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Original Article

A Survey of the Protective Effect of Vitamin B6 on Linezolid-Associated Hematological Dyscrasia

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Abstract

Hematological toxicities are considerable side effects of linezolid, which can restrict its administration. This study aims to evaluate the protective effect of vitamin B6 on linezolid-induced hematological dyscrasia, i.e., thrombocytopenia and anemia in poisoned patients. In this quasi-experimental (non-randomized, non-blinded) study, a number of 28 patients treated with linezolid and vitamin B6 were matched with 50 patients who received only linezolid. The hematological factors, including red blood cells (RBCs), hemoglobin (Hb), hematocrit (Hct), and platelets (PLTs) were assessed at baseline and on days 0, 1, 3, 5, and 7 during the linezolid treatment coarse. There were no considerable differences between the two groups in demographic characteristics, poisoning, vital signs, baseline laboratory test results, and mortality rates. Overall, patients who received linezolid+B6 had significantly higher RBCs, Hb, and Hct than those treated with linezolid alone ($P < 0.05$). Unexpectedly, patients in the treatment group had lower PLT counts compared to the control group with no significant differences ($P > 0.05$). According to our findings, the co-administration of vitamin B6 and linezolid was accompanied by a lower risk of anemia but no impact on preventing or reducing thrombocytopenia in patients with gram-positive bacterial infections.

Keywords: Anemia, Antibiotic, Thrombocytopenia, Nutritional supplement, Gram-positive bacteria, ICU, Hematological dyscrasia

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1. Introduction

In recent decades, gram-positive bacteria have played a prominent role in nosocomial infections and have constituted a significant health issue [1]. Considering the importance of multi-drug resistance (MDR) of these pathogens, controlling the infections by means of an appropriate antibiotic requires a specialist's qualified vision [2].

Linezolid is a synthetic antibiotic related to the class of oxazolidinones used to treat MDR gram-positive infections such as penicillin-resistant Streptococcus pneumoniae, vancomycin-resistant enterococci (VRE), and methicillin-resistance Staphylococcus aureus (MRSA), as well as anaerobic infections such as Nocardia and Mycobacteria [3,4]. As a bacteriostatic agent, this antibiotic acts through the inhibition of bacterial protein synthesis [5]. There have been some complications reported during linezolid utilization, including blood dyscrasia, lactic acidosis, serotonin syndrome, peripheral neuropathy, and optic neuropathy [6-9]. Bone marrow suppression is the leading cause of hematological toxicities, which can be reversed by discontinuing the drug [10]. The frequency of thrombocytopenia due to linezolid includes a wide range which varies from 7.5% to 64.7% [10]. Platelet destruction due to immune-related reactions in addition to myelosuppression would lead to this disorder [11]. The drug or its metabolite binds to the glycoprotein IIb/IIIa receptors on platelets' surface of which results in platelet degradation by antigen-antibody reactions [12].

Based on recent studies, various risk factors are associated with hematological toxicities [13-15]. Creatinine clearance rates of <60 mL/min, the duration of linezolid therapy of > 15 days, and hemodialysis were found to be considerable risk factors of linezolid-induced thrombocytopenia [13].

Spellberg *et al*. investigated the efficacy of the concomitant administration of vitamin B6 and linezolid in two cases for the first time [16]. They reported beneficial outcomes of vitamin B6 on the prevention or modification of the course of linezolid-associated cytopenias.

Therefore, this study aims to evaluate the protective effect of vitamin B6 on linezolid-induced hematological dyscrasia i.e. thrombocytopenia and anemia in poisoned patients.

