Short Term Low Dose Intravenous Ascorbic Acid in Functional Iron Deficiency Anemia in Hemodialysis Patients

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Abstract: Background: Anemia is a common complication in patients on chronic hemodialysis.Functional iron deficiency is a state in which insufficient iron is released from the reticuloendothelial system with failure of iron utilization and ineffective erythropoiesis. Vitamin C, or ascorbic acid, increases the release of iron from ferritin and the reticuloendothelial system, enhances iron utilization during heme synthesis, and has antioxidant properties improving sensitivity to rEPO. So, we aimed to study the effect of short term low dose treatment with intravenous ascorbic acid on iron homeostasis in cases of functional iron deficiency in chronic renal failure patients on regular hemodialysis. **Material and methods:** Sixty anemic patients with functional iron deficiency on regular hemodialysis were chosen and randomly divided into 2 groups. Group I: 30 patients received erythropoietin and iron therapy plus a dose of 300mg of IVAA /session for 2 months. Group II: 30 patients received erythropoietin and iron therapy only and follow up for 2 months. **Results:** In Group I, IVAA resulted in significant rise of; serum iron, hemoglobin and TSAT (p values<0.001). TIBC and serum ferritin were not significantly affected (p >0.05). In Group II, showed no significant changes. **Conclusion:** IVAA in a low dose of 300mg / session for a short period of 2 months was associated with raise hemoglobin, increase iron and TSAT significantly in spite keeping the dose of EPO constant without side effects in patients on hemodialysis with functional iron deficiency.
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1. Introduction:

Anemia is a common complication in patients on chronic hemodialysis. The Dialysis Outcomes Practice Pattern Study (DOPPS) involved several countries and showed that as hemoglobin concentrations decreased to less than 11 g/dL, there was a corresponding increase in the rates of hospitalization and mortality in patients with chronic kidney disease (Pisoni *et al.,* 2004). Erythropoietin (EPO) deficiency is the most important cause of anemia (Locatelli *et al.,* 2004).Correction of the anemia yields numerous benefits: a higher tolerance for physical activity, improvement of cognitive and cardiovascular functions, a better quality of life, reduced hospitalization, and lower mortality (Eknoyan 2001). Replacement therapy with recombinant erythropoietin (rEPO) is the key treatment of anemia. However, adequate storage of accessible iron in the body is required for inducing response to rEPO (Wingard *et al.,* 1995).

The most common cause of EPO hypo responsiveness (resistance) in hemodialysis (HD) patients is absolute or functional iron deficiency (FID), Other causes include chronic infection and inflammatory cytokines, such as interleukins (IL-1 and IL-6), and tumor necrosis factor (TNF-alpha), which are believed to cause the destruction of RBC precursors and decrease the number of erythropoietin receptors on progenitor cells (Wang *et al.,* 1995; Taniguchi *et al.,* 1997; Means, 2003), bone marrow malignancy, vitamin B12 and/or folate deficiency, secondary hyperparathyroidism, angiotensin-converting enzyme inhibitor therapy and aluminum toxicity (Chan *et al.,* 2005; Jalalzadeh *et al.,* 2012).

Hepcidin, an endogenous antimicrobial peptide secreted by the liver, has been identified (Deicher and Horl, 2006, Roy *et al.,* 2007, Zaritsky *et al.,* 2009) as controlling the level of plasma iron by regulating the intestinal absorption of dietary iron, as well as the release of iron from macrophages and the transfer of iron stored in the hepatocytes. Increase in hepcidin level in the course of inflammatory disease may be a significant mediator of the accompanying anemia. (Roy *et al.,* 2007, Zaritsky *et al.,* 2009).

Functional iron deficiency implies a state in which insufficient iron is released from the bone marrow with failure of iron utilization and insufficient erythropoiesis. It is characterized by high serum ferritin≥500ng/ml, and low transferrin saturation ≤20% (Tarng *et al.,* 1999).

