The Efficacy of Ascorbic Acid in Suboptimal Responsive Anemic Hemodialysis Patients Receiving Erythropoietin: A Meta-Analysis

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Background: *To determine the impact of adjuvant ascorbic acid therapy on erythropoietin-hyporesponsive, anemic patients undergoing hemodialysis.*
Data Sources: *The online databases of PubMed, Cochrane library, IPA, CINAHL, EMBASE, clinicaltrial.gov, WHO trial registry and PyschINFO were used.*
Study Selection: *Studies comparing ascorbic acid to a control, with participants receiving erythropoietin and hemodialysis, and reported outcomes for hemoglobin or transferring saturation.*
Data Extraction: *Two independent researchers reviewed titles and abstracts to determine relevance and extracted study design, dose, duration, baseline values, and outcomes.*
Data Synthesis: *Five studies met all the criteria and were used for final analysis. The calculated weighted mean difference between hemoglobin in the ascorbic acid group versus the control group was 0.96 g/dL (95% CI, 0.78 to 1.14). The calculated weighted mean difference between transferrin saturation in the ascorbic acid treatment group versus the control was 8.26% (95% CI, 6.59 to 9.94).*
Conclusion: *Adjuvant ascorbic acid significantly raises hemoglobin levels in patients with erythropoietin hyporesponsiveness undergoing hemodialysis. The significant rise in transferrin saturation indicates that this positive effect on erythropoietin response may be due to increased iron utilization.*

Keywords: *Ascorbic acid, Erythropoietin hyporesponsiveness, Hemodialysis, Anemia, Meta-analysis*

J Med Assoc Thai 2011; 94 (Suppl. 1): S134-S146
Full text. e-Journal: *http://www.mat.or.th/journal*

Anemia is a common complication in patients with end-stage kidney disease on hemodialysis. The causes of anemia are multifactorial, but erythropoietin deficiency due to decreased renal erythropoietin production is a major factor. Without adequate treatment, anemia poses a significant health risk and has been independently linked to left ventricular hypertrophy, poor cardiac outcomes and increased mortality[1,2]. Erythropoeisis stimulating agents (ESA) are the primary therapies to patients on hemodialysis for treatment of anemia. Recently, the updated Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that ESA should be administered to a usual Hb target in the range of 11-12 g/dl with the goal of reducing hospitalizations, cardiovascular morbidity and mortality[3]. Erythropoeisis also requires an adequate iron supply to the red blood cells to be effective. Absolute iron deficiency (defined by KDOQI guidelines[4] as transferrin saturation lower than 20%

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and ferritin level lower than 100 ng/mL) is one of the most common causes of ESA hyporesponsiveness.

Approximately 5-10% of patients with CKD exhibit suboptimal response to ESA[5] despite adequate iron stores. A number of factors including infection, hyperparathyroidism, and inadequate dialysis may also contribute to poor ESA response. In ESRD patients on hemodialysis, a state of functional iron deficiency may occur in which iron tends to be shifted out of the circulation and into the storage tissues, making it less available for erythropoeisis. Functional iron deficiency may be a consequence of chronic inflammation and is characterized by high serum ferritin (storage iron) and low transferrin saturation (circulating iron) together with suboptimal response to ESA[5]. Both KDOQI[4] and Anemia Working Group of European Best Practice (ERBP)[6] recommend that functional iron deficiency may be treated with intravenous iron therapy to achieve target ferritin 200-500 ng/ml and transferrin saturation 30-50%. More recently, intravenous iron therapy has been shown to raise hemoglobin (Hb) levels even in patients with serum ferritin levels higher than 500 ng/ml[7]. However, despite the current widespread use of intravenous iron, there are concerns that iron therapy may increase infectious complications, atherosclerosis and the long term risks of iron overload remain unknown[8,9].

The chronic inflammatory state associated with uremia and hemodialysis is associated with increased oxidative stress. Oxidative stress has also been shown to be associated with decreased responses to ESA[10]. Vitamin C (ascorbic acid) is an important water soluble antioxidant essential in many biological processes[11]. Several studies have shown that ascorbic acid may improve responsiveness to ESA in hemodialysis patients[12-25]. Vitamin C (ascorbic acid) could improve hemopoeisis by mobilizing iron from tissue stores thus increasing iron utilization[26]. Alternatively, vitamin C could increase Hb by acting as an antioxidant to protect against lipid peroxidation of red blood cell membranes and thereby prevent hemolysis[27]. However, studies using vitamin C in hemodialysis patients have generally been in the form of case series or were conducted in small numbers of subjects with conflicting results. Whether ascorbic acid could increase Hb levels in hemodialysis patients responding inadequately to ESA treatment remains uncertain. Recently, randomized trials of vitamin C in subjects on hemodialysis have been published. This study aims to systematically review all existing studies and determine the efficacy of intravenous ascorbic acid in hemodialysis patients on ESA treatment.

Material and Method

Search strategy

The following online clinical databases were electronically searched from its inception to December 2008; PubMed, Cochrane libraries, International Pharmaceutical Abstracts, CINAHL, EMBASE, PsychINFO, clinicaltrials.gov and World Health Organization trial registry. For each database a search was run within the full text using the keywords *hemodialysis OR haemodialysis AND vitamin C OR ascorbic acid*. There were no further restrictions put on any of these searches, including no language restrictions.