2. Materials and Methods

2.1. Study Design and Participants

This quasi-experimental (non-randomized, non-blinded) study included individuals diagnosed with laboratory-confirmed gram-positive bacterial infections between October 1st, 2019, and March 19th, 2020, in the toxicological intensive care unit (TICU), Loghman-Hakim Hospital in Tehran, Iran. Eligible patients were those aged 12 years or older and received linezolid for at least six days whose poisoning would not affect the hematological factors on admission. Exclusion criteria included: anemia (hemoglobin 13 < g/mL in male and 12 < g/mL in female and/or thrombocytopenia [platelet counts < 150 $\times 10^3/\mu L$) on admission, occurrence of lactic acidosis and/or serotonin syndrome before the initiation of linezolid therapy and hypersensitivity to linezolid [17, 18]. A number of 28 patients treated with linezolid and vitamin B6 were designated treatment group and were matched with 50 patients who received only linezolid (control group). The informed consent had been obtained from the patients themselves or their next of kin. The

study was approved by the Ethics Review Committee in Research Deputy Department of Shahid Beheshti University of Medical Sciences, Tehran, Iran (REC code, IR.SBMU.RETECH.REC.1398.832).

2.2. Procedures

We used linezolid intravenous injection (300 mL [600 mg]/bag, lot number P78R1, Oxatent® Abidi pharmaceutical company, Iran), and vitamin B6 intravenous injection (100 mg/2 mL, lot number 060, Vibsix®, Caspian Tamin pharmaceutical company, Iran) for this study. All eligible patients were intravenously given linezolid 300 mL (600 mg) twice daily for at least six days. The treatment group received vitamin B6 intravenously 1 mL (50 mg) twice daily as adjuvant besides linezolid.

Demographic data (age, sex, underlying disease), type of poisoning, vital signs, glomerular filtration rate (GFR), acute physiology and chronic health evaluation II (APACHE II), paraclinical factors, ICU and poison ward length of stay, linezolid treatment duration, blood product transfusion during treatment, and outcomes were recorded for all patients. Lab tests were assessed at baseline, including complete blood count [white blood cells (WBCs), red blood cells (RBCs), hemoglobin (Hb), hematocrit (Hct), platelets (PLTs)], liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], sodium, potassium, albumin, bilirubin-total, creatinine (Cr), prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). RBCs, Hb, Hct, and PLTs were also investigated on days 0 (a day before linezolid initiation), 1, 3, 5, and 7 throughout the treatment course. GFR was calculated using the Cockroft-Gault formula [13].

Hematological toxicities were defined as follows; thrombocytopenia as PLT counts $<150 \times 10^3/\mu L$ and anemia as Hb reduction ≥ 2 g/dL from the baseline [18,19].

2.3. Statistical Analysis

The statistical analysis was performed by SPSS (version 18, Chicago, Ill, USA). The categorical variables were expressed as number (percentage) and numerical variables as mean ± SD. The categorical variables were compared using the χ^2 test or Fisher exact test and other quantitative variables using the student's t-test or Mann-Whitney U test. We used repeated-measures ANOVA to compare the hematological factors differences on days 0, 1, 3, 5, and 7 throughout the treatment course. A P value of < 0.05 was considered significant.

3. Results and Discussion

3.1. Patient Demographic Characteristics

A number of 78 eligible patients were included in this study. The mean age was 40.83 ± 17.65 years, and 58 (74.36%) were male. Most drug toxicities were benzodiazepine (BZD) and methadone, with a mortality rate of 41% (32 out of 78 patients).

Twenty-eight patients were assigned to receive linezolid+B6 (treatment group) and 50 patients to linezolid alone (control group). The demographic and clinical characteristics of the patients were summarized in Table 1. There were no considerable differences between the two groups in demographic characteristics, poisoning [except aluminum phosphide (14.3% vs. 0%)], vital signs, baseline laboratory test results, GFR, APACHE II score, hematological toxicities, and death rate.

Linezolid treatment duration in linezolid+B6 and linezolid groups were 7.57 ± 2.33 and 8.42 ± 3.5 days, respectively ($P > 0.05$). In linezolid+B6 group, 10 (35.7%) patients received blood product transfusion during treatment, which had no difference compared to the control group ($P > 0.05$). The length of ICU [16.14 ± 8.3 days vs 23.04 ± 18.59 days ($P < 0.05$)] and poison ward stay in patients received B6 [1.25 ± 2.53 days vs 7.72 ± 15.47 days ($P < 0.01$)] were significantly lower than control group. The rates of thrombocytopenia and anemia in the linezolid+B6 and control groups were 75% vs 62% ($P > 0.05$) and 21.4% vs 24% ($P > 0.05$), respectively.