Vitamin C, or ascorbic acid, increases the release of iron from ferritin and the reticuloendothelial system, enhances iron utilization during heme synthesis, and has antioxidant properties improving

sensitivity to EPO (Chen *et al.,* 2003), Deira *et al.,* 2003) Vitamin C has been proposed to improve intestinal iron uptake and iron utilization by the erythron, and erythropoietin requirements decreased as long as patients received adequate vitamin C supplements (Deicher and Horl, 2003). It may be speculated that vitamin C antagonizes the action of hepcidin regarding the regulation of iron trafficking. Vitamin C could even affect hepatic hepcidin expression. If hepcidin indeed represents the key modulator of intestinal iron uptake, iron absorption should improve to a large extent with hepcidin antagonistic drugs. The long term safety of intravenous ascorbic acid (IVAA) remains undefined, with secondary oxalosis being the primary concern. This was not described with short term use of any of studies described (KDOQI; National Kidney Foundation, 2006).

The aim of this study was to assess the effect of short term low dose treatment with intravenous ascorbic acid on iron study in cases of FID in chronic hemodialysis patients.

2. Material and Methods

The study was approved by Institute Ethics Committee and patients gave signed consent and was conducted in two hemodialysis centers (Ain Shams University hemodialysis unit and Ahmed Maher teaching hospital) in Cairo as a prospective, cross sectional study. Sixty anemic patients with functional iron deficiency(FID) on with renal failure on regular hemodialysis (45% males and 55% females, mean age of 44.5 years) were to be included in the study

Inclusion criteria were as follows:(1) on HD therapy for at least 9 months, (2) All patients were on rEPO for 6 months or longer at a dose of 120-360 U/kg/week, (3) average Hb level of 11.0 g/dl or less for 3 months, (4) ferritin level ≥500 ng/ml, (5) transferrin saturation (TSAT) of ≤ 20%, and (6) received maintenance intravenous iron (25-100 mg/week).

Exclusion criteria were (1)clinical evidence of infective and/or inflammatory disease for at least 4 weeks before the study (2) Terminal diseases as malignancy and chronic liver disease with cirrhosis, (3) hemoglobinopathies, (4) evidence of significant bleeding during the past 3 months, and (6) and intact parathyroid hormone (i-PTH) level >500 pg/ml.

Patients were randomly divided by blind card selection method into two groups: Group I:30 patients representing the study group, receiving standard care (erythropoietin and iron therapy) plus a dose of 300mg of (IVAA) with each dialysis session for 2 months. Group II: 30 patients, representing the control group, receiving standard care only (erythropoietin and iron therapy only). During the study, all patients were maintained on daily supplements of folic acid (5 mg) and vitamin B6 and vitamin B12 (100 µg) per week.

Both groups were followed up for 2 months with the following parameters; hemoglobin (Hb) level, Serum iron, TIBC, Serum ferritin, and Transferrin saturation. Patients were assessed weekly for adverse events. A feedback sheet form was used to assess the side effects of AA supplementation, such as dizziness, faintness, fatigue, flank pain, and headache.

Iron therapy was stopped for all the patients if ferritin exceeded 800mg/dl. During the study, dosage of EPO was held constant (between 120 and 360 U/kg/week for each patient) according to the KDOQI guidelines.

Results were statistically analysed using the SPSS program 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. *P*-value of <0.05 was considered significant.

3. Results

This study was conducted on 60 patients (27 males and 33 females), the mean age was 44.5 years. All the patients were dialyzed for 4 hours three times a week, and the range of kt/v were comparable all of them completed the study.

The demographic and initial laboratory characteristics of patients of both groups at the beginning of the study is shown in table (1).

Table (1):Demographic and laboratory characteristics of patients in two groups at the beginning of the study.

	Group I (VITAMIN C) (n = 30)	Group II (CONTROL) (n= 30)	*P* Value
Age (year)	46.46±12.58	43.90± 13.98	0.458
Duration of dialysis (month)	70.32±51	60±40.24	0.388
HGB (g/dl)	7.85±0.96	7.88±1.09	0.931
MCV (fL)	87.45±7.47	84.40±6.52	0.098
TLC (Thousands)	6.30±1.77	6.07±1.88	0.624
PLT (Thousands)	223.86±64.41	215.03±31.79	0.503
Iron (mg/dl)	55.60±7.46	55.03±8.93	0.791
TIBC (mg/dl)	268.10±25.50	274.10±24.39	0.356
Ferritin (ng/dl)	1160.40±921.69	916.90±240.16	0.167
Transferrin saturation index%	20.85±3.22	20.05±2.99	0.327

There was no significant difference as regards any parameter between group 1 and group 2 rendering both groups liable for comparison.