Only randomized clinical studies were considered for final meta-analysis. Trials were collected for further review for the meta-analysis if they met all of the following criteria: 1) compared intravenous ascorbic acid therapy to a control 2) patients were receiving ESA 3) patients were on hemodialysis 4) reported outcome data included Hb, hematocrit (HCT), or transferrin saturation (TSAT), 5) follow-up greater than 1 month was selected to allow enough time for potential benefit of vitamin C on Hb to be observed[3]. Cross-over studies were also included but data were extracted only from the first phase of these studies to avoid problems of the carry-over effect[28].

Outcome Measures

The primary outcome used was post treatment Hb or Hct and change in Hb level (g/dL) or Hct from baseline to study completion. The secondary outcome used was TSAT post treatment and change in TSAT level (%) from baseline to study completion. For each of these outcomes difference between post-trial values for the treatment arm versus the control arm were also analyzed. In addition we also analyzed the effects of treatment of serum ferritin, ESA requirement and side effects of ascorbic acid.

Data extraction

Using standardized forms, data were extracted from each study by two independent researchers (BE, SM). The extracted data included; study design, study size, intervention dosage and duration, patient baseline characteristics, control description, and outcomes (Hb, TSAT, HCT, serum iron, and serum ferritin). In case of disagreement between the 2 reviewers, a third reviewer extracted the data and results were attained by consensus.

Further the methodological quality of each trial was assessed in several different ways. First, each trial was assessed using a quality scale developed by Jadad[29]. This quality scale reviews randomization, blinding methods, and the inclusion of reasons for withdrawals. The second measure of quality was done using a risk of bias assessment form developed by Cochrane[30]. This risk of bias assessment addresses sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.

Analysis

For analysis, a weighted mean difference was calculated. This weighted mean difference was calculated for the primary outcome Hb and for TSAT. For each of these outcomes the difference between changes and post-trial outcomes was calculated between Intravenous Ascorbic Acid (IVAA) treatment and placebo. The secondary outcomes included post-trial ferritin levels and ESA dose requirement. The weighted mean difference and 95% confidence intervals were calculated using the DerSimonian and Laird method[31] under a random-effects model. The Q-statistics and I-squared for test of heterogeneity were also performed[32,33]. The publication bias was assessed using the funnel plot method[34,35], asymmetry in the funnel plot suggested publication bias as well as Begg's test and Egger's test[36]. All tests performed were two-sided and a p-value < 0.05 was considered stastically significant. Sensitivity analyses were performed in hyporesponsive ESA patients and in studies with high quality. In addition, analyses were undertaken with fixed-effects model to determine the robustness of findings. To perform all statistical analyses, we used the Stata software, version 8.0 (Stata Corp. College Station, Texas), by employing the command "METAN".

Results

Study Selection

The computerized database searches produced 459 results (Fig. 1). The results were reviewed based on their titles and abstracts, followed by a review of the full manuscript for relevant articles. Of the 459 results, 426 were excluded based on the following inclusion criteria; because they did not compare ascorbic acid to a control (n = 217), because study participants were not on ESA (n = 10), because outcomes did not report Hb, hematocrit, or TSAT (n = 118), because study subjects were non-human (n = 3), or because the paper was not a clinical trial (n = 78). This left 33 studies to be included which was then narrowed down to 14 after removing duplicates. These 14 potentially eligible publications were then analyzed in greater detail.

The characteristics of the 14 relevant studies were reviewed in depth. Of the 14 initial studies, 9 were excluded (Table 1), leaving 5 studies for the final analysis. Three of the potentially eligible trials[13,24,25] were only available as abstracts and did not report outcome data sufficient for calculate treatment effect. Four trials[18,20-22] were removed because their study

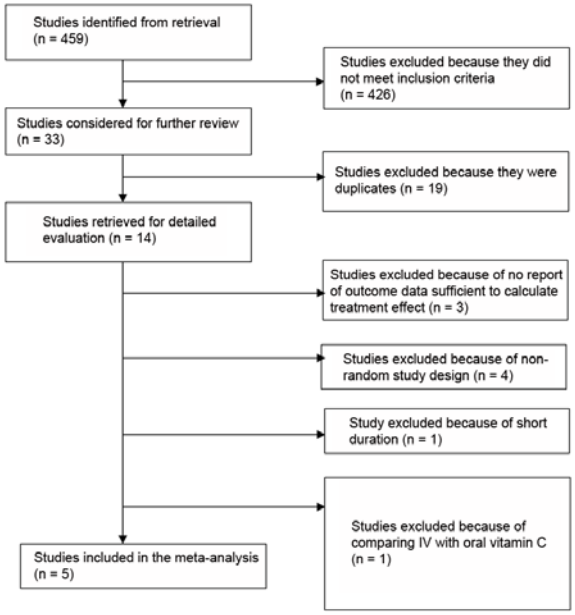

Fig. 1 Trial flow

Table 1. Studies excluded from analysis

First Author, Year	Reason for exclusion
Chan, 2005[14]	Compared Intravenous to oral vitamin C
Ogi, 2004[18]	Non-randomized study
Taji, 2004[20]	Non-randomized study
Tarng, 2004[23]	Provided only outcomes at day 7
Imada, 2001[25]	Available only in abstract form
Carter, 1999[13]	Available only in abstract form
Tarng, 1999[22]	Non-randomized study
Tarng, 1998[21]	Non-randomized study
Wyndham, 1980[24]	Available only in abstract form

RCT: Randomized controlled trial, Hb: hemoglobin

design was non-random. Two of them[21,22] placed patients with HCT > 30% in the control group and patients with HCT < 30% in the treatment group while another study[20] divided patients based on what day they received dialysis. The study of Ogi and colleagues[18] was removed because it was not specified as a randomized study. Another study[23] was removed from final analysis because the study lasted only 7 days which did not allow proper time for significant outcomes to be recorded. Finally one study[14] was removed from final analysis because it compared IV vitamin C vs. oral vitamin C preparation.