3.2. Trends of Hematological Factors in Treatment and Control Groups

Fig. 1 showed trends of hematological factors in treatment and control groups. RBCs in the treatment group showed a decreasing trend over time compared to the initial value (except day 3) (Figure 1A). According to Table 2, starting on day one, RBCs in the treatment group (n=16) were significantly higher than those in the control group (n= 31) ($P < 0.05$).

Based on Fig. 1B, Hb levels in the linezolid+B6 group illustrated fluctuations over time. In overall, patients who received linezolid+B6 (n=17) had significantly higher Hb levels starting on day 0, compared to those treated with linezolid alone (n=32) ($P < 0.05$) (Table 2).

Hct in the linezolid+B6 group possessed a slow reduction with time except day 3 (Figure 1C). It was considerably higher in treatment group (n=18) in comparison to the control group (n=32) from the baseline (day 0) ($P < 0.01$) as well as Hb chart (Table 2).

Unexpectedly, patients treated with linezolid+B6 (n=16) had lower PLT counts compared to control group (n=33) with no significant differences ($P > 0.05$) (Table 2). Additionally, both treatment and control groups showed upward trends in this hematological factor (Figure 1D).

3.3. Discussion

Administration of vitamin B6 at 50 mg twice daily would not prevent the linezolid-associated hematological dyscrasia, as there were anemic and thrombocytopenic patients in both treatment and control groups; however, it might decline the risk of anemia.

Vitamin B6 is a water-soluble vitamin metabolized to the active form of pyridoxal-5-phosphate [20]. The metabolite is a coenzyme of many reactions, such as decarboxylation and transamination. It is also involved in the

formation of δ-aminolevulinic acid from glycine and succinic acid, which is essential for the synthesis of the heme group in hemoglobin. Therefore, vitamin B6 deficiency would lead to hypochromic microcytic anemia [21].

Vancomycin is used as the first-line therapy for MRSA infections, including sepsis, endocarditis, osteomyelitis, infection of tissues, skin, and different kinds of pneumonia, including aspiration pneumonia and ventilator-associated pneumonia (VAP) [22,23]. In some cases, it is recommended to substitute vancomycin with linezolid since vancomycin is associated with some disadvantages, including nephrotoxicity, slow bactericidal activity, minimal penetration into lung tissue, and the emergence of resistant pathogens [24]. Although linezolid is not the first choice for MRSA infections and hematological toxicities may restrict its utilization, which requires close monitoring of these parameters for patients on linezolid therapy [25, 26].

Based on our literature review, there have been few studies that evaluated the effect of vitamin B6 on linezolid-induced hematological dyscrasia.

Spellberg *et al*., in a study of two cases with Mycobacterium abscesses infections with prolonged linezolid therapy, reported that the daily administration of 50 mg vitamin B6 for two weeks resolved their cytopenias [16]. While as in our study, this co-administration could only affect the anemia. The small sample size of Spellberg *et al*.'s study could not provide a reliable conclusion. In another study of patients with cancer, as the same our findings, beneficial effects of vitamin B6 (50 mg/day) on anemia but not thrombocytopenia and leukopenia were reported [27]. Similarly, in a study of septic patients, Deng *et al*. reported that combination treatment of linezolid and vitamin B6 might slow the reduction of RBC, Hb, and Hct levels, whereas no improvement was seen in PLT counts [28].

Moreover, Hanai *et al*. reported GFR<60 mL/min as a risk factor of linezolid-induced thrombocytopenia [13]. In our study, the average of this factor was more than 60 mL/min. Tajima *et al*. suggested that linezolid use for more than 14 days would increase thrombocytopenia occurrence [14]. This parameter was lower than 14 days in our treatment and control groups.

