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EFFECTS OF REPLACEMENT OF ASCORBIC ACID IN PATIENTS UNDERGOING HEMODIALYSIS: A CLINICAL TRIAL

Kleber Luiz da Fonseca Azevedo and Eudes Euler de Souza Lucena

State University of Rio Grande do Norte, Mossoró/RN

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Corresponding author:
Kleber Luiz da Fonseca Azevedo

ABSTRACT

Context: Anemia is common in patients with chronic kidney disease undergoing hemodialysis treatment, and oxidative stress and persistent inflammatory state are important for its genesis. Ascorbic acid, a known antioxidant, can serve as an adjunct to your management. **Objective:** to evaluate the effect of intravenous ascorbic acid's replacement in chronic renal patients undergoing hemodialysis. **Design, Setting, Participants:** We conducted a randomized, controlled, triple-blind clinical trial in 45 dialysis patients in a Dialysis Clinical Center, between October 2020 to February 2021.**Interventions:**an Experimental group received 500mg intravenous ascorbic acid after hemodialysis versusa group Control, which received placebo, for four months. **Main Outcome Measure:** Hemoglobin (monthly), transferrin and ferritin saturation (bimonthly), serum ascorbic acid (beginning and at the end of the intervention), and serum oxalate (after intervention) were evaluated. **Results:** Hemoglobin significantly reduced in the Control group, remaining stable in the Experimental group. When selecting only patients with hemoglobin below 12g/dl, there was an increase in their mean in the Experimental Group. Ferritin increased in the Control Group, while the transferrin saturation index increased in the Experimental group. Serum ascorbic acid was low in both groups and didn´t show a significant increase. Serum oxalate was considerably higher in the group that received ascorbic acid at the end of the study. **Conclusion:** The use Ascorbic Acid could prevent high hemoglobin variation in patients with chronic kidney disease undergoing hemodialysis; however, its routine use is not recommended.

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INTRODUCTION

Anemia is common in patients with chronic kidney disease on hemodialysis, and its origin is multifactorial[1]. Etiological factors include Erythropoietin deficiency, iron deficiency, iron functional deficiency[2], oxidative stress, chronic infection and inflammation, bone marrow malignancies, folate, and cyanocobalamin deficiency[3], secondary hyperparathyroidism[4], therapy with angiotensinsuppressing enzyme inhibitors, aluminum toxicity, among others. Several studies have been conducted to test adjuvant therapies aimed at increasing hemoglobin and lowering doses of EPOrh, making the treatment more effective and cost-effective[5]. Hemodialysis in patients with Chronic Kidney Disease leads to long-term ascorbic acid deficiency. It has been reported that each session reduces the serum level by 50-75%[6], in addition to insufficient consumption due to nausea, anorexia, potassium restriction and its degradation during the hemodialysis process[7]. Low levels of ascorbic acid are related to inflammatory activity[8], oxidative stress[9], secondary hyperparathyroidism[10] and, consequently, refractoriness to the treatment of anemia[11].

Ascorbic acid can improve hematimetric levels due to its antioxidant properties, in addition to mobilizing iron from its tissue deposits, increasing its bioavailability and its use in the synthesis of heme[12]. To date, 11 studies have been conducted evaluating the efficacy of intravenous ascorbic acid in the control of anemia, most in the late 1990s and during the years 2000 [13-23]. All studies imply increased hematimetric levels with ascorbic acid supplementation, in addition to increased iron bioavailability in patients with anemia and hyporesponsiveness to the stimulating agents of erythropoiesis or iron overload. Only the trial conducted by Keven *et al.* [17] evaluated patients on hemodialysis regardless of response to Human Recombinant Erythropoietin and with normal iron patterns. Therefore, the present clinical trial was conducted to evaluate the efficiency of ascorbic acid routinely made in improving hematimetric levels and iron bioavailability in patients with chronic kidney disease under hemodialysis, to investigate serum levels of ascorbic acid and oxalate, in addition to observing adverse events related to therapy.