Patient and Study Characteristics

Table 2 shows the characteristics of the five randomized studies included for final analysis[12,15-17,19]. A total of 86 patients (43 males) received intravenous ascorbic acid (IVAA) while 89 patients (42 males) were used as control. The mean age of patients in these studies ranged from 40.2 to 61.2. All patients were dialyzed 3-4 hours 3 times per week with mean study KT/V ranging from 1.2 to 1.5. All patients had been on dialysis for more than 6 months with the mean dialysis vintage from 32 to 59 months.

Two of the studies used 300 mg IVAA[12,19], two studies used 500 mg IVAA[16,17] and one study used 200 mg[15]. All of these studies administered IVAA three times per week with each dialysis session. One study[17] gave the control group a placebo and was double-blinded while control patients in the other studies[12,15,16,19] received no additional therapy. Three studies[12,15,17] had a duration of 6 months and the other two studies[16,19] used a 3 month duration. Two of the studies[16,17] were cross-over designed studies.

All of the included studies stated that patients were randomly assigned. One study[12] used a block type randomization, one study[16] used a computer generated random allocation sequence and the other three studies[15,17,19] did not indicate the type of randomization used. Allocation concealment was stated in only one study[12]. Only one study[17] used intent-to-treat analysis for their outcomes and the other studies[12,15,16,19] used per-protocol analysis. All included studies stated reasons for withdrawals. The overall quality of 3 studies[12,16,17] was rated as high (Jadad score of 3), while the remaining 2 studies[15,19] were rated as moderate quality (score of 2). Based on the overall risk of bias assessment, all studies were considered "unclear risk of bias".

All studies stated patient inclusion and exclusion criteria, but these varied importantly between different studies. Three studies focused on subjects with functional iron deficiency characterized by low TSAT and moderate to high serum ferritin[12,16,19]. Attahllah[12] is the only study focused only on subjects that fulfilled the criteria of having hyporesponsiveness to ESA treatment despite adequate iron stores[37]. Shahrbanoo[19] and Giancaspro et al[16] included subjects with more moderate ESA requirements. All three studies[12,16,19] listed above also excluded subjects with anemia corrected to achieve optimal target (above Hb 10.5 or 11 g/dl). The other 2 studies[15,17] did not exclude subjects with Hb corrected to Hb target (> 11 g/dl). Of these, Deira et al[15] indicated that patients under study had iron overload as defined by high serum ferritin and transferrin saturation, but did not specify a minimum ESA dose requirement. Keven et al[17] had the least stringent criteria and included all subjects with adequate iron stores on stable doses of ESA.

ESA dose was varied according to a pre-specified protocol in Attallah[12], adjusted without specified protocol in Keven[17] and kept constant in Giancaspro[16]. Deira et al[15] kept the dose of ESA constant in the first 3 months, but allowed adjustments to the ESA dose without a prespecified protocol during 3 to 6 months. No data for ESA dosing was available for Sharhrbanoo[19]. All patients had received intravenous iron therapy prior to study entry. In 2 studies[12,17], IV iron was continued according to a pre-specified protocol. IV iron was stopped in 2 studies at the start of the study[15,16]. The IV iron regimen was not available in 1 study[19]. Details of oral iron therapy were not given in any of the studies. Oral vitamin B and folic acid was continued in 2 studies[15,19] and Nephrocaps®, which contain vitamin B complex, folic acid and vitamin C (100mg), was given to both AA and control groups in Attalah et al[12].

All studies excluded subjects with overt causes for ESA hyporesponsiveness or confounding factors such as bleeding, active infection, or those requiring transfusion. Only the Attalah and Giancaspro studies[12,16] specifically excluded subjects with elevated C-reactive protein and hyperparathyroidism.

Effects on Hemoglobin

Hb is considered a better evaluation of red cell mass than Hct[4]. Since all included studies provided Hb data, whereas only the study of Shahrbanoo[19] provided Hct data, only the Hb data will be analyzed. The baseline mean hemoglobin values (Table 2b) ranged from 8.5 to 12.3 g/dl. The baseline Hb were similar between IVAA and control for all studies. Because Deira

Table 2. Randomized Studies of intravenous ascorbic acid (AA) included for meta-analysis

