Original Article

The Effect of Vitamin B_6 in the Prevention of Hematological Adverse Effects of Linezolid in Patients with Chronic Osteomyelitis: A Randomized Double-Blind Placebo-Controlled Clinical Trial

Kiana Shirani[1], Farzin Khorvash[1], Rasool Soltani[1,2], Behrooz Ataie[1], Mohammad Javad Tarrahi[3], Farideh Fallah[4]

[1]Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, [2]Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, [3]Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, [4]Department of Infectious Diseases, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract:

Background: Due to the contradictory results of the effects of Vitamin B6 in reducing the hematotoxic effects of linezolid, the present study aimed to investigate the possible role of Vitamin B6 administration in reducing linezolid-related hematological toxicities in patients with chronic osteomyelitis. **Materials and Methods:** In a randomized double-blind placebo-controlled clinical trial, patients with chronic osteomyelitis were randomly divided into two groups (n = 40 each): the intervention group received Vitamin B_6 40 mg twice daily from the beginning of treatment with linezolid and the control group received placebo with linezolid, both for 21 days. Blood variables including hemoglobin (Hb), white blood cells (WBC), and platelets (PLT) were measured at baseline and at the end of the 1st, 2nd, and 3rd weeks (days 7, 14, and 21) of the intervention. **Results:** There was no significant difference between the groups regarding the count of WBC and PLT and level of Hb at evaluated time points. Furthermore, there was a significant decreasing trend in all parameters within both groups; however, the decreasing trend of both PLT and WBC was slower in the intervention (Vitamin B6) group compared to the placebo group. **Conclusion:** Vitamin B6 has no significant effect in the reduction of hematological adverse effects of linezolid in chronic osteomyelitis patients. However, it could retard the decreasing trend of WBC and PLT counts.

Keywords: *linezolid, osteomyelitis, Physiological Effects of Drugs, Vitamin B6*

Introduction

Osteomyelitis is an uncommon but complicated condition with heterogeneous epidemiology.[1,2] Management of this condition without drug side effects is a puzzling issue for infectious disease specialists. It has been reported that hematogenous osteomyelitis is generally monomicrobial, while osteomyelitis due to contiguous spread is polymicrobial.[1] *Staphylococcus aureus* plays a considerable role in the pathogenesis of acquired osteomyelitis.[3] Unfortunately, the emergence of vancomycin and methicillin resistance among different strains of *S. aureus* has recently become a major problem.[4] Some microbiological studies have shown that methicillin-resistant *S. aureus* (MRSA) strains and coagulase-negative *staphylococci* play an important role in many cases of osteomyelitis caused by orthopedic surgery.[1]

Linezolid is a synthetic oxazolidinone antibiotic drug effective against several Gram-positive bacteria including streptococci, vancomycin-resistant enterococci, and MRSA.[5] Furthermore, prescription of linezolid has been suggested to fight Nocardia species, some anaerobes, and some mycobacteria.[6] Linezolid has been shown to have a high therapeutic potential in the treatment of osteomyelitis caused by resistant Gram-positive bacteria or nonresponsiveness to other possibly effective managements.[7] Although linezolid is widely used in the treatment of a wide range of diseases, its side effects on the body's hematological system should be considered.[8] It has been proposed that reversible suppression of myeloid tissue and immune-mediated toxicity are the possible reasons of linezolid-induced hematotoxicity, but the issue is open to discussion.[9,10] Anemia and thrombocytopenia are two serious side effects of linezolid that have led pharmacologists to try to manage.[10] Short-term use of linezolid has no significant

How to cite this article: Shirani K, Khorvash F, Soltani R, Ataie B, Tarrahi MJ, Fallah F. The effect of Vitamin B_6 in the prevention of hematological adverse effects of linezolid in patients with chronic osteomyelitis: A randomized double-blind placebo-controlled clinical trial. Adv Biomed Res 2022;11:67.

