Effect of short-term intravenous ascorbic acid on reducing ferritin in hemodialysis patients

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ABSTRACT

Resistance to recombinant erythropoietin (rEPO) in hemodialysis patients may be due to inadequate iron recruitment and defect in iron use. In this cross over randomized clinical trial, 30 hemodialysis patients with serum ferritin levels of ≥500 ng/ml, hemoglobin ≤11.0 g/dl, and transferrin saturation (TSAT) of 20% or less were administrated intravenous iron (50-100 mg/wk) and rEPO (120-360 U/kg/wk) for 6 months. Patients were excluded if there was a clear explanation for rEPO hyporesponsiveness. Patients were divided into two groups. Group1 received standard care and 500 mg of intravenous ascorbic acid (IVAA) with each dialysis session in the first week of each month for a total of 3 months. Group 2 received standard care only. After 2 month washout period, groups were crossed over. Each month hemoglobin (Hb) was assessed. Iron, TIBC (transferrin iron binding capacity), TSAT, iPTH (intact parathyroid hormone), liver enzymes, albumin and cholesterol levels were measured every 3 months. After 3 months of intervention, Hb significantly increased from 10.11 to 12.19 g/dl ($P < 0.001$; 95% confidence interval [CI] 2.7-1.4) and TSAT increased from 18.9 to 28.1% ($P = 0.008$; 95% CI 0.09-3), while ferritin and serum iron declined significantly from 1391 to 938 ng/ml ($P = 0.001$; 95% CI 216-689), 97.2 to 64.6 ($P = 0.001$; 95% CI 14.8-50.4) in the study group. Change of Hb over time in IVAA group was significant ($P < 0.0005$). There were significant differences between two groups in change of Hb level over time ($P < 0.0005$) and treatment effect ($P = 0.002$). Baseline laboratory tests were similar in the two groups and there was no carry over effect at phase 2. We showed that low amount of IVAA could reduce ferritin level and enhance Hb and TSAT, suggesting improved iron utilization.

Key words: Anemia, ascorbic acid, hemodialysis

Introduction

Anemia is common in patients with end-stage renal disease (ESRD) and is a risk factor for hospitalization and mortality.[1] The causes include blood loss caused by dialysis circuit, shortened red blood cell life, and poor production of erythropoietin, the most important reason for anemia.[2] Severe anemia is linked to adverse consequences[3] such as cardiac enlargement, ventricular hypertrophy, congestive heart failure, decreased cognitive and mental sharpness, and impaired immune responses.[4] Replacement therapy with recombinant erythropoietin (rEPO) is the key treatment for anemia. However, adequate storage of accessible iron in the body is required for inducing response to rEpo.[5]

The most common cause of EPO hyporesponsiveness in hemodialysis (HD) patients is absolute or functional iron deficiency. Other causes include chronic infection and inflammation, bone marrow malignancy, vitamin B12 and/or folate deficiency, secondary hyperparathyroidism, angiotensin-converting enzyme inhibitor therapy and aluminum toxicity.

In HD patients, ascorbic acid (AA) has an influence on improving sensitivity to EPO, either by increasing iron mobilization from tissue storage or by way of antioxidant effects.[6-10] In this study, we assessed whether short term treatment with intravenous AA (INAA) could diminish the high level of ferritin and raise Hb level.

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Materials and Methods

This study was conducted in March 2010 at two HD centers (Vali-asr and Shahid Beheshti Hospitals) in the Iranian provincial capital of Zanjan. We investigated the effect of IVAA in 30 HD patients (56.6% men and 43.3% women, mean age of 52.2 years). The inclusion criteria were as follows: (1) on HD therapy for at least 6 months, (2) on rEPO for 6 months or longer at a dose of 120-360 U/kg/wk, (3) average Hb level of 11.0 g/dl or less for 3 months, (4) ferritin level greater than 500 ng/ml, (5) transferrin saturation (TSAT) of 20% or less, and (6) received maintenance intravenous iron (25-100 mg/wk). Exclusion criteria were (1) bone marrow malignancy, (2) myelodysplastic syndrome, (3) evidence of chronic infection, (4) hemochromatosis, (5) hemoglobinopathies, (6) evidence of significant bleeding (decrease in Hb level ≥2 g/dl during the past 3 months, and (7) sign of vitamin B12 and/or folate deficiency and intact parathyroid hormone (i-PTH) level >300 pg/ml.

