ORIGINAL ARTICLE

The effect of oral zinc on hemoglobin and dose of erythropoietin in hemodialysis patients

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Background: In hemodialysis (HD) patients, low serum zinc level could cause hyporesponsivity to erythropoiesis-stimulating agents and lead to anemia. This study investigated the effects of oral zinc supplements on the required dose of erythropoietin in patients undergoing HD. **Materials and Methods:** In a double-blinded randomized trial, 76 HD patients were assigned to 2 groups of 38. One group (intervention) was treated with oral zinc supplements of 210 mg, daily for 6 months, and the other group (control) used placebo capsules for 6 months. The serum zinc level, hemoglobin level, and required dose of erythropoietin, albumin, ferritin, ferrous, and total iron-binding capacity were evaluated 3 and 6 months after intervention. **Results:** Repeated measures ANOVA did not show a significant increase in Hb level after 6 months of intervention ($P = 0.28$). However, the required dose of erythropoietin was decreased, but the changes were not statistically significant ($P > 0.05$). The changes in the other variables were not statistically significant. **Conclusion:** Oral zinc supplementation in HD patients could not increase hemoglobin level irrespective of their serum zinc level.

Key words: Anemia, erythropoietin, renal dialysis, zinc level

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INTRODUCTION

Anemia is a common complication of chronic kidney disease (CKD), especially in patients with end-stage renal disease.[1] Anemia could raise the risk of death and hospitalization.[2,3] This type of anemia is normocytic, normochromic, and hypoproliferative. Some factors could cause anemia in CKD patients which the two most prevalent are iron and erythropoietin deficiency.[4] Currently, erythropoietin agents are the most common treatments of anemia in these patients.[5]

Resistant to erythropoiesis-stimulating agents (ESAs) or hyporesponsiveness to ESA are the other important causes of anemia which are reported in up to 12.5% of patients undergoing hemodialysis (HD).[6] Iron deficiency, infection, inflammation, and depletion of several vitamins and minerals including Vitamin B_{12} and folate are associated with ESA hyporesponsiveness and resistance to ESA.[7,8]

Some previous studies indicated that the level of serum zinc is low in patients who underwent HD. It could be due to removing zinc during HD, low levels of serum albumin, inadequate intake, and reduced absorption from the gastrointestinal tract.[9] It should be noticed that, in addition to the role of zinc in metabolic processes, growth, and immune competence, it also has a significant role in hemoglobin synthesis and erythropoiesis.[10,11] On the other hand, a low level of

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serum zinc could intensify hemolysis during HD process and its mechanical damage.[12]

To our knowledge, the effects of oral zinc supplements on anemia and the required dose of erythropoietin are still in doubt. In this regard, some studies showed that oral zinc supplements could improve anemia in HD patients. Anemia improves in patients with high serum zinc levels. Regarding the anemia-improving effect of zinc supplementation, it was found that the hemoglobin level increased significantly[13,14] while it is in doubt in the study of Rasool *et al*.[15]

Due to the importance of treating anemia in ESRD patients, this study was conducted to evaluate the effects of oral zinc supplements on the required dose of erythropoietin in patients undergoing HD.

MATERIALS AND METHODS

Study design and population

This double-blinded randomized trial was done in Isfahan University of Medical Sciences, Iran, in 2021. Patients were selected from three hospitals including Al-Zahra, Nour, and Hojatieh. The inclusion criteria were as follows: age of above 18 years, suffering from end-stage renal disease patients undergoing HD, undergoing HD at least 2 times a week for more than 3 months, hemoglobin below 12 g/dl, ferritin more than 200 ng/ml, treating with erythropoietin, no pregnancy and breastfeeding, no presence of active malignancy, hepatic disease, coronary catheterization in the recent 3 months, and also consent for voluntary participation in the study. The exclusion criteria included no desire to maintain participating in the study, major surgery during the recent 3 months, active phase of infection, active bleeding, and death. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences (ethical code no: 1399.432, IRCT code: IRCT20200827048539N1). The study goals were described to the patients, and they assured about voluntary participation. The informed consent was completed by the participants.

5%, β =80%, and 1-β= 0.8. For compensating possible attrition, we consider attrition rate of 20%, thus we have two groups including 38 patients.