MATERIALS AND METHODS

At the Dialysis Center of the Assu Valley, in Assu, State of Rio Grande do Norte, Brazil, we randomized infants in a triple-blind, randomized controlled trial comparing the clinical consequences of use of Acid Ascorbic 500mg intravenously after each session of dialysis, versus standard practice between October 2020 and February2021. We assessed the eligibility of all patients in Dialysis Center and required at least 8000 UI per week of EPOrh for the treatment of anemia. Fifty-three of the 98 patients were selected according to the following inclusion criteria: 1) being over 18 years of age, 2) using a dose of Human Recombinant Erythropoietin at least 8000 IU per week, 3) performing at least three weekly hemodialysis sessions, 4) regularly using B complex and oral folic acid, 5) having arteriovenous fistula as access to renal replacement therapy, 6) having sessions lasting 4 hours, 7) be assiduous, 8) Being on hemodialysis program for at least three months. Exclusion criteria consisted of: 1) not using any therapies for anemia, 2) being on chronic use of ascorbic acid, 3) having vascular access failure, such as catheters with low blood flow, 4) being in the critical condition of health status, 6) undergoing hemodialysis at a reduced time or reduced dose; 7) have advanced heart or liver diseases; 8) to undergo kidney transplantation or to regain renal function in the middle of the study; 9) present malnutrition, with low body weight, 10) make use of immunosuppressants, chemotherapy, antivirals or immunobiologicals; 11) hypersensitivity reaction to some of the research components such as ascorbic acid or erythropoietin occur.Patients in hemodialysis were randomly assigned to receive 500 mg of Ascorbic Acid Intravenously three times a week, after each session of hemodialysis– the Acid Ascorbic group (Experimental). This group received 500 mg of Ascorbic Acid, contained in 5 ml of the ampoule (Hypofarma – Institute of Hypodermia and Pharmacy Ltda, composed of sodium hydroxide, hydrochloric acid, sodium disulfide, dehydrated disodium edetate and water for injectables, in addition to the active ingredient), diluted in 15 ml of 0.9% Saline Solution, infused three times a week after the end of hemodialysis. The Control group received placebo, which consisted of 20 ml of 0.9% saline solution, after each hemodialysis session. To allow the blinding of the participants, each syringe was sealed and named after the patient, because the solution with Ascorbic Acid acquired a yellow-citrine coloration, which differed from the transparent staining of the physiological solution at 0.9%.All blood products used in this trial were collected by nursing staff of the clinic and prepared according to local institutional practice.

Research coordinators randomly assigned eligible patients using Microsoft Excel (2019). An initial sample size calculation indicated a sample size of 80 subjects (40 subjects in each group, with a two-tailed α of 0.05 and a (1-β) of 0.80) for a difference group receiving at least 8000 UI/week of EPOrh. We estimated an abandonment rate of 20% and mortality rate of 10% during the 4-month period required to carry out the study, yielding a total sample size of 60 subjects. One of the 53 eligible patients did not consent to the study. After informed consent, the remaining 52 patients were randomly assigned and, the concealed randomization was performed by using a 1:1 allocation ratio with blocks of 4 to have balance between the 2 groups. Twenty-three patients were randomly assigned to receive standard care plus 500 mg of intravenous vitamin C (Hypofarma – Institute of Hypodermia and Pharmacy Ltda) with each dialysis session (total of 1500 mg/week; group 1), whereas 22 patients were randomly assigned to receive standard care only (group 2). Study investigators, research coordinators, attending care teams and the patients were blinded to treatment allocation. The primary outcome was composed of increased human hemoglobin associated with the use of Ascorbic Acid, compared to the reduction in the group that did not receive the intervention. In addition to hemoglobin, the four main biochemical parameters that composed the composite outcome were: ferritin, transferrin saturation, ascorbic acid, and sea oxalate.All values of primary outcomes that were present on the day of randomization were recorded. We followed patients on hemodialysis over 4 months to verify that they met the limit and definition for one of the complications included in the compound outcome. Individual complications had to occur after the randomization point (receiving the initial transfusion) to be included as part of the primary outcome.Data collection was performed by analyzing monthly biochemical values recorded in the medical records of the selected patients, feeding the research database was built on the software platform SPSS® (*Statistical Package for Social Sciences*) version 22.0. The frequency distribution of continuous variables was measured by the Kolmogorov-Smirnov Testand asymmetry. The Mann Whitney test was used for independent samples and Wilcoxon for dependent samples, when the frequency distribution didn´t obey normality. For continuous variables with normal distribution, the Student's T test was used for independent samples and t-paired test for dependent samples. The value of "p" used as significant was < 0.05. The outcomes (hemoglobin, ferritin, transferrin saturation, oxalic acid and seric ascorbic acid and Human Recombinant Erythropoietin dosage) were compared between groups and intragroup at different observational moments. Bleeding, infections, and hospitalizations were monitored during the study period in patients of both groups.This project was approved by the Research Ethics Committee of the State University of Rio Grande do Norte, under opinion number: 4,624,962, CAAE: 16208719.9.0000.5294. It received consent from the Assu´s Centre of Dialysis management to carry it out, and all participants signed the Free and Informed Consent Term. The study was registered in clinicaltrials.gov clinical trial registry database as U1111-1254-7035. The procedures were in accordance with the ethical standards of the committee responsible for human experimentation referred to above and with the Helsinki Declaration of 1975, revised in 2013.