It should be mentioned that, as this study was performed in toxicological ICU, the poisoning background of the patients could lead to hematological disorders on admission. Therefore, only those patients were selected whose toxicity had not affected the hematological factors on admission.

3.4. Strength and Limitations

In the current study, we enrolled 28 and 50 patients in treatment and control groups, respectively, which included a larger population than previous studies. Also, the number of patients in the control group was twice higher than that in the treatment group indicating the study's intense power.

Additionally, some patients were discharged or died before the completion of the treatment course, and therefore it was impossible to follow their lab results. Despite excluding all anemic and thrombocytopenic patients and those toxicities affecting the hematological factors on admission, the effects of other medications administered due to patients' poisoning backgrounds were inevitable, which might disturb the patients' hematological lab results. Therefore, we could not observe sharp reducing trends in these parameters.

4. Conclusion

According to our findings, the administration of vitamin B6 at a dose of 50 mg twice daily could have beneficial effects for patients who received linezolid. On the other hand, this co-administration was accompanied by a lower risk of anemia but no impact on preventing or reducing thrombocytopenia in patients with gram-positive bacterial infections. We suggest that future studies with larger sample sizes and higher doses of vitamin B6 should be warranted to investigate the efficacy of this vitamin.

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Tables:

Table 1. Demographic and Clinical characteristics of 78 patients.

Variables	All patients (n=78)	Linezolid+B6 (n=28)	Linezolid (n=50)	P value
Age, mean± SD (years)	40.83 ± 17.65	38.68 ± 15.79	42.0 ± 18.66	0.423
Gender, n (%)				0.66
Male	58 (74.36)	20 (71.4)	38 (76)	-
Female	20 (25.64)	8 (28.6)	12 (24)	-
Underlying diseases, n (%)				
COPD	5 (6.4)	1 (3.6)	4 (8.0)	<0.001
Cancer	2 (2.6)	1 (3.6)	1 (2.0)	<0.001
Hepatitis C	1 (1.3)	0 (0)	1 (2.0)	0.003
Pneumonia	1 (1.3)	0 (0)	1 (2.0)	<0.001
Coronary heart disease	3 (3.8)	2 (7.1)	4 (8.0)	<0.001
Neurological disorder	7 (9.0)	4 (14.3)	4 (8.0)	0.001
No or unknown underlying disease	62 (79.5)	21 (75.0)	41 (82.0)	0.32
Poisoning at baseline, n (%)				
BZD	31 (39.7)	9 (32.1)	22 (44)	0.305
Methadone	31 (39.7)	8 (28.6)	23 (46)	0.131
Tramadol	13 (16.7)	5 (17.9)	8 (16)	0.833
Amphetamine	9 (11.5)	3 (10.7)	6 (12)	0.865
Aluminum phosphide	4 (5.1)	4 (14.3)	0 (0)	0.006
Opiate	15 (19.2)	7 (25)	8 (16)	0.333
Other poisoning [a]	12 (15.4)	7 (25)	5 (10)	0.078
Vital signs at baseline, mean± SD				
Temperature (°C)	37.27 ± 0.59	37.18 ± 0.59	37.31 ± 0.6	0.34
Heart rate (/min)	96.05 ± 22.75	96.68 ± 18.02	95.7 ± 25.18	0.86
Respiratory rate (/min)	15.81 ± 5.6	15.11 ± 5.9	16.2 ± 5.4	0.41
Systolic pressure (mmHg)	115.38 ± 25.17	111.71 ± 24.35	117.43 ± 25.64	0.34
Diastolic pressure (mmHg)	70.0 ± 16.71	69.82 ± 19.1	70.1 ± 15.43	0.94
Paraclinical factors at baseline, mean± SD				
WBC ($\times 10^3/\mu L$)	12.45 ± 6.2	12.7 ± 6.58	12.3 ± 6.02	0.77
RBC ($\times 10^6/\mu L$)	4.76 ± 0.81	4.8 ± 0.78	4.7 ± 0.83	0.71
Hb (g/dL)	14.33 ± 2.7	14.72 ± 2.5	14.1 ± 2.8	0.34
Hct (%)	41.83 ± 7.2	42.34 ± 7.1	41.5 ± 7.3	0.64
PLT($\times 10^3/\mu L$)	225.97 ± 77.05	222.96 ± 70.22	227.66 ± 81.27	0.8
AST (U/L)	260.63 ± 694.42	370.5 ± 812	197.86 ± 617.71	0.3
ALT (U/L)	626.34 ± 2648.68	1293.64 ± 4218.63	245.02 ± 830.06	0.2
Sodium (mEq/L)	138.29 ± 3.41	137.78 ± 4.2	138.58 ± 2.9	0.33
Potassium (mmol/L)	4.27 ± 0.79	4.26 ± 0.92	4.27 ± 0.72	0.94
Albumin [b] (g/dL)	3.83 ± 0.85	3.7 ± 0.54	4.1 ± 0.79	0.16
Bilirubin-Total (mg/dL)	1.23 ± 1.26	1.37 ± 0.97	1.15 ± 1.6	0.57
Creatinine (mg/dL)	1.56 ± 1.0	1.57 ± 0.83	1.55 ± 1.1	0.92
PT(sec)	14.68 ± 2.44	14.97 ± 2.3	14.51 ± 2.53	0.43
PTT(sec)	31.37 ± 7.91	31.89 ± 8.73	31.07 ± 7.49	0.67
INR	1.39 ± 0.47	1.47 ± 0.46	1.35 ± 0.49	0.33
GFR at baseline, mean± SD (mL/min)	67.54 ± 28.41	64.84 ± 27.52	69.06 ± 29.07	0.53
APACHE II [c], mean± SD	15.62 ± 7.15	16.31 ± 8.06	15.06 ± 6.54	0.65
ICU length of stay, mean± SD (day)	20.56 ± 15.97	16.14 ± 8.3	23.04 ± 18.59	0.03
Poison ward length of stay, mean± SD (day)	5.4 ± 12.8	1.25 ± 2.53	7.72 ± 15.47	0.006
Linezolid treatment duration (day)	8.1 ± 3.4	7.57 ± 2.33	8.42 ± 3.5	0.26
Blood product transfusion, n (%)	37 (47.43)	10 (35.7)	27 (54)	0.121
Hematological toxicities after treatment, n (%)				
Thrombocytopenia	52 (66.7)	21 (75.0)	31 (62.0)	0.53