Patients were also excluded if they developed bone marrow malignancy, myelodysplastic syndrome, hemochromatosis, or blood loss of 500 ml or greater during the 8-month study period. The study was approved by Institute Ethics Committee and patients gave signed consent. Study duration was 8 months (6 months to perform the study and 2 months wash-out period). Iron therapy was stopped for all the patients at the time of hyperferritenemia. During the study, dosage of EPO was held constant (between 120 and 360 U/kg/wk for each patient).

Blood samples for Hb, Hct (hematocrit), serum iron, TIBC, ferritin, and TSAT were obtained at baseline, monthly, and at the end of the study. In addition, iPTH, liver enzymes, albumin, and cholesterol were measured every 3 months.

Patients were randomly divided into two groups. In the first phase of the study, group 1 (15 patients) received standard care and adjuvant therapy of 500 mg of IVAA after each dialysis session, three times a week, during the first week of each month (total of 1500 mg/month). Group 2 (15 patients) received standard care. After 3 months, we had 2 months of IVAA washout period. In the second phase of the study, groups were crossed over and IVAA was administrated to group 2 for 3 months similar to the first phase. Patients were assessed monthly for adverse events. A feedback form was used to assess the side effects of AA supplementation, such as dizziness, faintness, fatigue, flank pain, and headache. During the study, all patients were administered daily supplements of folic acid (5 mg) and vitamin B6, as well as 125 mg AA after each session of HD, and vitamin B12 (100 mg) per week. This trial was approved by committee of research ethics of Zanjan University of Medical Sciences. (Trial Registration Number: IRCT138904263325N3).

The analysis was on an intent-to-treat basis. All statistical analysis was performed using SPSS for windows (version 17) software. Means of quantitative variables were compared using Student's *t*-test between two groups. In the case of discontinuous variables, chi-square test was applied. Response to AA in the study group before and after intervention was assessed with paired samples *t*-test analysis. The repeated measures analysis of variance model was used to assess the effect of AA on change of Hb over time and difference of this effect between two groups (treatment effect and time × treatment interaction). All *P*-values were two-tailed and a *P*-value of <.05 was considered significant.

Results

Ninety-eight HD patients were screened and 30 of them met inclusion criteria. These 30 patients (17 men and 13 women, with the mean age of 52.29 ± 16 years) were randomly chosen for two groups. All of them completed the study and were included in the analysis [Figures 1 and 2]. The mean dialysis duration was 44.5 months. All the patients were dialyzed for 4 hours three times a week, and the range of kt/v were comparable. Table 1 shows demographic and laboratory features of the participants in the two groups. In both groups from the beginning and during the two phases of study, the level of Hb, serum iron, serum ferritin, TIBC, TSAT, calcium, phosphor, aspartate aminotransferase and alanine aminotransferase, albumin, iPTH, cholesterol, and dosage of EPO were the same. Carry over effect was not seen at phase 2 of the study [Table 2]. After 3 months of the intervention, Hb increased from 10.11 to 12.19 g/dl ($P < 0.001$; 95% confidence interval [CI] 2.7-1.4), ferritin decreased from 1391 to 938 ng/ ml ($P = 0.001$; 95% CI 216-689), TSAT increased from 18.9% to 28.1% ($P = 0.008$; 95% CI 0.09-3),and serum iron decreased from 97.2 to 64.6 ($P = 0.001$; 95% CI 14.8-50.4) in the study group. All the above changes were significant. In the control group, change of Hb, ferritin, and other

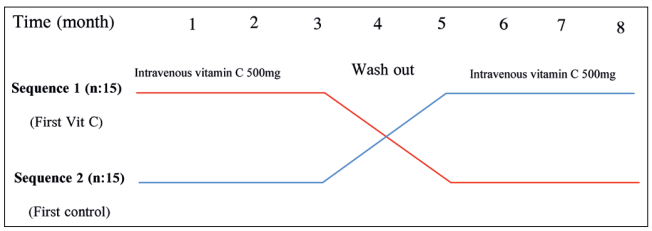

Figure 1: Flow chart of the study: Double-blind, two-period randomized cross-over study