Address for correspondence:
Dr. Farideh Fallah, Department of Infectious Disease, Alzahra Hospital, Isfahan University of Medical Sciences, Shohadaye Soffe Street, Isfahan, Iran.
E-mail: faridehfallah.1352@gmail.com

Received: 30 August 2021
Revised: 02 November 2021
Accepted: 02 November 2021
Published: 26 August 2022

Access this article online

Website: www.advbiores.net
DOI: 10.4103/abr.abr_274_21
Quick Response Code:

side effects. However, its hematological adverse effects limit its long-term use, and this issue should be given more attention in some patients with poor bone marrow function.[11] The aforementioned toxic effects, including anemia and thrombocytopenia, occur in cases who receive linezolid for 14 days.[12] So far, several studies have investigated the role of Vitamin B_6 (pyridoxine) in reducing the hematotoxic effects of linezolid. Plachouras *et al*., investigated the possible effects of Vitamin B_6 prescription in cases that received linezolid for osteomyelitis and did not find a considerable benefit of this agent against linezolid-induced myelosuppression.[13] In another study, Spellberg *et al*. assessed the role of Vitamin B_6 in the prevention of linezolid-related cytopenias.[14] The results showed a positive effect of this vitamin in reduction of the side effects of linezolid. Due to the contradictory results of the studies in this regard, the present study aimed to investigate the possible role of Vitamin B6 administration in reducing linezolid-related hematological toxicities in patients with chronic osteomyelitis.

Materials and Methods

Study design and patients

This was a randomized double-blind placebo-controlled clinical trial conducted from September 2019 to February 2020 in Al-Zahra Hospital affiliated to Isfahan University of Medical Sciences (IUMS), Isfahan, Iran. The study was registered in the Iranian Registry of Clinical Trials (IRCT code: IRCT20150721023282N13). The study protocol was approved by the ethics committee of the IUMS (Ethics code: IR.MUI.MED.REC.1399.289). Accordingly, informed consents were obtained from all participants.

The inclusion criteria for subjects to enter the study were age >18 years; diagnosis of chronic osteomyelitis based on clinical, laboratory, and imaging evidence including high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); positive probe-to-bone test; presence of sinus tract on physical examination; and periosteal reaction in magnetic resonance imaging and prescription of linezolid for treatment during the first 2 weeks of therapy. The exclusion criteria were taking any other drug with myelosuppressive effect; severe anemia (hemoglobin [Hb] <8 g/dl); leukopenia (white blood cells [WBC] <4500); and thrombocytopenia (platelets [PLT] <150,000) before starting linezolid treatment.

Patients who met the inclusion criteria were randomly and equally divided into two groups: (1) the intervention group who received Vitamin B_6 tablets (Amin Pharmaceutical Co., Iran) at a dose of 40 mg twice daily from the initiation of treatment with linezolid (Oxatent, Dr. Abidi Pharmaceutical Co., Iran) 600 mg oral tablets twice daily and (2) the control group who received placebo tablets (manufactured by the faculty of pharmacy of IUMS) twice daily and linezolid 600 mg oral tablets twice daily. The placebo tablets were quite similar to the drug pills in terms of shape, size, and color and were made of the inactive substance lactose. Randomization was performed by block randomization method using blocks of four and random number table for selection of blocks. The prescribing physician, the data collector, the laboratory staff, and the patients were all blind to the type of intervention.

Assessments

A total of 21 days of intervention were required for every included patient. Blood variables including Hb, WBC count, and PLT were measured at the beginning of intervention and at the end of the 1st, 2nd, and 3rd weeks (days 7, 14, and 21) of intervention and recorded in the patient information form. Furthermore, at each visit by the infectious disease specialist, cases were assessed for possible changes in clinical status. Furthermore, CRP and ESR were measured at the start of and during the study for monitoring the response to therapy.