Procedures and outcome assessment

Seventy-six patients who had the eligible criteria were included. Participants were divided into 2 groups of 38 by permuted block randomization with block size 4 [Figure 1]. Random concealment was done by labeling the treatments and generated random digits indicating groups' allocation as A and B. The zinc capsules were from Dineh Pharmaceutics Company Industry, Iran. The form of each tablet was 210 mg zinc gluconate which contained 30 mg of elemental zinc. The placebo capsules were prepared in the same shape, size, and color with the zinc capsules by School of Pharmacy and Pharmaceutical Sciences at Isfahan University of Medical Sciences. Zinc and placebo capsules were separated into two boxes and randomly named A and B by a staff in this school.

Data were gathered by a two-part checklist. The first part was about demographic data such as age, sex duration of HD, educational level, and history of diabetes mellitus, cancers, polycystic kidney, kidney transplantation, use of drugs, and the kinds of dialysis access such as graft, fistula, and catheter.

The second part was laboratory information including serum zinc level, hemoglobin, albumin, iron (Fe), total iron-binding capacity, ferritin, and also data such as required erythropoietin dosage, urea reduction ratio (URR), and KT/V, before, 3, and 6 months after intervention.

Participants used one capsule once a day for 6 months. All of the participants underwent treatment with routine dose of erythropoietin, iron and also consumed one tablet of supplementary drugs containing zinc such as Nephro-Vite, daily. Blood sampling was repeated 3 and 6 months after intervention and documented. The required erythropoietin dosage, URR, and KT/V were measured and calculated 3 and 6 months after the intervention. Serum zinc level was measured by Biorex kits, which was similar in all the three laboratories.

Statistical analysis

Statistical analyses were performed using SPSS software 2021 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean values ± standard deviation (SD) and categorical variables were expressed as frequency (percentage). Normality of continuous variables was checked using Shapiro–Wilk test and Q-Q plot. Independent samples *t*-test and Chi-squared test were used for comparing basic continuous and categorical variables between two groups. Repeated measures ANOVA was used for evaluating within and between groups changes in main study outcomes. Mauchly's test was used for evaluating sphericity. When sphericity was violated, multivariate approach was adopted for data analysis. We also compared the main study outcomes at each time point between the two groups using an independent sample *t*-test or Mann–Whitney *U*-test.

RESULTS

In this study, the mean ± SD age was 51.21 ± 13.76 and 47.92 ± 15.84 years in placebo and zinc groups, respectively ($P > 0.05$). The mean duration of HD was

40.84 ± 37.97 in the placebo and 32.39 ± 27.94 months in the zinc group ($P > 0.05$). The two intervention groups were comparable in terms of all other basic characteristics [Table 1]. Both groups had no statistical difference in basic characteristics.

Repeated measured ANOVA did not show a significant increase in Hb level after intervention ($P = 0.28$). In this study, however, the required dose of erythropoietin was decreased, but the changes were not statistically significant ($P > 0.05$). There were not any significant changes in serum iron level. Furthermore, the changes in the other variables were also not statistically significant ($P > 0.05$). The mean changes of parameters and their comparison in pre- and postintervention in zinc supplement and placebo groups are shown in Table 2.

DISCUSSION

Our findings revealed that zinc supplements in 210 mg (30 mg elemental zinc) mg for 6 months could increase Hb level but not decrease the required erythropoietin dosage in 6 months of intervention. However, the dose of erythropoietin was decreased in the post 3 and 6 months, but it was not statistically significant. This result is not consistent with the findings of Kobayashi *et al*.[13] In their study, polaprezinc (a chelated form of zinc and L-carnosine) was prescribed to the participants in 34 mg, daily for 12 months. They showed a significant reduction in erythropoietin dose. In another study, Fukushima *et al*.[14] showed that erythropoietin dosage could be reduced to the levels below baseline with polaprezinc (containing 34 mg) in 12 weeks. Furthermore, they believed that zinc supplementations could improve anemia in a shorter time in patients with erythropoietin-hyporesponsiveness.[14] In another study, Takahashi described that zinc supplementations could increase hematocrit level and red blood cells and also reduce need to erythropoietin.[16]

In the present study, the baseline serum level of zinc did not increase significantly between the case and control groups. The mean level of zinc increased in post 3 months (85.80 ± 10.85), but it had no changes in post 6 months (85.32 ± 11.39) in the intervention group. However,