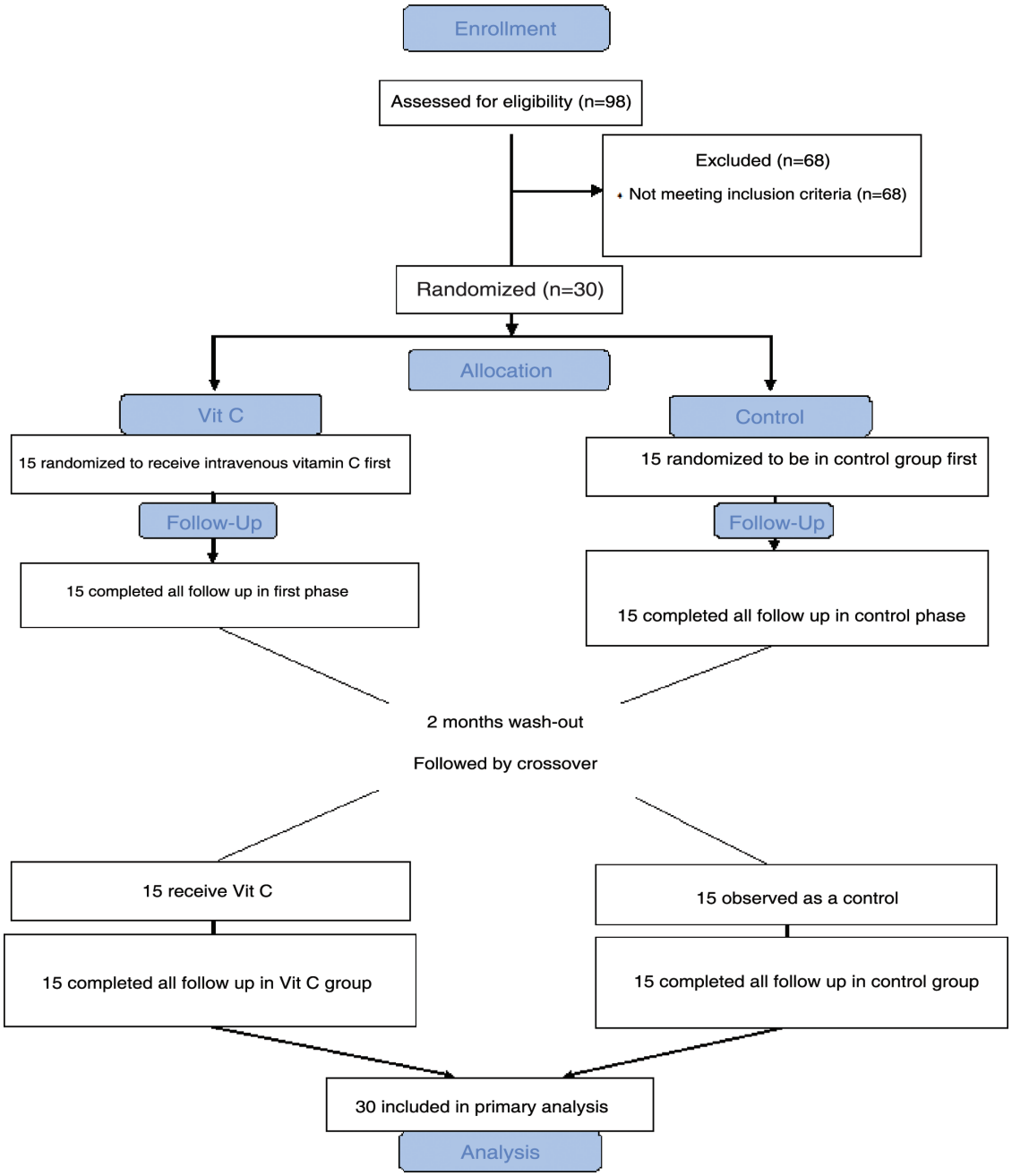

Figure 2: Study design

variables was not significant [Table 3]. Trend of Hb over time in intervention and control group is shown in Figure 3. Change of Hb over time in AA group was significant ($F = 26.8$, $P < 0.0005$), but in control group was not significant. There was significant difference between the two groups' Hb level over time ($F = 14.2$, $P < 0.0005$). The results also showed a significant treatment effect ($F = 10.9$, $P = 0.002$) [Table 4].