RESULTS

From 53 subjects included in the clinical trial, 26 (49%) were randomly allocated to receive intravenous ascorbic acid and 27 (51%) to receive placebo as shown in the CONSORT flowchart (Figure 1).

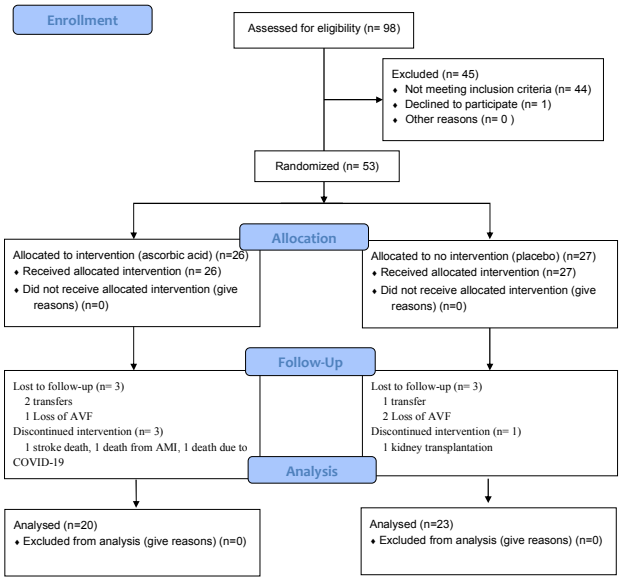

Figure 1. Clinical Trial Flow Deiagram

During the study period, 3 patients discontinued due to city transfer after 2 months of intervention, 2 patients had arteriovenous fistula malfunction and dropped out of the study, 2 patients died due to COVID-19, 1 patient died due to AMI and decompensated CHF, 1 patient died from stroke, 1 patient underwent kidney transplantation leaving the hemodialysis program. In the end, there were 20 participants in group I (Experimental Group) and 23 in group II (Placebo Group). It is noteworthy that during the study period there was discontinuity of patients; 03 due to city transfer, 02 malfunction of arteriovenous fistula, 04 died (COVID-19, AMI, ICC AVEH) and 01 patient underwent kidney transplantation leaving the hemodialysis program.

Table 1. Distribution of the sample according to demographic and clinical variables Assu, RN 2021

Variables	Experimental group	Control group	
Number of participants	20	23	p value
Demographic			
Age (years)	*46.60 ± 11.36*	*44.57 ± 13.28*	*0,495**
Sex (M/F)	*12/8*	*12/11*	
Clinics			
Dry weight (Kg) basal	*68.91 ± 18.08*	*66.26 ± 14.31*	*0,618**
Mean UF (L) basal	*2.18 ± 1.47*	*2.20 ± 0.66*	*0,288**
Basal EPOrh (IU/kg/sem)	*169.32 ± 74.60*	*125.60 ± 66.16*	*0,084**
basal kT/V	*1.37 ± 0.09*	*1.37 ± 0.05*	*0,176**

M: male, F: female, Kg: kilograms; L: liters; IU: International Units *Mann-Whitney U Test Source: search data