Sample size calculation

The following equation was used for sample size calculation:

$$N = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (S_1^2 + S_2^2)}{d^2}$$

Where N is the required sample size in each group, d is the difference between the groups, S is the standard deviation, $Z_{1-\alpha/2}$ is the standard normal z-value for a significance level $\alpha = 0.05$, which is 1.96, and Z_{β} is the standard normal *z*-value for the power of 80%, which is 0.84. According to Hb values in a previous study,[15] the S and d quantities were considered 16 and 11, respectively. Therefore, a calculated sample size of at least 33 patients in each group was obtained.

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 24.0 (SPSS Inc., Chicago, IL, USA). Chi-square test was used for comparison of gender, while repeated-measures analysis of variance and independent-samples *t*-test were applied to compare continuous quantitative variables within and between groups, respectively. $P < 0.05$ was considered as statistically significant difference.

Results

Over the study period, 127 patients were evaluated for eligibility, of whom 97 patients met the inclusion criteria. However, 87 patients accepted to participate in the study and were randomized. During the intervention, four patients from the intervention group (two patients due to the addition of co-trimoxazole to the drug regimen and two patients due to regret to participate) and three patients from the placebo group (two patients due to early discontinuation of linezolid and one patient due to regret to participate) were excluded from the study. Therefore, finally, 80 participants, including 40 subjects in each

group, completed the study. The age range of patients in the intervention and placebo groups was 41–85 years and 38–80 years, respectively. Table 1 shows the comparison of patients of the two groups regarding baseline demographic and clinical variables. As shown, there was no significant difference between the groups in terms of baseline values.

Table 2 shows the changes of evaluated hematological parameters during the study and their comparison between the both groups. As seen, for all parameters, there was no significant difference between the groups in all evaluated time points. Furthermore, as shown, there was a significant decreasing trend in all parameters within both groups; however, as depicted in Figure 1, the decreasing trend of both PLT and WBC was slower in the intervention (Vitamin B6) group than the placebo group.

Discussion

In the present study, the effect of Vitamin B6 consumption on linezolid-induced hematotoxicity was investigated. So far, several studies have suggested the role of Vitamin B6 in anemia. It has been reported that Vitamin B_6 plays a crucial role in hematopoiesis and a deficiency in Vitamin B_6 and iron can cause a special type of anemia called microcytic hypochromic anemia.[15]

Based on our literature review, the present study is the first to investigate the effects of Vitamin B_6 on reducing linezolid-associated hematotoxicity in patients with chronic osteomyelitis; however, some studies have examined the role of Vitamin B6 in patients with sepsis or cancer. Deng *et al*. investigated the effects of Vitamin B_6 therapy for sepsis cases with linezolid-related cytopenias.[16] According to their results, taking Vitamin B6 during the course of treatment with linezolid can prevent the pathological reduction of hematological parameters such as red blood cells, Hb, and PLT. In another study, Youssef *et al*. surveyed the possible effects of Vitamin B_6 in the prevention of linezolid-induced hematotoxicity in subjects with malignancies.[17] They reported that taking Vitamin B6 at a dose of 50 mg per day could have positive effects on anemia but did not have significant results in preventing linezolid-associated leukopenia and thrombocytopenia. Based on the results of the present study, in the group receiving Vitamin B6, the trend of changes is less than the group receiving placebo. For example, the trend of PLT decreasing in the intervention group decreased after day 14. Although there was no significant difference between the two groups in the present study, clinically; it was important for us to slow down the reduction of hematological parameters such as Hb, PLT, and WBC that occurred on day 14.

