eta=0.012 F=0.25	P=0.16 F=2.03
Urine microalbumin	P=0.17	7.2±1.08	8.3±1.08	P=0.048 Eta=0.02 F=0.50	P=0.79 F=0.07
SD: Standard deviation. A P-value less than 0.05 was considered a significant level.					

The study showed that the amount of urine microalbumin in the intervention group was reduced than the control group, and the frequency of AKI in the intervention group was lower than the control group ((Table 4; P =0.02). In this efficacy trial, efficacy was 66%, although the results of explanatory analysis (pet protocol) and intention to treat analysis (effectiveness) are the same. NNT analysis in this study was equal to 2. Therefore, one case of AKI can be prevented by prescribing selenium for two patients with systemic infection.

Table 4. Comparison of AKI in two groups

Group	AKI		P value
	Yes	No	
Control	11(73.3%)	4(26.7%)	0.02
Intervention	5(33.3%)	10(66.7%)	

Discussion

Treatment of systemic infections is an important concern. Vancomycin is known as a major basis for Control of infections. However, one of the limitations is vancomycin-induced AKI. This study showed that the frequency of AKI was lower in patients treated with selenium in addition to vancomycin than in patients treated with vancomycin alone. In the intervention group, the reduction of post-treatment urine microalbumin compared to baseline was higher than the reduction of BUN and Cr. A study by Ali Shabana et al. on rats in Pakistan in 2017 showed that vitamin E was statistically effective in preventing vancomycin-induced nephrotoxicity (12).

Rasoul Soltani et al. 2020 in Isfahan showed that vitamin E and vancomycin reduce the risk of AKI (acute kidney injury) development (13). In a study on rats in Turkey, Kara et al. showed that vitamin E could modulate amikacin-induced histomorphological changes (such as tubular epithelial necrosis) as an antioxidant (14).

Manali et al. revealed that vitamins E and N acetylcysteine (NAC) have potential therapeutic effects in cases with gentamicin-induced nephrotoxicity in rats. Although, these changes were not statistically significant (15). It is also notable that all of these studies examined the effect of vitamin E on nephrotoxicity, and most of them were performed on rats. However, in this study, we evaluate the impact of selenium on humans. Another research by Ademuyiwa demonstrated the synergistic effect of vitamin E and selenium in reducing gentamicin nephrotoxicity in rats (16). A similar study in rats by Nazıroğlu et al. on the impact of selenium and vitamin E on cisplatin- induced nephrotoxicity demonstrated a statistically positive difference (17).

In a study conducted in China from 2012 to 2019 by Hee Jan et al., Cr and BUN were measured before and after vancomycin with vitamin C consumption. They concluded that vitamin C significantly reduced vancomycin-induced nephrotoxicity (9).

However, our study evaluated the effect of selenium on vancomycin-induced AKI. The prevention of kidney damage due to oxygen-free radicals following aminoglycoside administration has been done in animals using antioxidants, but there is no study with high-level evidence on the effect of antioxidants in human samples. Our study showed a significant decrease in urine microalbumin, and the frequency of AKI was lower in the intervention group than in the control group. In this efficacy trial, efficacy was 66%, although the results of explanatory analysis (pet protocol) and intention to treat analysis (effectiveness) are the same because the patients were hospitalized and the drugs were given under the doctor's direct supervision. Still, some other studies must be conducted to evaluate the efficacy of this drug in human samples. The limitation of the current trial was the small sample size; therefore, it is recommended that more studies be conducted with a larger sample size.

Conclusion

Our study showed to reduction of vancomycin-induced AKI in selenium users. However, more studies with larger sample sizes are needed for more reliable findings.

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