Anemia	18 (23.08)	6 (21.4)	12 (24.0)	0.8
Patients' outcome, n (%)				
Cure	38 (48.71)	15 (53.6)	23 (46.0)	0.52
Cure with sequel	8 (10.26)	4 (14.3)	4 (8.0)	0.31
Death	32 (41.02)	9 (32.1)	23 (46.0)	0.23

[a]Organophosphorus, Heart disease medications, Neurological-related medications.
[b]Linezolid+B6, n=15, linezolid, n=8, [c] Linezolid+B6, n=13, Linezolid, n=16.

Table 2. Repeated-measures ANOVA results for hematological factors; Red blood cells (RBCs), hemoglobin (Hb), hematocrit (Hct), and platelets (PLTs).

Hematological factors	Time of observation (day)	Linezolid+B6	Linezolid	P value
RBC [a] $\times 10^6/\mu L$	**0**	3.975±0.84	3.58±0.52	0.051
	1st	3.88±0.91	3.44±0.50	0.035
	3rd	4.00±0.79	3.41±0.53	0.004
	5th	3.87±0.87	3.41±0.58	0.036
	7th	3.91±0.70	3.28±0.58	0.002
Hb [b] g/dL	**0**	11.45±1.92	10.01±1.60	0.007
	1st	11.12±2.11	9.76±1.58	0.015
	3rd	11.46±1.97	9.62±1.28	0.0001
	5th	10.99±2.07	9.77±1.56	0.025
	7th	11.42±1.63	9.54±1.68	0.0001
Hct [c] %	**0**	35.79±6.57	30.83±5.10	0.005
	1st	34.08±6.39	29.97±4.10	0.008
	3rd	35.59±6.04	29.72±3.70	0.0001
	5th	34.29±6.82	29.73±4.68	0.007
	7th	34.69±5.16	29.34±4.91	0.001
PLT [d] $\times 10^3/\mu L$	**0**	187.87±135.45	205.12±117.72	0.65
	1st	188.25±136.71	205.39±123.44	0.66
	3rd	212.12±178.84	225.06±124.94	0.76
	5th	189.75±130.42	256.39±128.36	0.097
	7th	208.37±121.61	233.21±129.52	0.52