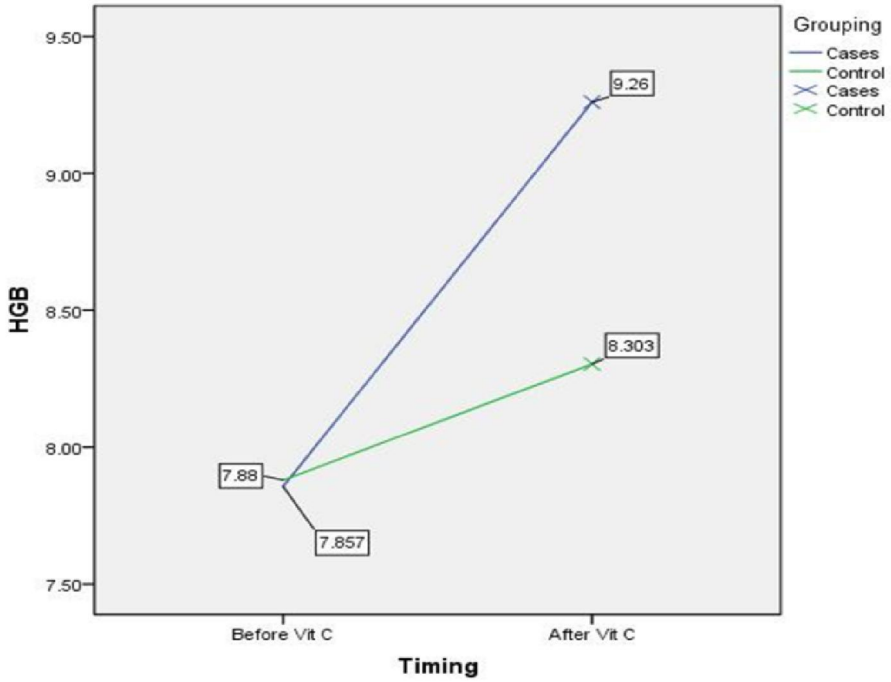
Response to IVAA in study group I and change of variables in control group (Group II) after 2-month treatment period is shown in table (2):

Table (2): Change of variables in Group I and Group II before and after treatment

	Group	Before Treatment	After Treatment	*P*
Hb (g/dl)	Group I	7.85 ±0.96	9.26 ±1.17	<0.001
	Group II	7.88 ± 1.09	8.30±0.61	0.06
Iron (mg /dl)	Group I	55.6± 7.46	71.63±23.50	<0.001
	Group II	55.03±8.93	56.63±9.11	0.49
Ferritin (ng/dl)	Group I	1160.4 ± 921.69	828.6±375.13	0.07
	Group II	916.9 ±240.16	909.06±256.48	0.90
TIBC (mg/dl)	Group I	268.1±25.50	263.26±26.45	0.92
	Group II	274.1±24.39	283±19.32	0.12
TSAT %	Group I	20.85±3.22	34.16±11.19	<0.001
	Group II	20.05±2.99	20.09±3.67	0.97

Comparative analysis of the laboratory results revealed that there was a significant difference before and after treatment with IVAA in group I as regards mean values of Hb (p<0.001), serum iron (p <0.001) and TSAT level (p <0.001). IVAA could elevate Hb, serum iron and TSAT significantly. In contrast, group II showed no significant change, in Hb, serum iron, or TSAT, in mean values before and after the study period (all p values>0.05). In group I, Serum ferritin showed a downward trend which is statistically insignificant (p =0.07) while TIBC showed no significant change (p >0.05). In group II, there was insignificant change neither in serum ferritin nor in TIBC before and after the study. Change in the mean values of Hb in both groups after 2 months is shown in figure 1 and change in Hb levels and serum iron in group I after treatment with AA is shown in figures 2 and 3.