Study	Study Design	AA Dose [mg]	Duration [mo]	n [males]	Inclusion (Exclusion) criteria	ESA dose adjustment	Intravenous Iron	Age [years]	Months on HD	Baseline Laboratory data [AA , Con]
Shahrbanoo, 2008	RCT	300	3	AA 15 [6] Con 16 (6)	Hb < 11, TSAT < 30, Ferritin > 300, ESA > 6000 U/wk	N/A	All prior IV Fe. Dose during study N/A	AA 54 (3) Con 54 (4)	AA 37 (26) Con 36 (14)	KT/V: 1.2 (0.0), 1.2 (0.0)
Attallah, 2006	RCT	300	6	AA 20 [9] Con 22 [10]	Hb < 11, TSAT < 50, Ferritin > 500, ESA>450U/kg/w, (PTH > 500, CRP > 20)	Adjust (with protocol) to Hb 11.5 to 12.5 g/dl	IV Fe to all Adjusted by protocol (same amount IV Fe in each group)	AA 51 (5) Con 49 (6)	AA 32 (9) Con 32 (8)	KT/V: 1.4 (0.1), 1.5 (0.1) Alb: 3.7 (0.1), 3.6 (0.1), PTH: 308 (67), 311 (77) CRP: 2.8 (1.3), 2.8 (1.3)
Keven, 2003	RCT*, #	500 [!]	6	AA 30 [14] Con 30 [13]	Hb N/S, TSAT > 20, Ferritin > 100	Adjust (no protocol) to Hb 11 to 12 g/dl	IV Fe 100 mg q2W to all unless Ferritin > 800	AA 40 (10) Con 42 (14)	AA 52 (46) Con 46 (47)	KT/V: 1.2 (0.2), 1.3 (0.3) Alb: 4.0 (0.5), 3.9 (0.6) PTH: 197 [9-919], 108 [100-2536] CRP: 3.1 [3-77], 3 [3-84]
Giancaspro, 2000	RCT*	500	3	AA 12 [7] Con 12 [6]	Hb < 10, TSAT < 20%, Ferritin > 300, (PTH > 400, CRP > 5)	No adjustment	IV Fe withheld at randomization	AA 61 [31-74] Con 59 (22-72)	AA 44 (19) Con 48 (14)	KT/V: 1.2 (0.1), 1.3 (0.1) Alb: 3.6 (0.1), 3.7 (0.1) PTH: 183 (45), 216 (42) CRP: 2.5 (1.0), 3.8 (2.0)
Deira, 2003	RCT	200	3	AA 9 [7] Con 9 [7]	Hb N/S, TSAT > 30, Ferritin > 800, ESA N/A	0-3 mo no adjustment 3-6 mo adjustment (no protocol)	IV Fe withheld at randomization	AA 60 (22) Con 60 (15)	AA 59 (52) Con 47 (28)	KT/V: 1.1 (0.2), 1.35 (0.1) PTH: 357 (321), 117 (86) CRP 9 (7), 13 (16)

Data shown as mean (SD) or [range] . AA: intravenous ascorbic acid, Con: Control, ESA: erythropoeisis stimulating agent, Hb: hemoglobin [g/dl], TSAT: transferring saturation [%], Ferritin [ng/mL], PTH: parathyroid hormone [pg/ml]. CRP: c-reactive protein [mg/L], Alb: serum albumin (g/L),IV: Intravenous; Fe: iron , RCT: Randomized controlled trial, *Cross-over study design; # double blinded study; [$]One week duration; [!]Placebo used for control arm; [!!]Oral ascorbic acid used for control arm; [@] regimens were 3 times per week; [@@]regimen was 7 times per week; NA: not enough information is available to determine;

Table 2b. Laboratory data and recombinant erythropoietin dose

Studies	Base line Hemoglobin (g/dL)		Post treatment Hemoglobin (g/dL)		Baseline TSAT (%)		Post treatment TSAT (%)		Baseline Ferritin (ng/mL)		Post treatment Ferritin (ng/mL)		Baseline ESA dose (IU/kg/BW or IU/week)		Post treatment ESA dose (IU/kg/BW or IU/week)	
	AA	Con	AA	Con	AA	Con	AA	Con	AA	Con	AA	Con	AA	Con	AA	Con
Attallah, 2006	9.3 (0.7)	9.3 (0.5)	10.5^{+} (0.9)	9.6** (0.8)	28.9 (2.2)	28.7 (1.6)	37.3^{+} (3.0)	29.3** (2.8)	774 (144)	770 (157)	732 (149)	724 (157)	477 (19)	474 (19)	429^{+} (25)	447 (33)
Keven, 2003	9.7 (1.2)	10.3 (1.4)	11.4^{++} (1.6)	11.0 (1.6)	28.2 (10)	30.1 (14)	38.5^{++} (19.3)	31.9 (11.5)	382[105-1372]	259[100-2536]	381[105-1166]	263[105-1998]	8567 (3114)	6967 (3178)	7200^{+} (3994)	7667 (3356)
Giancaspro, 2000	9.2 (0.2)	9.1 (0.2)	10.0^{++} (0.3)	9.0 (0.2)	17.5 (0.6)	17.9 (0.5)	25.7^{++} (1.7)	18.4^{+} (1.0)	572 (40)	484 (53)	398^{++} (55)	450 (50)	131 (35)	145 (29)	N/A	N/A
Shahrbanoo, 2008	8.5 (1.2)	8.5 (1.1)	9.6^{+} (1.4)	8.4 (1.3)	25 (4.8)	24.6 (3.2)	37.2^{+} (7.2)	24.9 (4.7)	832 (252)	787 (268)	672^{+} (343)	793 (285)	N/A	N/A	N/A	N/A
Deira, 2003	12.3 (1.9)	12 (1)	12.3 (1.5)	11.7 (1.2)	43.5 (21)	43.8 (12)	50 (21)	32^{+} (11)	1300 (469)	1104 (219)	1154^{+} (458)	925$^{\square}$ (333)	72.6 (46)	46.9* (39)	66.2 (39)	44.4 (30)