Table 1: Demographic and clinical information

Variables	Placebo (n=37), n (%)	Intervention (zinc, n=38), n (%)	P*
Age	51.22±13.77	47.92±15.84	0.34
Duration of dialysis (months)	40.54±37.97	32.39±27.94	0.29
Number of dialysis per week	2.84±0.38	2.87±0.41	0.74
Sex			
Male	24 (64.9)	26 (68.4)	0.74
Female	13 (35.1)	12 (31.6)	
History of disease			
Diabetes			
Yes	16 (43.2)	11 (28.9)	0.20
No	21 (56.8)	27 (71.1)	
HTN			
Yes	26 (70.3)	23 (60.5)	0.38
No	11 (29.7)	15 (39.5)	
Polycystic kidney			
Yes	1 (2.7)	1 (2.6)	>0.99
No	36 (97.3)	37 (97.4)	
Access dialysis			
Fistula	14 (40)	16 (42.1)	0.494
Graft	2 (5.7)	5 (13.2)	
Permacath	19 (54.3)	17 (44.7)	
Drugs			
Iron source injection			
Yes	21 (60)	21 (55.3)	0.683
No	14 (40)	17 (44.7)	
Angiotensin II receptor blockers			
Yes	4 (11.4)	8 (21.1)	0.268
No	31 (88.6)	30 (78.9)	
Angiotensin-converting enzyme inhibitors			
Yes	0	1 (2.6)	0.999
No	35 (100)	37 (97.4)	

*Resulted from independent sample *t*-test for continuous and Chi-squared or Fisher's exact test for categorical data. HTN=Hypertension

Table 2: Mean changes and comparison of parameters in pre- and postintervention in zinc supplement and placebo groups

Variables	Times			P_{time}	$P_{time\times Intervention}$	$P_{Intervention}$**
	Pre	Post 3 months	Post 6 months			
Zinc						
Placebo	82.43±17.50	88.91±25.12	80.97±11.41	0.062	0.334	0.89
Intervention*	82.32±16.73	85.80±10.85	85.32±11.39	0.331		
P#	0.978	0.502	0.108			
Hb						
Placebo	9.96±1.48	10.53±1.55	10.61±1.71	0.167	0.764	0.28
Intervention	10.28±1.36	11.42±2.16	11.10±2.05	0.217		
P#	0.067	0.048*	0.344			
Albumin						
Placebo	3.83±0.38	3.84±0.33	3.82±0.34	0.091	0.476	0.90
Intervention	3.83±0.37	3.77±0.59	3.85±0.36	0.506		
P#	0.927	0.518	0.661			
Fe						
Placebo	133.26±119.8	99.61±105.29	101.60±73.48	0.191	0.466	0.23
Intervention	98.05±71.57	88.81±71.63	92.70±69.28	0.705		
P#	0.137	0.608	0.596			
TIBC						
Placebo	306.25±87.36	341.31±82.54	322.83±346.05	0.115	0.145	0.76
Intervention	313.18±66.01	324.76±74.83	346.05±91.60	0.024		
P#	0.702	0.372	0.278			
Ferritin						
Placebo	443.99±276.77	319.70±235.40	437.74±280.06	0.028	0.111	0.73
Intervention	388.81±439.54	400.79±427.88	492.84±461.15	0.113		
P#	0.532	0.305	0.495			
KT/V						
Placebo	1.47±1.50	1.50±1.70	21.70±120.81	0.626	0.592	0.30
Intervention	1.40±0.32	1.41±0.32	1.35±0.37	0.492		
P#	0.766	0.739	0.326			
URR						
Placebo	0.62±0.06	0.66±0.14	0.67±0.12	0.044	0.273	0.09
Intervention	0.69±0.11	0.69±0.86	0.70±0.15	0.809		
P#	0.001	0.251	0.435			
Erythropoietin (mU/mL)						
Placebo	7657.14±6130.65	9228.57±8499.43	8257.14±8056.21	0.411	0.165	0.52
Intervention	8697.37±8086.98	7157.89±8264.30	6315.79±7530.50	0.282		
P#	0.540	0.295	0.291			
Tsat (Fe/TIBC)						
Placebo	0.47±0.44	0.37±0.47	0.34±0.28	0.279	0.627	0.195
Intervention	0.34±0.27	0.31±0.27	0.29±0.23	0.363		
P#	0.604	0.501	0.536			

