

Efficacy and Safety of Oral Versus Intravenous Vitamin C in Hemodialysis Patients with Functional Iron Deficiency

Espahbodi F, Kashi Z, Ala S, Hendoii N

Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, I.R. Iran.

Hemodialysis patients (HD) with functional iron deficiency (FID) often develop resistance to recombinant human erythropoietin (rHuEpo). Recent studies suggest that intravenous ascorbic acid (IVAA) may circumvent rHuEpo resistance, while oral AA is readily attainable. The aim of this study was to evaluate efficacy and safety of oral versus intravenous vitamin C in FID and whether this can improve anemia in hemodialysis patients.

Materials and Methods: In this study, 31 hemodialysis patients with serum ferritin >100 µg/L, transferrin saturation (Tsat) <30% and Hb<11g/dL were selected and randomly divided into the oral and IV groups. The IVAA group received vitamin C 1.5 g, administered weekly and the oral group, 125 mg vitamin C daily for two months. Hb, ferritin, serum iron, Tsat and serum oxalate were measured at the beginning of the study and 2 months later. Independent-sample T-Test were used for intergroup comparison. P value <0/05 was considered significant.

Results: Mean Hb difference was 1.1±0.7 g/dL in the oral and 0.1±1 g/dL in the IVAA group, being significantly higher in the oral group (p=0.02). There were no significant differences between the two groups in the delta means of ferritin & Tsat (p=0.5, p=0.3). Delta means of serum oxalate in the 2 groups were 0.05±0.4 mg/L, and 0.1± 0.3

mg/L respectively, difference not significant (p=0.3).

Conclusion: Oral AA significantly increased Hb in HD patients suffering from FID. Considering the feasibility and cost-effectiveness, clinicians could consider oral instead IVAA in rHuEpo hyporesponsive patients undergoing HD.

Key Words: Anemia, Functional iron deficiency, Oral, IV, Vitamin C, Hyperoxalate

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Introduction

Anemia is one of the most important complications in chronic renal failure. It is primarily due to insufficient secretion of EPO following kidney failure. Recombinant EPO (rHu EPO) is useful in correction of anemia in renal failure and sufficient response to EPO requires sufficient storage of accessible iron.¹ Although there is an overload of iron supplement in most hemodialysis patients (HD) improper response to EPO may be due to incomplete iron metabolism.² In these patients, Transferrin saturation (Tsat) and serum iron are low, whereas iron stores are high or normal.^{3,4} Therefore iron therapy may cause hemosiderosis. Ascorbic acid (AA), as an antioxidant, can increase iron release of ferritin and the reticuloendothelial system accelerates available iron.^{5,7}

Correspondence: Fatemeh Espahbodi, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, I. R. Iran

E-mail: ftespahbodi@yahoo.com

It seems that vitamin C could help mobilization of iron from tissue storage and increase available iron.⁵⁻⁷ Some studies have indicated an intravenous (IV) effect of AA on increasing hemoglobin (Hb) and T_{sat} level in Haemodialysis (HD) patients with iron overload,⁸⁻¹³ but only two studies have been done about oral AA in HD with Functional Iron Deficiency (FID) by Chan.¹⁴ In the first study, the effects of 250 mg AA, oral and IV, three times a week were compared for two months. In the second study, patients received 500 mg oral AA, three times a week, for 3 months and Hb was compared before and after intervention.

In these 2 studies, vitamin C had no effect on Hb. Average levels of base line Hb was over 11 g/dL and therefore patients did not have severe anemia. Since Chan's patients did not take placebos, his studies were not blind.

Although there is an overload of iron supplement in most haemodialysis patients anemia strongly influences the quality of life, and injectable drugs are costly. The aim of this study was evaluate the efficacy and safety of oral versus intravenous AA on functional iron deficiency (FID) and whether or not this can improve anemia in HD patients.

Materials and Methods

This single blind clinical trial was performed in 2005, in 3 medical centers in Mazandran province. (Imam Khomeini and Fatemeh Zahra hospitals in Sari and Imam Reza hospital in Amol).

All haemodialysis patients were selected based on the inclusion criteria which were Hb <11 mg/dL, Hematocrit (Hct) less than 33%, serum ferritin >100 mg/L and transferrin saturation lower than 30% (without any changes in the past 2 months), using EPO for at least 6 months, and CRP lower than 2 plus. Exclusion criteria were recipients of iron supplementation, blood or vitamin C in the past 2 months, acute infection (active liver

disease), GI tract bleeding, acute ischemia or symptomatic heart failure.

Of 139 patients referred, 31 were included and blood samples were taken for measurement of Hb, Hct, serum iron, ferritin, TIBC, serum oxalate and transferrin saturation [measured by (Fe/TIBC).100; they were then divided into 2 groups randomly, based on patient list number.