Discussion

Management of anemia in patients with ESRD with EPO has been a major advance. The use of EPO has decreased the amount of blood transfusions and enhanced the quality of life in the ESRD patients.[11] EPO hyporesponsiveness is reported in HD patients.[12,13] To resolve EPO hyporesponse, it has been recommended that the dosage of EPO be gradually increased.[6] However, the probable undesirable side effects related to the use of high erythropoietin doses[14] in theory has led physicians to reduce the dosage of erythropoietin.

Erythropoietin hyporesponsiveness has been described as

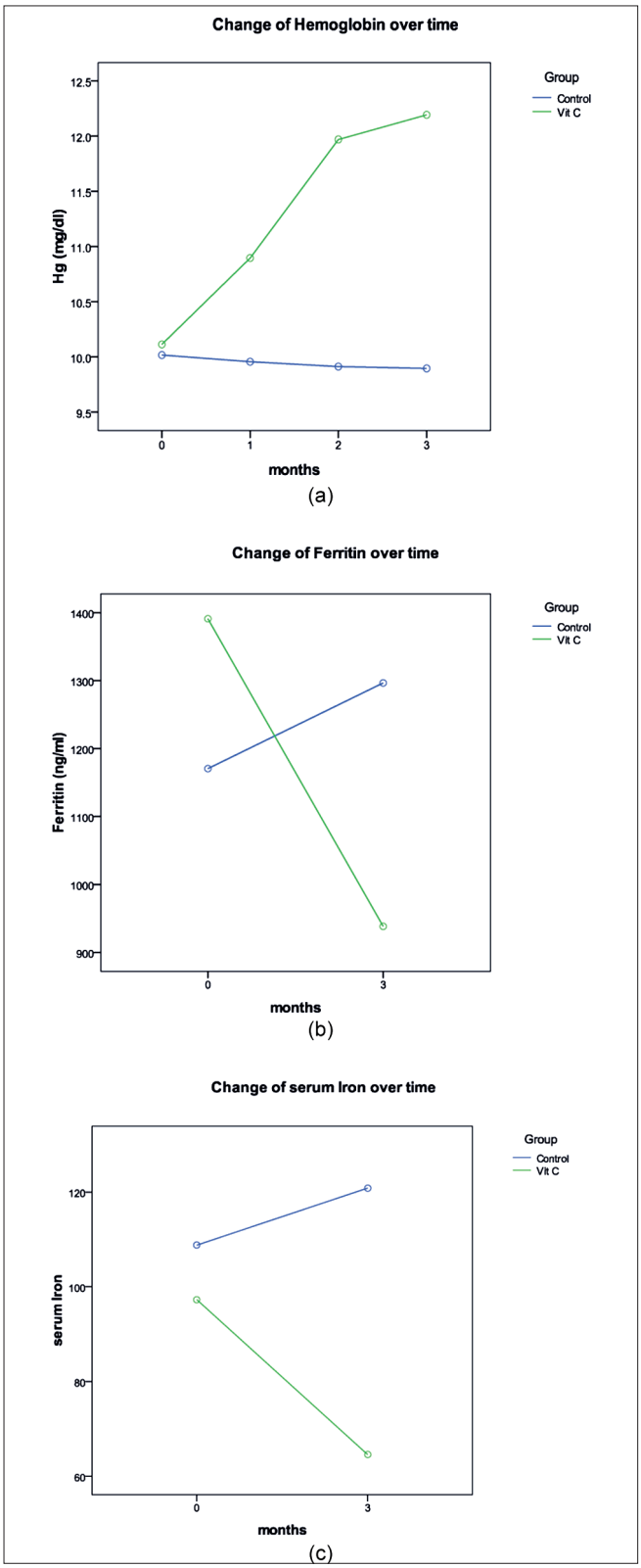

Figure 3: Change of Hg (a), ferritin (b) and serum iron (c) in two groups over time (time effect). The effect of time is not the same for both groups and there is time and treatment interaction

the failure to achieve a Hb concentration target of 11 g/dl, despite the use of an EPO dosage equal to at least 500 U/kg/wk.[15]