Table 1: Baseline demographic and clinical characteristics of study patients

Parameter	Placebo group (*n*=40)	Intervention group (*n*=40)	*P**
Gender, male/female	28/12	35/5	0.056
Age (years)	58.47±16.16	53.51±12.50	0.15
Weight (kg)	72.20±14.85	75.51±13.54	0.31
Height (cm)	169.86±8.46	173.46±8.34	0.07
WBC (cells×10^3/μL)	8.72±3.11	8.65±3.04	0.91
PLT (cells×10^3/μL)	260.40±87.164	250.30±95.462	0.62
Hb (g/dL)	10.61±1.81	11.26±2.35	0.16

The values are presented as mean±SD. WBC: White blood cell count, PLT: Platelet, Hb: Hemoglobin, SD: Standard deviation

Table 2: The comparison of changes of evaluated hematological parameters in the study groups during the study

Parameter	Time	Placebo group (*n*=30)	Intervention group (*n*=30)	*P*
WBC (cells×10^3/μL)	Baseline	8.72±3.11	8.65±3.04	0.91
	Day 7	8.48±3.54	8.44±3.37	0.96
	Day 14	7.57±2.55	7.98±2.93	0.51
	Day 21	7.12±2.51	7.58±2.64	0.43
P		<0.001	0.002	
PLT (cells×10^3/μL)	Baseline	260.40±87.16	250.30±95.46	0.62
	Day 7	251.87±89.99	244.97±94.96	0.74
	Day 14	243.26±87.47	227.82±87.25	0.43
	Day 21	211.84±80.50	218.97±83.29	0.70
P		<0.001	<0.001	
Hb (g/dL)	Baseline	10.61±1.81	11.26±2.35	0.16
	Day 7	10.38±1.67	11.12±2.27	0.10
	Day 14	10.17±1.74	10.93±2.42	0.11
	Day 21	10.12±1.56	10.91±2.24	0.07
P		0.002	0.02	

The values are mean±SD. WBC: White blood cell count, PLT: Platelet, Hb: Hemoglobin, SD: Standard deviation

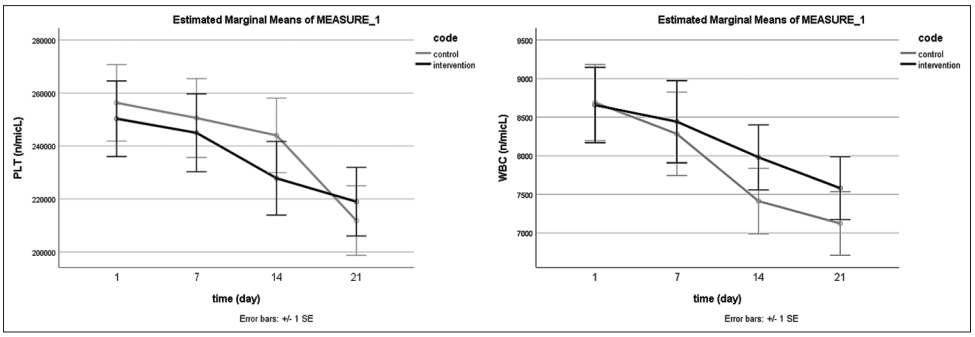

Figure 1: The trend of changes of platelets and white blood cells in both groups during the study

In the current study, we were confronted with some limitations. One of the main limitations was a few numbers of patients who participated in the present randomized clinical trial study. As we all know, more samples need to make a truthful conclusion. In addition, we had no history of taking antibiotics and associated resistance in cases, and this issue may confront our results with the unwanted bias. Another limitation is the lack of accurate information about the cause of osteomyelitis in patients and also the lack of knowledge about the mono-organism or multi-organism of the disease. One of the strengths of the present study was the lack of significant differences in age and sex of patients. As we know, the similarity of the two groups in clinical trial studies plays an important role in the reliability of the results.

Conclusion

Vitamin B6 has no significant effect in the reduction of hematological adverse effects of linezolid in chronic osteomyelitis patients. However, it could retard the decreasing trend of WBC and PLT counts. More studies with larger sample size and higher doses are recommended to determine the exact effect of this vitamin on linezolid-induced myelosuppression.