The oral group took half of a 250 mg chewable tablet daily (daro pakhsh) with 5 ml intravenous normal saline three times a week, injected directly into the venous HD line (placebo) for 8 weeks; the IV group took 500 mg/5mL of injectable vitamin C (daro pakhsh) three times a week, via the some route, with half of placebo tablet (prepared in the Sari pharmacy school) daily for 8 weeks. Compliance of patients was checked by counting of tablets every 2 weeks.

Two groups were matched for Hb and ferritin. Duration of study, drug regimens such as folic acid, vitamin B12, L-Carnitine were given and all patients received EPO three times a week.

At baseline and after two months, Hb, serum iron, TIBC, transferrin saturation and serum ferritin were measured. Hb was evaluated by the Coulter counter (T890), serum iron was measured using the spectrophotometric method (Zist chemistry), saturation transferrin and serum ferritin were measured by the Gama counter (RIA) and Kt/v was calculated using the Daugirdas single pool model. Serum oxalate was measured by Enzymical method (Merk). Inter-assay coefficients of variation for Hb serum iron, serum ferritin, TIBC and serum oxalate were below 1.1, 5.4, 7.8, 2.4 and 5.3 respectively.

Statistical analysis: The results were expressed as Mean±SE. Statistical analyses were performed using the SPSS version 10/0 (statistical package for social sciences). Independent t-test was used to compare the results between groups at baseline; Paired t-test was used for within group comparisons for pre- and post-treatment. P<0.05 was considered significant.

Results

Thirty-one qualified haemodialysis patients were randomized to IV AA (n=15) and oral AA (n=16) groups; 22 patients completed the study, 12 patients in the oral AA group and 10 patients in the IV AA group. The remaining nine patients (IV AA n=5, oral AA n=4) did not complete the study due to death from heart attack [IV (n=1), oral (n=1)], incorrect use of EPO [IV (n=2), oral (n=1)], allergic reaction to vitamin C, such as urticaria and tongue fissuring [IV (n=1), oral (n=1)], GI upsets, e.g pain and heartburn [oral (n=1)], and blood transfusion after randomization [IV (n=1)].

Of the patients, 54% were women and 46% men; all women had amenorrhea. The most important reason of chronic renal failure was hypertension with diabetes mellitus. All patients were dialysed 4 hours, 3 times a week (Table 1).

Table 1. Baseline data in patients studied

	IV	Oral
Number	10 (4 male, 6 female)	12 (6 male, 6 female)
Mean age (years)	55.45±6.8	55.55±6.1
HD duration (years)	2.7± 3.7	2.9±1.4
KT/V	1.28±0.05	1.3±0.04
Causes of RF		
DM	4	5
HTN	3	4
others	3	3

There were no significant differences between Hb, serum iron, serum ferritin, serum oxalate levels in the oral and IV groups at baseline (Table 2).

Table 2. Baseline concentrations of HB, ferritin, Fe, Tsat and oxalate in patients studied

	Base IV mean±SD	Base oral mean±SD	P value
Hb (g/dL)	8.4±1.5	8.6±0.8	0.7
Fe (µg/L)	77.2±56.1	108.5±37.8	0.1
Ferritin (µg/L)	729.7±838.7	675.1±343.1	0.8
Tsat (%)	19.25±12.8	29.5±8.7	0.03
Oxalate(mg/L)	1.7±4	1.7±0.8	0.3

Effect on blood Index: Mean Hb difference was 1.1 ± 0.7 g/dL in the oral and 1 ± 0.1 g/dL in IV AA.

This difference was significantly higher in the oral group ($p=0.02$) (Fig. 1).

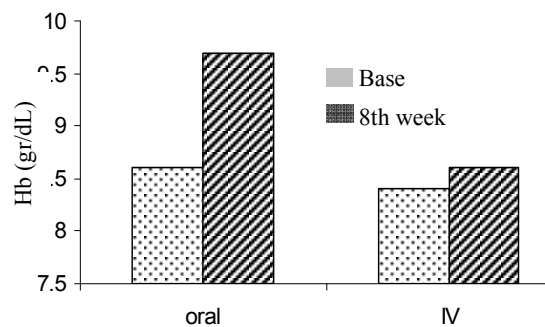


Fig. 1. Mean Hb before and after intervention in case and control groups

There were no significant differences between two groups in delta mean of ferritin & Tsat ($p=0.5$, $p=0.3$). Mean serum ferritin differences during treatment were -182 ± 10.6 µg/L and 263 ± 24.6 µg/L in the oral and IV groups respectively (Fig. 2).