Table 1: Demographic and laboratory characteristics of patients in two groups

Characteristics/group	Vitamin C (*n* = 15)	Control (*n* = 15)	*P*
Age (years)	51.8 ± 16	52.4 ± 14	0.5
Gender F/M	6/9	7/8	0.7
Duration of hemodialysis (months)	38.9	45.8	0.3
EPO dosage (units/week)	9133	8533	0.6
Hb (g/dl)	10.1 ± 1.8	10.0 ± 1.8	0.8
Serum iron (mg/dl)	97.2 ± 58	108 ± 89	0.7
Ferritin (ng/ml)	1391 ± 560	1170 ± 764	0.2
TIBC (mg/dl)	347 ± 58	343 ± 58	0.7
TSAT (%)	18.9%	18.1%	0.1
Serum albumin (mg/dl)	4 ± 0.6	4.3 ± 0.8	0.1
iPTH (pg/ml)	289.6 ± 98	269 ± 87	0.7
ALT (U/L)	18.7 ± 9	18.3 ± 10	0.3
AST (U/L)	21.5 ± 12	23.5 ± 15	0.5
Cholesterol (mg/dl)	185.8 ± 40.1	175.9 ± 50.5	0.4
Calcium (mg/dl)	9.6 ± 1.2	9.3 ± 1.1	0.4
Phosphor (mg/dl)	5 ± 1	4.8 ± 1.1	0.5

Table 2: Comparison of two groups at the beginning of phase 2

Characteristics/group	Vitamin C (*n* = 15)	Control (*n* = 15)	*P*
Hb (g/dl)	10.2 ± 1.6	9.7 ± 2	0.4
EPO dosage (units/week)	8866	8666	0.7
Serum iron (mg/dl)	155 ± 62.6	268 ± 21.1	0.2
Ferritin (ng/ml)	1317 ± 975	1023 ± 460	0.3
TIBC (mg/dl)	345 ± 68	340 ± 48	0.7
Serum albumin (mg/dl)	4.8 ± 0.8	4.5 ± 0.4	0. 5
iPTH (pg/ml)	223 ± 23.3	314 ± 36.8	0.4
ALT (U/L)	19.5 ± 12	13.2 ± 4	0.1
AST (U/L)	26.6 ± 6	27.3 ± 5.6	0. 4
Cholesterol (mg/dl)	185.8 ± 50	196.9 ± 42	0.2
Calcium (mg/dl)	9.5 ± 1.2	9.1 ± 1.1	0.4
Phosphor (mg/dl)	5.2 ± 1.4	4.5 ± 0.6	0.08

Iron deficiency is one of the reasons for anemia in patients with ESRD. Iron deficiency can be found more frequently with EPO administration.[16] However, HD patients may suffer from anemia, despite an iron overload. Administration of EPO can minimize iron overload.

In patients with kidney diseases, especially those getting dialysis, iron tends to be shifted out of circulation into storage tissues, making it less available for erythropoiesis. The syndrome of decreased accessibility of storage iron is referred to as "functional iron deficiency anemia." This condition characterized by low TSAT, despite normal or increased total body iron storage (TSAT ≤ 20% and ferritin ≥500 ng/ml).[17] AA is involved in several phases of iron transport. It could release iron into the circulation and help induce EPO reaction.[12,17-21]

In this study, we used IVAA in patients who had hyperferritenemia and EPO hypo responsiveness and found that the use of low amount of IVAA for short duration improved anemia and reduced the high level

of ferritin. Attallah *et al*., in addition to standard care, administrated 300 mg of IVAA for 6 months with each session of dialysis for patients who were on EPO therapy for ≥6 months at a dose ≥450 U/kg/wk. In the AA group, Hb levels increased significantly and as a result the dosage of EPO was changed as well.[22] In this study, a total dosage of 4500 mg IVAA for 3 months was used compared with a total dosage 21,600 mg IVAA used for 6 months in Attalla's study. Our results showed significant increase in hemoglobin level from 10.11 to 12.19 g/dl.