*Intervention: Zinc supplementation; **P value resulted from repeated measured ANOVA; #Resulted from independent t-test or Mann–Whitney U-test. Hb=Hemoglobin; Fe=Iron; TIBC=Total iron-binding capacity; URR=Urea reduction ratio; Tsat=Transferrin saturation

these changes were not statistically significant. These results are not consistent with Sharifian *et al*.[17] and Younan *et al*.[18] They treated their patients with zinc sulfate (containing 250 mg elemental zinc/day) and elemental zinc (containing 50 mg elemental zinc/day), respectively, for 6 weeks. Their results indicated that both mean serum zinc level and mean hemoglobin increased in 6 weeks. In this way, Younan *et al*. showed that there is a positive relation between increasing serum zinc level and correction of anemia.[18] It seems that the dose of zinc was low to increase serum zinc level. In this regard, Wang *et al*. in their meta-analysis described that the effective median intervention time was 60 days and the median zinc dose was 45 mg/day.[19]

Most of the authors reported low zinc concentration in the serum of patients undergoing HD. They indicated that 78% of patients on HD had low plasma zinc concentration.[20,21] In this regard, Rahamtalla said that in patients with renal failure, zinc level significantly decreased compared to the control group.[22] In renal failure, patients have disturbances

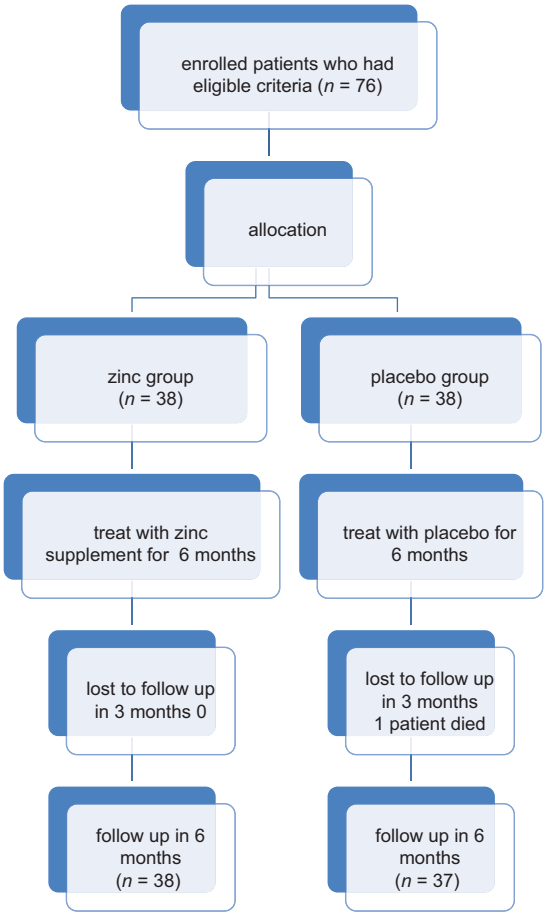

Figure 1: CONSORT flow diagram

in acid-base balance leading to acidic blood pH, therefore low zinc levels in these patients are believed to be due to the shift of zinc into red blood cells under acidic conditions.[23]

Based on the findings of Wang *et al*., no statistical significance was found in albumin level and hemoglobin.[19] Although, Nishime *et al*. indicated that lower serum zinc concentration could be associated with hypoalbuminemia.[24] In our study, albumin level had not experienced any notable changes since hypoalbuminemia was not common in our study participants.

In this study, the prescription of 30 mg per day of elemental zinc supplementation for 6 months in HD patients did not significantly increase hemoglobin level and the erythropoietin dose did not decrease which might be due to the short duration of study. Moreover, increasing hemoglobin level can be a consequence of the zinc effect.

Our study had some limitations including low number of participants and short time of study. It is suggested to do another survey with more sample size and longer time for intervention and also with different doses of zinc supplements. In addition, only zinc gluconate was used in our study. The use of other forms of zinc, such as zinc sulfate, is recommended for future research.There are many parameters may have effect on EPO response such as serum PTH, phosphorus, CRP levels, etc. Therefore, it would be better to consider these factors in the forthcoming studies.

CONCLUSION

Oral zinc supplementation in HD patients could not significantly increase hemoglobin level irrespective of their serum zinc level.

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Conflicts of interest

There are no conflicts of interest.

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