Data shown as Mean (SD) or [95% CI]. ESA: Erythropoeiesis stimulating agent,; AA: Intravenous ascorbic acid; Con: control. *$p < 0.05$, **$p < 0.01$ vs. AA; $^{+}p < 0.05$,$^{++}p < 0.01$ vs. baseline

et al[15] kept the dose of ESA constant in the first 3 months, but allowed adjustments to the ESA dose during 3 to 6 months, post treatment data for the first 3 month period will be analyzed to minimize confounding effects from ESA dose adjustments. Hemoglobin levels rose significantly in patients treated with IVAA (Table 2b). The weighted mean difference between post-treatment values in the IVAA patients and the control patients was 0.96 g/dL (95% CI, 0.78 to 1.14) indicating a significant rise (Fig. 2a). The test for heterogeneity was also not significant (p = 0.63) with I^2 of 0%. The funnel plot test did not reveal asymmetry indicating absence of publication bias. The Begg's and Egger's tests were performed and revealed no publication bias (p-value 0.46 and 0.33, respectively). Similar results were seen when changes of Hb values were used, the weighted mean difference between changes of outcomes values in the IVAA versus control group was 0.86 g/dL (95% CI, 0.76 to 0.96).

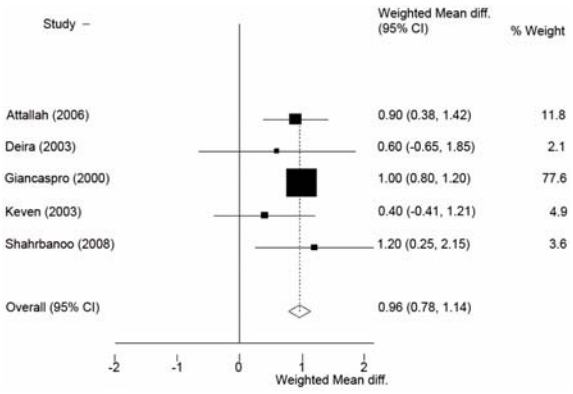

Fig. 2a Difference between post-treatment Hb values

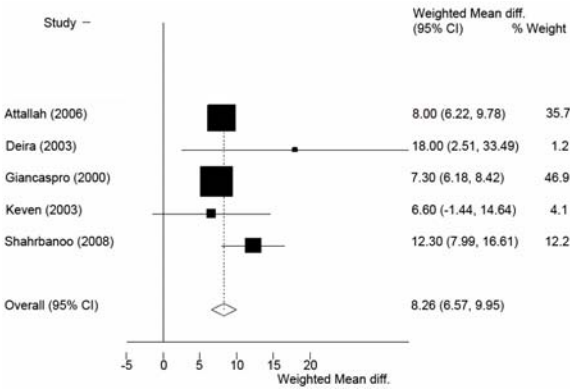

Fig. 2b Difference between post-treatment TSAT values

Effects on Transferrin Saturation, Ferritin, and ESA Dose Requirement

Baseline mean TSAT values for included studies ranged from 17.5 to 30.1% reflecting differences in inclusion criteria (Tables 2, 2b). The baseline TSAT was similar between IVAA and controls. Compared to control patients, transferrin saturation levels rose significantly in patients treated with IVAA (Table 2b). The weighted mean difference between post-treatment values in the IVAA patients versus that in the control patients was 8.26% (95% CI, 6.56 to 9.94), this indicates a significant rise (Fig. 2b). The test for heterogeneity was also not significant (p = 0.15) with I^2 of 40.7%. When the change values were used, the weighted mean difference between change values in the IVAA versus control group was 7.81% (95% CI, 7.27 to 8.36). The magnitude of increase of TSAT in both analyses was not different, indicating the robustness of the findings. The mean baseline ferritin ranged from 259 to 1,300 ng/mL. The baseline ferritin was similar between groups in all included studies[12,15-17,19]. When ferritin post-treatment values were analyzed, the weighted mean difference in the IVAA versus control group was -32.97 (ng/mL) (95% CI, -91.52 to 25.59). Serum iron was reported in only 2 studies[15,19]. In one study[19], no change was observed between controls and IVAA or after therapy. Deira[15] reported a decrease in serum iron in the control group after 6 months whereas this was unchanged in the IVAA group. Another study[12] commented that the serum Fe did not change with IVCC or controls but did not provide data.

ESA dose at baseline was available in 4 studies (Table 2b). There was a 10 fold difference between the doses of ESA in different studies ranging from 46.9 IU/kg/w to 477 IU/kg/week. The ESA requirement at baseline was similar between groups for all studies except Deira[15]. Adjustment to the ESA dose was permitted in 3 studies[12,16,17]. In Attallah[12] the mean ESA dose required at the study completion was significantly lower than that at baseline for the IVAA group by 10% whereas the dose for the control group was decreased by 5.6% (p = NS). Similarly, Keven[17] reported a significant reduction of 16% in ESA dose after IVAA, whereas the dose was not significantly changed in the control group. Deira[15] maintained a constant ESA dosing regimen for the first three months but allowed adjustments for the 3 to 6th month period. When the baseline data is compared to the end of 6 months, Deira[15] also showed a 22% reduction in dose of ESA dose in the IVAA group whereas the

dose increased by 6%, in controls, although these differences were not significant probably because of the large range of ESA doses used in this study.