Table 2. Hemoglobin, Ascorbic Acid, Ferritin, and Intragroup and Intergroup transferrin saturation (Experimental or Control). Intergroup oxalate at the end of observation Assu, RN 2021

Variable biochemistry	Average ± standard deviation		*p value*
	Experimental Group (20)	Control Group (23)	
Hemoglobin T0	12.56 ± 2.46 g/dL	13.29 ± 1.99 g/dL	0,292*
Hemoglobin T4	11.82 ± 1.84 g/dL	11.70 ± 2.12 g/dL	0,840*
p value	0,361***	0,031***	
Ascorbic Acid T0	0.44 ± 1.22 mg/L	0.76 ± 1.47 mg/L	0,554**
Ascorbic Acid T4	1.73 ± 3.08 mg/L	5.72 ± 19.05 mg/L	0,218**
p value	0,086#	0,132#	
Oxalate T4	33.85 ± 12.37 µmol/L	17.30 ± 12.23 µmol/L	0,000**
Ferritin T0	361.82 ± 345.53 ng/mL	221.33 ± 250.05 ng/mL	0,070**
Ferritin T4	474.80 ± 491.83 ng/mL	338.18 ± 284.55 ng/mL	0,600**
p value	0,286#	0,005#	
Sat. Transfer. T0	37.46 ± 27.59 %	35.16 ± 22.01 %	1,000**
Sat. Transfer. T2	29.53 ± 13.88 %	34.42 ± 18.25 %	0,140**
Sat. Transfer. T4	38.83 ± 15.14 %	43.09 ± 19.81 %	0,062**
p value	0.025 (T2-T4)#	0.140 (T2-T4)#	
EPOrh T0	169.32 ± 74.60 IU/kg/week	125.60 ± 66.16 IU/kg/week	0,084**
EPOrh T4	141.43 ± 164.24 IU/kg/week	129.13 ± 141.95 IU/kg/week	0,641**
p value	0,107#	0,709#	
	Experimental Group (7)	Control Group (6)	
Hemoglobin T0	10.17 ± 0.96	10.72 + 1.99	0,662**
Hemoglobin T4	12.28 ± 1.93	12.03 + 1.82	0,491**
p value	0,018#	0,184#	

Sat. Transf.: transferrin saturation; EPOrh: Human Recombinant Erythropoietin; T0: Time zero (September/2020); T2: second month (December/2021); T4: end of study (February/2021) *T-Student Test **Mann-Whitney U Test ***Paired T-Test #Wilcoxon signed-ranks test Source: search data

BASELINE CLINICAL AND DEMOGRAPHIC VARIABLES: The demographic (gender and age) and clinical (dry weight, mean ultrafiltration, dose of Human Recombinant Erythropoietin and kT/V) *at baseline* of patients were similar in both groups. No significant differences were found between the baseline clinical characteristics in the intervention and control groups (Table 1).

EFFECT OF ASCORBIC ACID ON HEMOGLOBIN: The participants showed a significant reduction in the mean of the human hemoglobin in the Control Group (n=23), with a reduction from 13.29 ± 1.99 g/dL to 11.70 ± 2.12 g/dL, with p value = 0.031, when comparing the mean at the beginning and at the end of the study, but a change in hemoglobin mean without statistical significance in the Experimental group (from 12.56 ± 2.46 g/dL to 11.82 ± 1.84 g/dL, p value=0.361) (Table 2).

When it was selected only patients who had hemoglobin <12 g/dL at the beginning of the study, we observed an increase in hemoglobin in the Experimental Group at the end of the observation period, with statistical significance (10.17 ± 0.96 g/dL 12.28 ± 1.93 g/dL, p = 0.018, n=7), which was not observed in the Control group (p= 0184) (Table 2).

EFFECT OF ASCORBIC ACID ON FERRITIN and TRANSFERRIN SATURATION: When comparing intragroup ferritin levels, in the Control group there was an increase in the mean (221.33 ± 250.05 →338.18 ± 284.55 µ g/L), with statistical significance (p = 0.005) in relation to the beginning of the trial. On the other hand, in the Experimental group there was no significant increase in ferritin in relation to the beginning of observation (p= 0.286). In the Experimental group, transferrin saturation increased significantly in the last two months (32.10% to 35.15%, *p value* = 0.025). However, for the Control group, there was no statistically significant change (*p value* = 0.140), as seen in Table 2.