[a]Linezolid+B6, n=16 and linezolid, n= 31. [b] Linezolid+B6, n=17 and linezolid, n= 32.
[c]Linezolid+B6, n=18 and linezolid, n= 32. [d] Linezolid+B6, n=16 and linezolid, n= 33.

Figures:

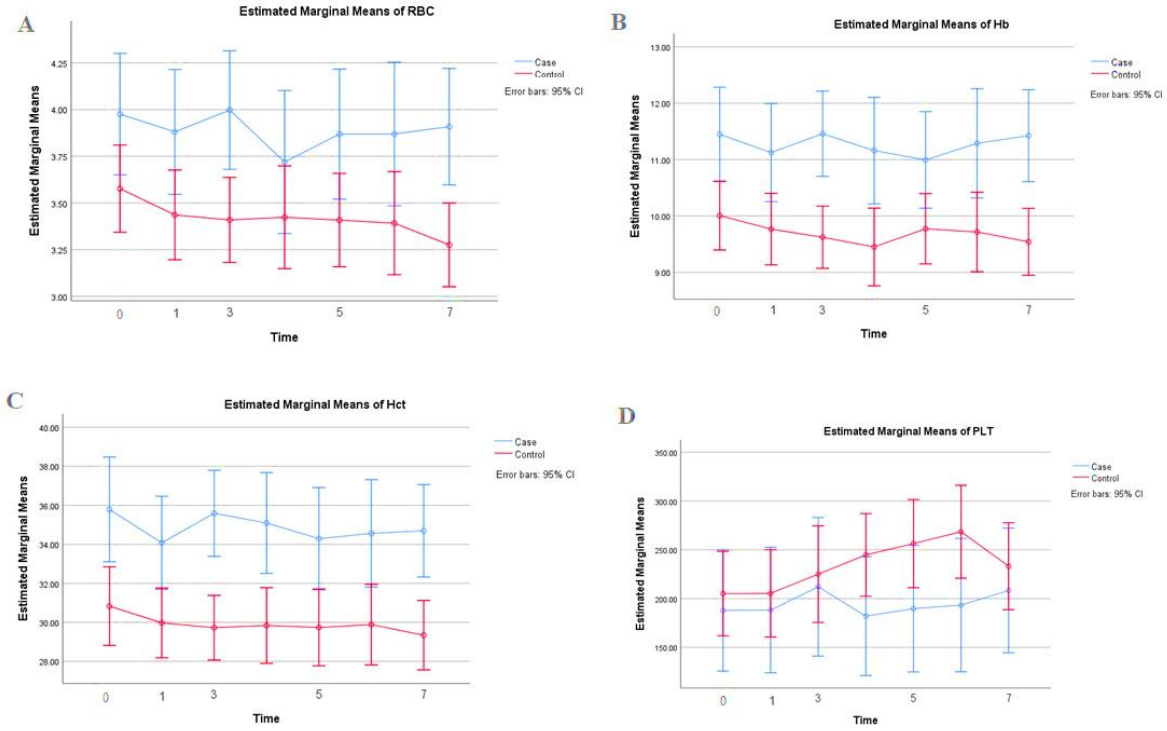

Figure 1. Trends in hematological factors; A) Red blood cells (RBCs), B) hemoglobin (Hb), C) hematocrit (Hct), and D) platelets (PLTs).