Withdrawals and side-effects

Two studies[12,19] commented on immediate side-effects of drug infusion. Shahrbanoo[19] reported 1 episode of chest pain, 2 of nausea, 2 of fatigue with IVAA that did not require discontinuation of the drug with no side effects reported in control. Attalah[12] reported no side-effects using specific questionnaire. Reasons for study withdrawals were not segregated by treatment group in 2 studies. In 3 studies[12,15,17], the combined reasons for study withdrawals were for IVAA : gastrointestinal bleed (1), tuberculosis (1), transfusion (1), transition to peritoneal dialysis (1); for controls: transfusion (1). Attalah[12] reported 11 hospitalization episodes for IVAA group (1.1 episode per patient year) and 12 hospitalizations for the control group (1.2 episode per year). The causes of hospitalizations (IVAA, controls) were: infections (4,4), myocardial infarction (3,4), gastrointestinal bleed (2,2) during the study, others (2, 2).

Sensitivity Analyses

In sensitivity analyses, we included only the study of Attahllah et al[12] and Shahrbanoo et al[19] stating that their patients were ESA hyporesponsive, and found that the weighted mean difference between post-treatment values of Hb level in the IVAA patients versus that in the control patients was 0.81 g/dL (95% CI, 0.65 to 0.96). Similar findings were found when using the difference between change in the IVAA versus control group (Weighted Mean Difference of 0.97 g/dL (95% CI, 0.51 to 1.43). The analysis yields similar results for TSAT, as compared to the main analysis. For ferritin level, the similar trend of lowered ferritin was found to be without statistical significance.

In analysis including only studies with Jadad score of 3 or higher, it was found that the weighted mean difference between post-treatment values of Hb level and TSAT in the IVAA patients versus that in the control patients was 0.96 g/dL (95% CI, 0.77 to 1.14) and 7.49% (95% CI, 6.55 to 8.42), respectively. The results of analyses with fixed-effects model were not different from the main analyses.

Discussion

Currently, the role of ascorbic acid in the treatment of anemia remains controversial. The 2006 KDOQI Guideline[4] stated that there is insufficient evidence to recommend the use of vitamin C, the European Best Practice Guidelines suggested that the correction of impaired vitamin C resistance could reduce resistance to ESA therapy, but did not recommend routine use[38]. To our knowledge, this is the first meta-analysis of randomized, controlled trials conducted to determine the potential benefits of intravenous ascorbic acid for anemic management in hemodialysis patients on ESA treatment. Our findings demonstrate that ascorbic acid improves Hb levels by 0.96 g/dl and TSAT by 8.3%. Furthermore, this is often accompanied by lower ESA requirement suggestive of improved ESA responsiveness. There were minimal short term side effects associated with intravenous ascorbic acid therapy.

The studies included in this meta-analysis represent diverse groups of the hemodialysis population with regards to iron status, ESA resistance, and iron and ESA adjustment protocols. Patients with absolute iron deficiency were excluded. Three of the studies[12,16,19] are focused on patients, who have not achieved target Hb (Hb < 11g/dl) despite moderate to high doses of ESA and moderately high serum ferritin levels (> 300 to 500 ng/mL) and low to moderate TSAT (< 20 to 50%) consistent with functional iron deficiency. The terms relatively resistant or "hyporesponsive" to ESA are used when the target Hb is not reached, despite erythropoeitin doses greater than 300 to 450 international units/kg/week in the absence of iron deficiency[37]. Of these three studies[12,16,19], Attalah[12] is the only study that specifically included only subjects with ESA resistance on high doses of ESA, whereas Giancaspro[16] and Shahrbanoo[19] also included patients on more moderate ESA doses. Deira et al[15] specifically included subjects with marked iron overload with both elevated serum ferritin and TSAT. However, this study also included subjects with Hb within the therapeutic range or higher (Hb > 11) and low ESA doses. Keven et al[17] had the broadest inclusion criteria with subjects with Hb within the therapeutic target range and serum ferritin ranging from just over 100 to 10,000 ng/mL incorporating patients with normal iron status, functional iron deficiency, and iron overload. Keven et al[17] found that 65% of subjects had a positive response to intravenous ascorbic acid. There were no significant differences in many clinical parameters between responders and non-responders, although the response rate tended to be higher in iron overloaded subjects. Despite such different populations and study designs, this meta-analysis show that there was no significant heterogeneity with regards to the effect of ascorbic

acid on the increase in Hb suggesting that the benefit of vitamin C may be observed in hemodialysis patients with adequate iron stores across a broad range of ESA requirement and serum ferritin levels.