Acknowledgments

The current study was financed by IUMS Deputy of Research, Isfahan, Iran. We appreciatively thank the nursing staff of Al-Zahra hospital for their assistance.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Urish KL, Cassat JE. *Staphylococcus aureus* osteomyelitis: Bone, bugs, and surgery. Infect Immun 2020;88:e00932-19.
2. Hedrich CM, Morbach H, Reiser C, Girschick HJ. New insights into adult and paediatric chronic non-bacterial osteomyelitis CNO. Curr Rheumatol Rep 2020;22:52.
3. Nasser A, Azimi T, Ostadmohammadi S, Ostadmohammadi S. A comprehensive review of bacterial osteomyelitis with emphasis on *Staphylococcus aureus*. Microb Pathog 2020;148:104431.
4. Thitiananpakorn K, Aiba Y, Tan XE, Watanabe S, Kiga K, Sato'o Y, *et al.* Association of mprF mutations with cross-resistance to daptomycin and vancomycin in Methicillin-Resistant *Staphylococcus aureus* (MRSA). Sci Rep 2020;10:16107.
5. Hashemian SM, Farhadi T, Ganjparvar M. Linezolid: A review of its properties, function, and use in critical care. Drug Des Devel Ther 2018;12:1759-67.
6. Zahedi Bialvaei A, Rahbar M, Yousefi M, Asgharzadeh M, Samadi Kafil H. Linezolid: A promising option in the treatment of Gram-positives. J Antimicrob Chemother 2017;72:354-64.
7. Nordmann P, Rodríguez-Villodres A, Poirel L. A selective culture medium for screening linezolid-resistant gram-positive bacteria. Diagn Microbiol Infect Dis 2019;95:1-4.
8. Pratama NY, Zulkarnain BS, Soedarsono, Fatmawati U. Hematological side effect analysis of linezolid in MDR-TB patients with individual therapy. J Basic Clin Physiol Pharmacol 2021;32:777-81.
9. Sharma S, Syal A, Gupta M, Tahlan A, Kaur B. Reversible myelosuppresion with prolonged usage of linezolid in treatment of methicillin-resistant *Staphylococcus aureus*. Cureus 2020;12:e10890.
10. Alsultan A. Determining therapeutic trough ranges for linezolid. Saudi Pharm J 2019;27:1061-3.
11. Bayram N, Düzgöl M, Kara A, Özdemir FM, Devrim İ. Linezolid-related adverse effects in clinical practice in children. Arch Argent Pediatr 2017;115:470-5.
12. Giunio-Zorkin N, Brown G. Real-life frequency of new-onset thrombocytopenia during linezolid treatment. Can J Hosp Pharm 2019;72:133-8.
13. Plachouras D, Giannitsioti E, Athanassia S, Kontopidou F, Papadopoulos A, Kanellakopoulou K, Giamarellou H. No effect of pyridoxine on the incidence of myelosuppression during prolonged linezolid treatment. Clin Infect Dis 2006;43:e89-91.
14. Spellberg B, Yoo T, Bayer AS. Reversal of linezolid-associated cytopenias, but not peripheral neuropathy, by administration of vitamin B6. J Antimicrob Chemother 2004;54:832-5.
15. Kawakami T, Nakazawa H, Kawakami F, Matsuzawa S, Sudo Y, Sakai H, *et al.* Successful treatment of X-linked sideroblastic anemia with ALAS2 R452H mutation using vitamin B6. Rinsho Ketsueki 2018;59:401-6.
16. Deng J, Su LX, Liang ZX, Liang LL, Yan P, Jia YH, *et al.* Effects of vitamin B6 therapy for sepsis patients with linezolid-associated cytopenias: A retrospective study. Curr Ther Res Clin Exp 2013;74:26-32.
17. Youssef S, Hachem R, Chemaly RF, Adachi J, Ying J, Rolston K, *et al.* The role of vitamin B6 in the prevention of haematological toxic effects of linezolid in patients with cancer. J Antimicrob Chemother 2008;61:421-4.