EFFECT OF ASCORBIC ACID ON ASCORBIC ACID AND SERIC OXALATE: The level of seric ascorbic acid didn´t diverge between the groups before the intervention (p = 0.554), nor was there a difference between the groups after 4 months of observation (p = 0.218) (Table 2). For patients in the Intervention group, serum Ascorbic Acid levels at the end of the study didn´t differ significantly from the beginning of the study (p = 0.086). The same goes for patients in the Control group: serum Ascorbic Acid levels didn´t differ from the beginning in relation to the end of the trial (p = 0.132). However, in relation to the level of seric oxalate, the Experimental group showed a considerably higher seric level in relation to the Control group (p = 0.000) when measured at the end of the assay (Table 2).

EFFECT OF ASCORBIC ACID ON THE DOSE OF ERYTHROPOIETIN: The comparison of the means between the groups didn´t reveal statistical difference in relation to the EPOrh dosage during the different months of observation. When comparing the means over the intervention period, intragroups, the dose of EPOrh decreased in the first two months both in the Experimental group (p = 0.010) and in the Control group (p = 0.006), however, on average, there was no difference in the EPOrh dosage at the end of the intervention in relation to the dose used at the beginning of the trial, in both groups (Experimental Group: *p value* = 0.107 versus Control Group: *p value* = 0.709) (Table 2).

ADVERSE EVENTS: Throughout the intervention, 03 patients presented asthenia (01 in the Control group and 2 in the Experimental group), 01 patient reported increased menstrual bleeding, 01 reported a feeling of weakness in the lower limbs, 01 reported headache after hemodialysis and 01 reported nausea (all the Experimental group). There were no reports of gastrointestinal bleeding, nephrotic cramps, infections, or hospitalizations.

DISCUSSION

In the present trial, intravenous ascorbic acid was effective in preventing hemoglobin fluctuation during the 4-month intervention period. This finding may result from its properties in increasing the half-life of red blood games, reducing oxidative stress and cytokine activity, reducing lipid peroxidation and endothelial dysfunction[4]and reducing the expression of cytokines by fibrous osteitis. When considering only patients with hemoglobin below 12g/dL, hemoglobin increased significantly at the end of the intervention, suggesting a greater usefulness of adjuvant therapy in this specific group. Although not as important as hemoglobin at low levels, fluctuations in high hemoglobin amplitude havealready been shown to be an important risk factor for hospitalization and increased mortality in patients with Chronic Renal Disease on hemodialysis[20]. All trials using Ascorbic Acid as adjuvant therapy, associated with standard therapy with Human Recombinant Erythropoietin, demonstrated increased hemoglobin levels. However, the doses used in the studies varied widely. On average, 300 mg to 500 mg of ascorbic acid was used after each hemodialysis session, and the intervention period ranged from 8 weeks to 12 months[13-23]. The findings revealed an increase in transferrin saturation at the end of the intervention in the Experimental group, while the Control group showed an increase in serum ferritin levels, which may reflect a greater deposit of less usable forms of iron. Ascorbic Acid can slow the degradation of intracellular soluble ferritin in the insoluble fraction of hemosiderin (a form of iron storage not usable for organic functions, which can be stored in various organs, including the kidneys), resulting in an increase in the intrinsic iron pool in the reticuloendothelial system. This would increase the bioavailable iron for transferrin to be used in erythropoiesis. In the bone marrow, Ascorbic Acid also maintains the reduced form of iron, which is the form used for incorporation into protoporphyrin[13]. We didn´t observe an increase in serum levels in the Experimental group during the intervention months. On average, serum levels of Ascorbic Acid were low in both groups at the beginning (Experimental: 0.44 ± 1.22 mg/L *versus* Control: 0.76 ± 1.47 mg/L) and at the end of the trial (Experimental: 1.73 ± 3.08 mg/L versus Control: 5.72 ± 19.05 mg/L), with no statistically important difference. However, serum oxalate levels were significantly higher in the Experimental Group in relation to Control at the end of the 4 months of study (Experimental Group: 33.85 ± 12.37 µmol/L versus Control Group: 17.30 ± 12.23 µmol/L, *p value* = 0.000). The trial by Tarng *et al*. (1998)[18] showed no increase in seric levels in the Group responsive to Ascorbic Acid (n=10) over the course of 8 weeks using 300mg of Intravenous Ascorbic Acid three times a week. In a study conducted by Chan *et al.* (2005)[23], 21 hemodialysis patients who received Ascorbic Acid (10 patients received 250 mg orally and 11 patients received 250 mg intravenously three times a week for 8 weeks, with no control arm) with an increase in plasma Ascorbic Acid, with no difference between the routes of administration. The same study showed a significant increase in plasma oxalate levels, also without difference in the route of administration. Our study was consistent with the findings of Chan *et al.* (2005), in relation to serum oxalate, but no significant changes in serum Ascorbic Acid levels were observed. Loss of Ascorbic Acid during hemodialysis is not well understood. With normal renal function, renal tubular resorption ensures that the consumption of Ascorbic Acid is only in metabolism. For renal loss, serum concentration should be higher than 0.9 mg/L. In contrast, even hemodialysis patients with Ascorbic Acid deficiency will have their blood levels reduced by dialysor[22]. This unregulated loss may help explain the low plasma AA concentration (< 0.5 mg/L) observed in our patients. Our results indicate that even patients in the Experimental group may not reach an adequate plasma concentration. It is noteworthy that there was a reduction in the dose of Human Recombinant Erythropoietin in both groups in the first two months of observation, both with statistical significance (Experimental: p = 0.010; Control: p = 0.006), probably due to the presence of high hemoglobin in both groups at the beginning of the study, causing both to experience a significant reduction in the prescribed erythropoietin dose. A longer observation period, in addition to an increase in sample size, could be necessary for more distinct results to be observed. This dose reduction was not sustained, since, on average, the doses increased again in the last two months of the trial, with no statistical difference between the groups at the end of the *study (p value* = 0.641).