Results also revealed that there was a significant change in TSAT mean value of group I after treatment with IVAA(p <0.001) while no significant difference in TSAT mean value took place of group II after 2 months as shown in figure(4).



Figuer (1): Change in Hb level after 2 months in both groups.

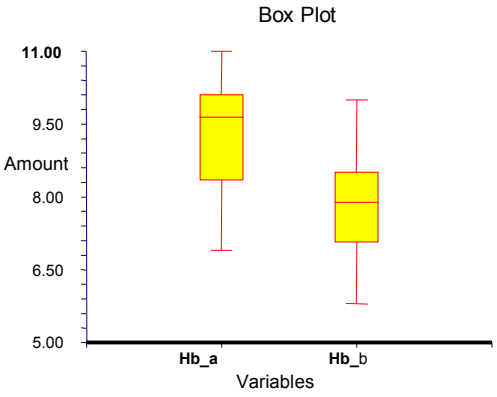


Figure (2): Hb before and after administration acid in group I

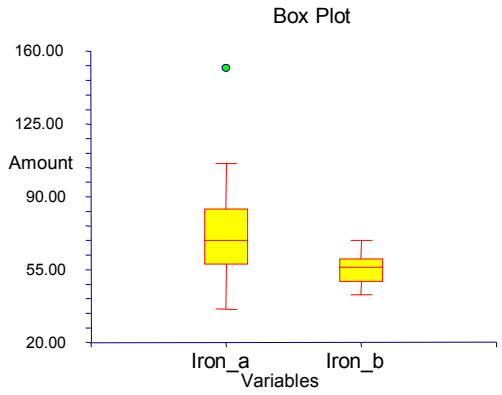


Figure (3): serum Iron before and after administration of IV ascorbic of IV ascorbic acid in group I

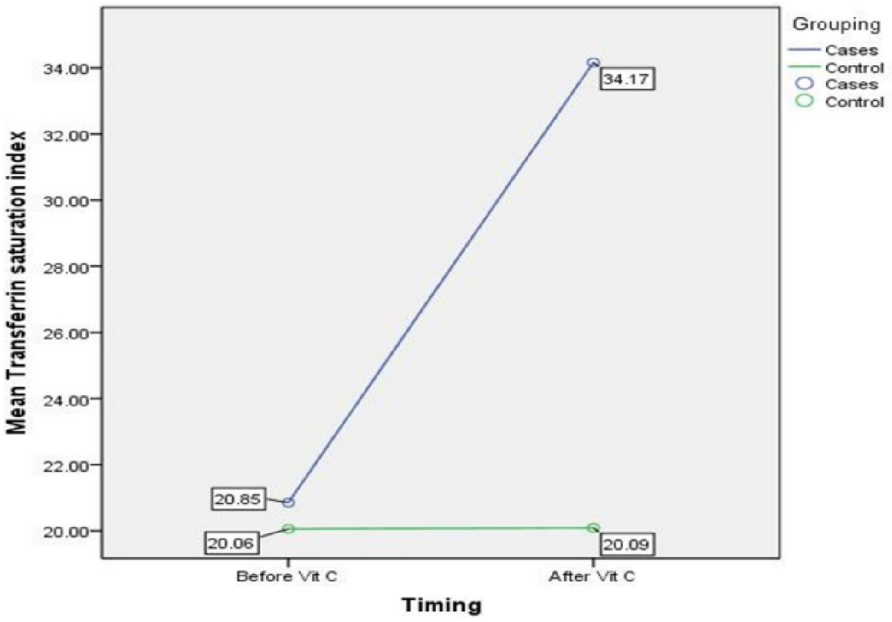


Figure (4): TSAT level after 2 months in both groups

4. Discussion

Anemia is a common complication and predictor of morbidity and mortality in hemodialysis patients (Locatelli *et al.,* 2004).In HD patients, anemia is linked to inflammation and oxidant stress and is associated to the uremic syndrome (Eknoyan, 2001). Patients may require much higher than usual doses of erythrocyte stimulating agents (ESAs) in order to maintain the recommended hemoglobin target of ≥11 g/dl (Chen *et al.,* 2003, KDOQI; National Kidney Foundation, 2006) Erythropoietin hyporesponsiveness has been described as 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/week (Wingard *et al.,* 1995, KDOQI; National Kidney Foundation, 2006)