The consistency of our research results in all sensitivity analyses indicates the robustness of our findings. These sensitivity analyses were performed in various subgroups *i.e.*, analysis including only studies rated with high quality, analysis using fixed-effects model, analysis using changes of outcomes instead of post-treatment values and analysis in patients with functional iron deficiency and moderate to severe ESA resistance. In the studies, in which ESA dose adjustments were permitted, the Hb often increased despite lower ESA doses after IVAA. The ESA-Hb index (ESA dose per Hb in g/dl) can be useful to assess responsiveness to ESA. In a group with moderate ESA requirement, Keven[17] found that ESA-Hb index decreased significantly by 28% in the IVAA treated group indicating improved responsiveness to ESA, whereas the ESA-Hb index did not change in the control group. Attalah et al[12] found a similar reduction of 20.3% in mean ESA-Hb index from 51.3 to 40.9 (IU/kg/week per g/dl Hb) in ESA resistant subjects after IVAA. A similar trend in improvement of ESA response was also observed in iron overloaded subjects without ESA resistance.

Hemodialysis subjects have a degree of chronic inflammation leading the redistribution of iron out of the circulation into the iron stores (a process in which hepcidin has a central role)[39]. These features suggest sequestration of the excess iron in low-turnover pools with decreased iron bioavailability. The mechanism of improved erythropoietic efficiency after vitamin C treatment has not been elucidated fully, but mobilization of storage iron and increased utilization in the red blood cells are probably major factors. Experimental studies indicated that vitamin C is involved in iron transport, iron uptake and sequestration and heme synthesis[40-42]. Ascorbic acid could increase ESA responsiveness by increasing the intracellular labile iron pool in the reticuloendothelial system leading to mobilization to transferrin and thus increasing the bioavailability of iron[43]. This study found that intravenous ascorbic acid improved TSAT supporting the benefit of ascorbic acid in iron metabolism via increasing transferrin uptake. There is no heterogeneity in this effect on transferrin in patients across different studies despite inclusion of patients with a broad range of serum ferritin.

In addition, vitamin-C effect may enhance transferrin-independent iron uptake by tissues by reducing ferric to ferrous iron[44] and allows iron release from ferritin and hemosiderin pools[9,26]. Increased mobilization from inert tissue stores and improved iron utilization may explain the change in tissue iron binding capacity and reticulocyte Hb content without a significant change in serum iron levels[12]. The levels of serum ferritin were not consistently changed in the studies included for the meta-analysis by intravenous ascorbic acid. The differences observed may relate to the intravenous iron protocols in different studies. In studies[15,16] where intravenous iron therapy was stopped, the serum ferritin decreased compared to baseline values, presumably due to increased iron mobilization. In studies[12,17] where maintenance intravenous iron was given, the serum ferritin appeared to be unaffected by intravenous ascorbic acid, suggesting replenishment of iron stores by the intravenous iron.

Ascorbate levels frequently are decreased in patients on dialysis therapy as a result of insufficient dietary intake and loss during dialytic procedures[45]. In hemodialysis patients, responsiveness to ESA correlated with plasma ascorbate levels[46]. Thus, the results observed in these studies may be in part due to correction of vitamin C deficiency. The doses used in the studies included in this meta-analysis ranged from 200 mg per week to 500 mg given three times per week, which should be sufficient to restore plasma ascorbate levels in the majority of patients[47,14]. However, since none of the studies included in the meta-analysis measured plasma ascorbate levels, it is not possible to conclude that the levels of plasma ascorbate had been normalized in all of treated patients.

Increased oxidative stress is often found in patients with chronic kidney disease on hemodialysis therapy[48]. Increased reactive oxygen species formation and decreased antioxidant levels could lead to cytokine release, endothelial dysfunction, and could contribute to the chronic inflammatory state and ESA hyporesponsiveness[10,49]. Some of the observed effects of vitamin C on Hb levels may have arisen from its property as an antioxidant to reduce oxidative injury and systemic inflammation. Consistent with this is the finding that changes in iron indices and improvement in Hb were associated with a significant decrease in C-reactive protein levels in the ascorbate-treated group[12]. Oxidative injury may also lead to lipid peroxidation of erythrocyte membrane increasing their susceptibility to both osmotic and mechanical stresses. In previous studies, intravenous vitamin C

supplementation protected against such oxidative damage and hemolysis[27]. None of the studies included for analysis in this study, however, examined red blood cell life span or hemolysis.

In these studies, vitamin C was well tolerated with minimal short term side effects. Only one of the included studies reported hospitalization details over a 6 month period. In this study, the rates for hospitalizations were similar to placebo with similar incidence of infectious and cardiovascular complications. None of the current studies included in this meta-analysis provide long term follow-up data. Hence the long term safety of ascorbic acid cannot be evaluated based on these studies.

Secondary oxalosis is a major concern with prolonged therapy in hemodilaysis patients with intravenous ascorbic acid[50,51]. Plasma oxalate levels are typically increased 30- to 40-fold in patients on hemodialysis compared with healthy individuals because of decreased renal excretion[52]. Excessive increases in oxalate concentration may result in tissue deposition of calcium oxalate crystals[53]. Ascorbate is partially metabolized to oxalate and thus intravenous ascorbic acid may enhance oxalate formation[45]. Previous studies have shown that serum oxalate tends to increase with intravenous ascorbic acid although the extent of the increase may vary[14,47]. In the studies included for this meta-analysis, the levels of plasma oxalate were not determined. The long term risks of elevated oxalate concentrations is still unknown, but it has been related to increased risk for myocardial infarction, vascular access failure, and muscle weakness[45].