Among the limitations presented by the present study, the main one refers to the selection of the sample studied. First, it is possible that the used dose of 500mg of Ascorbic Acid (chosen due to the dose available in the formulation of the ampoules used) overtime the dose needed to achieve therapeutic effects of the drug, in addition to increasing plasma oxalate levels. In previous trials, the same therapeutic results were achieved at a dose of 100-300 mg per session and hemodialysis[23]. In addition, the groups were formed not only by those with hemoglobin below 12.0g/dL (the upper limit determined by KDIGO 2012), but by all those who used Human Recombinant Erythropoietin above 8000 IU per week.Therefore, the selection of patients with high hemoglobin may have sublimated some findings that would become more evident if only patients with therapy refractory to high doses of erythropoietin were included, in addition to having influenced the decrease in hemoglobin in the placebo group. The number of participants involved (n = 43) and the intervention time were reduced, and there was no follow-up period after the intervention. There was no measurement of plasma oxalate at the beginning of the study, which prevented the comparison between the groups and the analysis of their intragroup elevation, in addition to the that both oxalate and plasma ascorbic acid should have been measured more frequently, a measure limited by the high laboratory cost of the tests. The possibility of ferritin increases due to increased inflammatory activity could not be delayed by dosing markers of inflammatory activity, such as C-reactive protein or hemosedimentation velocity.

Conclusion

The study suggests that Ascorbic Acid three times a week after hemodialysis sessions was effective in maintaining hemoglobin levels, avoiding increased ferritin, and increasing transferrin saturation. Adverse events related to supplemental therapy were scarce and self-limited over the four-month period. Although the reduced sample number of patients with hemoglobin below 12g/dL (who presented increased hemoglobin with Ascorbic Acid) is a limiting factor, this result suggests a greater benefit in patients with low hemoglobin. Due to the high concentration of serum oxalate acquired by the Experimental group in relation to the Control group, Ascorbic Acid supplementation should be recommended only for patients with high-dose refractory anemia of Human Recombinant Erythropoietin, and with constant monitoring of the oxalemia level. Longer studies with a higher number of participants and more frequent measurements of Ascorbic Acid and oxalate are needed to determine smaller, safer, and more effective doses of Ascorbic Acid supplementation, without increasing the risks of hiperoxalemia and other adverse events.

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