Dialysis patients may have functional iron deficiency. This is characterized by the presence of adequate iron stores as defined by conventional criteria, but an inability to sufficiently mobilize this iron from the liver and other storage sites to adequately support erythropoiesis even with the administration of ESAs. Among such patients, the serum ferritin level is either normal or elevated (sometimes markedly), but the transferrin saturation typically is about 20 % or less (Tarng and Huang, Chan *et al.,* 2005, 1998; Jalalzadeh *et al.,* 2012)

Our results showed significant increase in mean values of hemoglobin level in group I treated with AA from 7.85 ± 0.96 to 9.26 ±1.17 (p<0.001) in comparison to group II (p>0.05) which received standard care only. Our results agreed with the results

of Attallah *et al.* (2006), who used, in his study the same dose of IVAA but for six months. Moreover, his patients were on EPO therapy for ≥6 months at a dose ≥450 U/kg/wk. They also agreed with another study by Jalalzadeh *et al.* (2012), who used a higher dose than ours (500 mg of IVAA for three months). Vitamin C improved responsiveness to EPO, either by augmenting iron mobilization from its tissue stores or through antioxidant effects Jalalzadeh *et al.* (2012). Vitamin C can be used as an effective adjuvant therapy to EPO in hemodialysis patients, this was on accordance to Giancaspro *et al.* (2000), Chan *et al.* (2005), Fumeron *et al.* (2005), and Attallah *et al.* (2006),

In our study there was significant increase in serum Iron from 55±7.46 to71.63±23.5 (p<0.001) and consequently TSAT level from 20.85±3.22 to 34.16±11.19 (p<0.001) in Group I which received Vitamin C in comparison to Group II which did not (p>0.05). Our results coincide with the results of Kang *et al.*,2012 who used 500mg of IVAA for 3 months. Kang attributed this finding to facilitation of release of iron, by IVAA, from its stores (Jalalzadeh, *et al.,* 2012).In the study of Attallah *et al.* (2006), they found, also, an increase of the TSAT level but was not accompanied by the increase of serum iron.
TIBC showed no significant changes in both groups (p>0.05) which also agreed with Kang *et al.* (2012) and Jalalzadeh *et al.* (2012), but was in contrast to Attallah *et al.* (2006), who found a significant decrease of TIBC. This contrast could be explained by the longer duration of the Attallah study.

As regards serum ferritin, in Group I, it dropped from 1160.4±921.69 down to 828.8±375.13 but the p<0.07 was statistically insignificant. In group II there was no significant change in serum ferritin (p>0.05). Our results come in accordance with Atallah *et al.* (2006) and Keven *et al.* (2003) who experienced trivial significant drop of serum ferritin after use of IVAA. This probably resulted from continued administration of iron as maintenance therapy (Attallah *et al.* 2006):.

As regards safety of IVAA, the KDOQI guidelines (2006) reported that secondary oxalosis was not described with any of short term use of IVAA of any of the studies. In our study a total dosage 7200 mg IVAA for 2 months was used compared with a total dosage 21,600 mg IVAA used for 6 months in Attallah's *et al.* (2006) study. Moreover, chronic hemodialysis patients generally have lower plasma AA levels because of loss during dialysis, increased consumption or inadequate dietary intake (Macdougall, 2001, Attallah *et al.,* 2006, Handelman, 2007). So, in our study we do not think that secondary oxalosis is a possible complication of IVAA. In our study patients were assessed monthly for adverse events. A feedback sheet form was used to assess the side effects of AA supplementation, such as dizziness, faintness, fatigue, flank pain, and headache. None of our patients suffered IVAA.

Conclusion:

IVAA in a low dose of 300mg / session for a short period of 2 months is sufficient to raise hemoglobin, increase iron and TSAT significantly in spite keeping the dose of rEPO constant without side effects in patients on hemodialysis with functional iron deficiency.

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