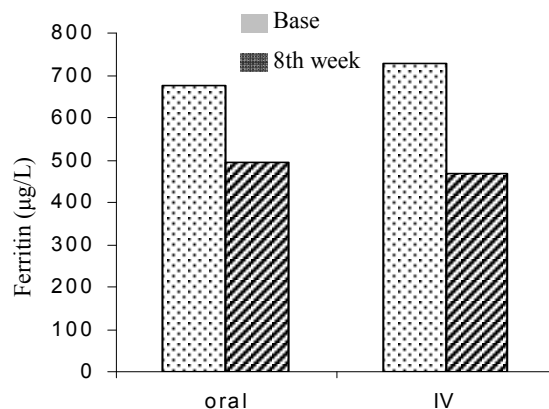


Fig. 2. Mean ferritin before and after intervention in case and control groups

Mean differences in Tsat were 2.5 ± 10.2 % in the oral and 1.1 ± 4.8 % in the IV groups (Fig. 3). Delta means of serum oxalate in oral and IV AA were 0.05 ± 0.4 mg/L and 0.1 ± 0.3 mg/L respectively without significant differences ($p=0.3$).

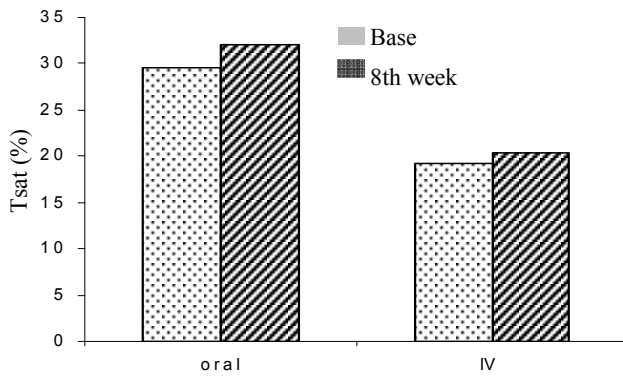


Fig. 3. Mean Tsat before and after intervention in case and control groups

Discussion

In this study, Hb increased in both groups (oral and IV) after two months, being significant in the oral group; after two months, Tsat increased and serum ferritin decreased in both groups.

Some HD patients with anemia have inadequate response to EPO that may be caused by iron deficiency, inflammation, and vitamin B₁₂ or folate deficiency.¹⁵⁻¹⁹

It seems that inadequate iron mobilization and defective iron utilization are the important mechanisms of EPO hyporesponsiveness. These patients have serum ferritin over 100 µg/L (without inflammation) but are unable to take advantage of high iron level to improve their anemia.⁶

Recent studies show that vitamin C can correct this type of anemia affecting the iron metabolism due to its antioxidant effect. Resistant anemia in iron overload patients can be corrected by AA,⁸⁻¹³ given intravenously.

Tarng studied 46 hemodialysis patients with serum ferritin more than 500 µg/L, Hct above 30%. All patients took vitamin C, 300 mg, three times a week IV for two months. Finally 37 patients completed the study and among them, 18 patients responded appropriately, Hb increased from 8.8 to 10.7 and EPO dosage decreased to 2/3.⁹ In a cross-over study designed by Keven, 63 hemodialysis patients, without considering resistance to

EPO and iron level, were given 500 mg IV, vitamin C or placebo three times a week, without the washout. At the end, two-thirds of patients had good response to vitamin C. Hb increased at least 1 gr/dL.¹³ Regarding oral vitamin C, of two studies done by Chan, the first one was a cross over study; effects of 250 mg oral vitamin C, three times a week, were compared with those of 250 mg IV vitamin C for two months, in the second study, Hb level of 212 hemodialysis patients (received 500 mg oral vitamin C) was checked at baseline and again after three months. In the first study, 21 of 30 patients and in the second, 153 patients, completed the study; vitamin C had no effect on anemia.¹⁴

Our study differs from others. In Chan's studies, patients had Hb less than 12 g/dL and Hct less than 36%. The average Hb at baseline was more than 11 g/dL. Therefore all patients did not have severe anemia, but in our study, the average Hb was less than 9 g/dL. Chan's study did not pay attention to folate and B12 storage which are very important in EPO response. In our study, patients took folic acid and B12 during the study. In Chan's study, patients were not given placebos and the study was not blind.

In our study, all patients had serum ferritin over 100 µg/L but in Chan's, serum ferritin was more than 500 µg/L. Although certain studies claim that haemodialysis patients with serum ferritin >100 µg/L are similar to patients with a lack of iron deficiency,^{20,21} it's not clear how much ferritin is needed to start treatment with vitamin C. An overload of ascorbic acid has been implicated in the development of hyperoxalemia in dialysis patients, which may develop into secondary oxalosis with an increased risk of cardiac, vascular and bone disease.²²

In this study, although serum oxalate was measured, it did not increase significantly; there were no differences between both oral and IV groups at this dosage of vitamin C.

There are some limitations in our study; number of cases, treatment time and loss of patients, although Worst-Best analysis

showed no effects of the cases lost in the final results.

This study revealed that oral vitamin C can improve functional anemia in haemodialysis patients. Some advantages of oral vitamin C are the low price and its easy use. Since anemia treatment has advantages like life improvement, increase in patients' lives and decrease of treatment cost, it is recommended

that further studies be conducted on the efficacy of oral vitamin C and its side effects; also investigations of larger groups, treatment durations, and dosages are needed to determine precise ferritin levels for initiation of vitamin C treatment to obtain optimum response.

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