Ascorbic acid is usually used as a potent antioxidant. However, at high doses, it can act as a pro-oxidant, either directly or through mobilization of iron leading to cellular toxicity or increased risk of atherosclerosis[11,54]. The significance of the pro-oxidant effects of ascorbic acid at more modest doses used in these studies remains uncertain. Although *in vitro* studies[55] show a potential pro-oxidant effect of intravenous ascorbic acid in hemodialysis patients, a protective effect of ascorbic acid on oxidative stress markers have generally been observed *in vivo*[56,57].

Certain limitations exist in our study. First, our study did not include grey literature. It could be interpreted that some papers might not be included. Second, the number of studies included in our analysis was small which might lower the power of the tests of publication bias. Despite the non-significant results of all tests for publication bias, we cannot be certain that publication does not exist. However, we have done our best by exhaustively searched for studies in any language from numerous databases. Third, even though we selected to include homogenous studies in the analysis, certain heterogeneity may still exist in our study, especially patient population. Because of the lack of statistical heterogeneity, we can be confident that the overall estimated effect can be applied in the range of population included in this study.

Our results are also limited by short term follow-up and low numbers of patients included in this meta-analysis. Long term follow-up studies are necessary to establish the risks of oxidative stress and oxalosis. Larger numbers of patients are also necessary to detect serious and rare side-effects. This study provides support for large randomized trials using intravenous ascorbic acid to be conducted in hemodialysis patients to confirm its effectiveness and long term toxicity. More studies are also needed to define the role for ascorbic acid and to identify the optimal dosing regimen and the best combination with parenteral iron as well as to identify the patient categories that would benefit most from treatment.

In conclusion, our study provides additional evidence that intravenous ascorbic acid given 3 times a week after hemodialysis for a 3 to 6 month period in addition to current or previous intravenous iron may be beneficial in the treatment of anemia in subjects on hemodialysis. In spite of different study designs and patient groups, ascorbic acid has been shown to increase Hb and TSAT consistently across a broad range of hemodialysis patients with different levels of serum ferritin and ESA requirements. In addition, ascorbic acid increases ESA responsiveness in subjects with functional iron deficiency. Given its low cost, and great tolerability profile, ascorbic acid may be an attractive option as an adjuvant therapy in hemodialyis anemic patients. However, further well-controlled studies are needed before this form of therapy can be generally recommended, especially until the risks are more clearly defined and there is evidence that such treatment provides long term clinical benefit beyond simply reducing ESA doses and raising Hb levels slightly.

Potential conflicts of interest

None.

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ประสิทธิภาพของกรดแอสคอร์บิกในผู้ป่วยฟอกเลือดที่มีภาวะโลหิตจาง และไม่ตอบสนองต่อยา erythropoietin

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***วัตถุประสงค์**: เพื่อศึกษาผลการให้กรดแอสคอร์บิกในผู้ป่วยฟอกเลือดที่มีภาวะโลหิตจาง และไม่ตอบสนองต่อยา erythropoietin*

***แหล่งข้อมูล**: สืบค้นจากฐานข้อมูลออนไลน์ ได้แก่ PubMed, Cochrane library, IPA, CINAHL, EMBASE, clinicaltrial.gov, WHO trial registry และ PyschINFO*

***การคัดเลือกงานวิจัย**: เลือกงานวิจัยที่เปรียบเทียบ กรดแอสคอร์บิก กับกลุ่มเปรียบเทียบ ในผู้ป่วยฟอกเลือดที่ได้รับยา erythropoietin และมีการระบุค่าฮีโมโกลบินหรือ transferring saturation ในรายงานผลการศึกษา*

***การสกัดข้อมูล**: นักวิจัย 2 คน คัดเลือกและทบทวนงานวิจัยที่สอดคล้องกับเกณฑ์คัดเลือกงานวิจัย ข้อมูลที่สกัดได้แก่ รูปแบบการศึกษาวิจัย, ขนาดยา, ระยะเวลาให้ยา, ค่าฮีโมโกลบิน หรือ transferring saturation ที่เริ่มต้นและสิ้นสุดการศึกษา*

***การสังเคราะห์ข้อมูล**: การทบทวนวรรณกรรมอย่างเป็นระบบ พบว่ามีงานวิจัย 5 เรื่อง ที่ผ่านเกณฑ์คัดเข้าพบว่าฮีโมโกลบินมีความแตกต่างโดยค่าเฉลี่ยระหว่าง กรดแอสคอร์บิก กับกลุ่มเปรียบเทียบ เป็น 0.96 กรัม/เดซิลิตร (95% CI, 0.78-1.14) ขณะที่ transferring saturation มีค่าความแตกต่างโดยเฉลี่ย 8.26% (95% CI, 6.59-9.94)*

***สรุป**: การให้กรดแอสคอร์บิกในผู้ป่วยฟอกเลือดที่มีภาวะโลหิตจางและไม่ตอบสนองต่อยา erythropoietin สามารถช่วยเพิ่มระดับของฮีโมโกลบิน และ transferring saturation อย่างมีนัยสำคัญ การเพิ่มขึ้นของ transferring saturation แสดงว่าการตอบสนองต่อยา erythropoietin ที่ดีขึ้นอาจเกิดขึ้นจากความสามารถของร่างกายในการใช้เหล็กได้ดีขึ้น*