Due to the loss of this water-soluble vitamin during the process of HD and inadequate intake from diet, HD patients are prone to subclinical AA deficiency. Therefore, routine AA supplementation for HD patients is suggested to be prescribed, whether or not they are receiving EPO.[23-27] According to the measurements used in the above study, our subjects did not have AA deficiency, because they were taking 125 mg of AA after each session of HD. So, one can assume that our patients' storage of AA was not only low, but perhaps they even had sufficient supply. Therefore, they did not need to receive high amounts of IVAA supplement. In any case, we did not check the level of AA, so this could be considered as a limitation of our study.

Table 3: Response to vitamin C in study group (paired samples *t*-test analysis) and change of variables in control group after 3-month treatment period

Characteristics	Group	Before treatment	After treatment	*P*
Hb (g/dl)	Vit C	10.11	12.19	<0.001
	Control	10.01	9.89	0.73
Serum iron (mg/dl)	Vit C	97.2	64.6	0.001
	Control	108	120	0.25
Ferritin (ng/ml)	Vit C	1391	938	0.001
	Control	1170	1296	0.38
TIBC (mg/dl)	Vit C	347	341	0.36
	Control	343	344	0.86
TSAT (%)	Vit C	18.9%	28.1%	0.008
	Control	18.1%	19.2%	0.4
Serum albumin (mg/dl)	Vit C	4	3.8	0.11
	Control	4.3	4	0.06
iPTH (pg/ml)	Vit C	289	246	0.44
	Control	269	297	0.45
ALT (U/L)	Vit C	18.7	25.4	0.06
	Control	16.3	18.8	0.29
AST (U/L)	Vit C	21.5	27.6	0.20
	Control	23.5	21.1	0.28
Cholesterol (mg/dl)	Vit C	185	178	0.26
	Control	175	177	0.85
Calcium (mg/dl)	Vit C	9.6	9.4	0.43
	Control	9.3	9.6	0.24
Phosphor (mg/dl)	Vit C	5	5.2	0.40
	Control	4.8	4.8	0.87

Effect of AA on iron indices and ferritin concentration in three trials[8,21,28] was different, while changes in ferritin level were moderate. Petrarulo and Giancaspro[29] and Ogi *et al*.[30] found a poor response even with higher and lower doses of IVVC, which were administrated for 3 months. There are other studies, too, that have not shown any benefit in the administration of AA.[31]

Erythropoietin dose have been adjusted by researchers in many trials, except in Giancaspro, *et al*.[32] study, in which the dosage was held constant. In our study, this measurement was also held constant.

Intravenous iron was given in all studies in either constant or adjusted doses except for the study by Sezer *et al*.[33] We did not administer iron during this study.

There are some concerns related to potential of secondary oxalosis with AA.[34,35] It is particularly relevant to HD patients, who have increased serum oxalate levels.[36] We did not measure the plasma oxalate level, which is another limitation of our study.

The main differences of the presented study from the others are as follows: (1) the erythropoietin dosage was not changed to maximum and instead was kept constant; (2) at the time of hyperferritenemia, patients did not get IV iron; and (3) by considering the number of times and the amount that IVAA was administered, our patients used low dosage of AA (500 mg, three times a week, during the first week of each month, for a total of 3 consecutive months). The decision to use the lower dosage was based on limiting the probable collection of oxalate in patients, because we were not measuring oxalate levels.

We have found significant increases in Hb and Hct during the 3 months of IVAA treatment, while ferritin levels decreased. We did not discover any adverse events with this short-term dose of AA. However, further studies are needed to determine at what ferritin levels maximum response from AA treatment could be attained, and to ascertain the best dosage interval for optimal effect and minimal possible toxicity.

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Table 4: Change in hemoglobin level in two groups

Hemoglobin	Baseline	After 1 month	After 2 months	After 3 months	F, *P* value (time effect)	F, *P* value (treatment effect)
Vitamin C group	10.11 ± 1.8	10.8 ± 1.7	11.9 ± 1.7	12.1 ± 1.6	26.8, <0.0005	10.9, 0.002
Control group	10.0 ± 1.8	9.9 ± 1.9	9.9 ± 1.6	9.8 ± 2	0.07, 0.97	

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