Original Article

Comparison of Erythropoietin alone with Erythropoietin plus oral Ascorbic Acid in Treatment of Anemia in Chronic Kidney Disease Patients

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Abstract

Objective: To compare the efficacy of "Oral ascorbic acid in combination with erythropoietin" with "standard dose of erythropoietin alone" in renal anemia in terms of mean hemoglobin rise.

Materials and Methods: A total of 70 CKD patients with anemia, 18 to 70 years of age of both genders were included. Patients with laboratory-proven iron deficiency anemia, obvious blood loss, pernicious anemia, hyperparathyroidism, and contraindications for erythropoietin or ascorbic acid were excluded. It is important to mention here that dialysis patients were also excluded from the study. The patients were randomly selected and placed in two groups. Group A (erythropoietin alone) & Group B (erythropoietin plus oral ascorbic acid), by using the lottery method. Outcome variable like hemoglobin was measured at 2, 4 and 6 months.

Results: Mean age was 48.90 ± 13.53 years. The male to female ratio was 1.6:1 with 43 (61.43%) males and 27 (38.57%) females. Mean pre-therapy hemoglobin was 9.40 ± 1.03 g/dl in Group A while it was 9.42 ± 0.98 g/dl in Group B and mean post-therapy hemoglobin in Group A was 9.34 ± 1.06 g/dl while in Group B, it was 10.37 ± 1.16 g/dl with a P-value of 0.0002 which is statistically significant.

Conclusion: The study concluded that standard dose erythropoietin plus Oral ascorbic acid in CKD anemia is more effective as compared to erythropoietin alone.

Keywords: Chronic kidney disease, Erythropoietin, Ascorbic acid, Anemia.

Introduction

CKD (Chronic kidney disease) has become a major health issue worldwide. For all the practical purposes, CKD is defined as either kidney damage or GFR (Glomerular filtration rate) of less than 90 ml/min/1.73m^2 for at least 3 months. Hypertension and diabetes are the leading cause of CKD ultimately progressing to ESRD (End Stage Renal disease) requiring renal replacement therapy (RRT). As CKD progresses, patients encounter many complications like anemia, bone mineral disease (BMD), reduced quality of life, increasing health expenditures, and premature deaths. In a population-based study conducted in South Asia to see the prevalence of CKD, unfortunately, Pakistan has the highest CKD prevalence when compared with India, Nepal, Bangladesh, and Sri Lanka.[1] In the survey conducted in Karachi in 2011, 25.3% of the participants were found to have some degree of reduced GFR with 5% having GFR <60 ml/min.[2]

Renal anemia (defined as hemoglobin of less than 10mg/dL) is a common finding in patients with chronic kidney disease. It is frequently normocytic and normochromic and typically a diagnosis of exclusion. Although renal anemia has multifactorial etiology, the main culprit is erythropoietin (EPO) deficiency. Erythropoietin is a hormone that is produced endogenously by the kidneys and helps in the maturation of RBCs. Other mechanisms which contribute to the development of anemia include bone marrow suppression by uremia, persistent state of inflammation, decreased iron absorption, increased levels of hepcidin, and vitamin deficiencies.[3] Stauffer ME et al demonstrated in his study that prevalence of anemia is increased as CKD progresses; at stage 1 it was 8.4 % and increased to 53.4% at stage 5.[4]

Anemia in CKD and hemodialysis patients is associated with increased mortality and hospitalization rates. However, the use of recombinant human erythropoietin (rhEpo) has altogether changed the management of anemia in the past three decades. It has been observed that some patients respond poorly to erythropoietin therapy. Iron deficiency is the major reason behind erythropoietin hypo-responsiveness although the contributory role of chronic inflammation, oxidative stress, and some erythropoiesis inhibitory factors has also been evaluated.[5]

Ascorbic acid (AA) is a vital nutrient and its role in the management of anemia has been evaluated in the hemodialysis population in many different studies. Ascorbic acid increases the delivery of iron from the ferritin and reticuloendothelial system and therefore elevates iron use during heme synthesis. Tanjim Sultana et al studied the role of ascorbic acid and found it helpful in decreasing EPO dose requirement in hemodialysis patients.[6]

Since higher mortality and morbidity are associated with anemia in CKD patients, careful correction of anemia carries major benefits in terms of improvement in quality of life, and better tolerance for physical effort. EPO is not only expensive, the higher than standard dose of EPO is associated with poor outcomes. So, proving the beneficial effects of ascorbic acid in the treatment of renal anemia can help us achieve better outcomes at a lower EPO dose.

Materials and Methods

This RCT was done from July 2019 to August 2020 in the Nephrology department of a tertiary care hospital. 70 patients of both genders with CKD (excluding dialysis patients) and anemia (Hb<10 g/dl) and age between 18-70 years were included. Patients with iron deficiency anemia, pernicious anemia, blood loss, hyperparathyroidism, and contraindications for erythropoietin or ascorbic acid were excluded.

After taking informed consent, the patients were selected randomly and placed in two groups i.e. Group A (erythropoietin alone) and Group B (erythropoietin plus oral ascorbic acid), using the lottery method. Group A patients were treated with erythropoietin alone: 50 IU/kg twice weekly) and Group B patients received erythropoietin 50 IU/kg two times a week along with daily 500 mg oral ascorbic acid. All patients were followed by taking contact numbers and home addresses over a period of 6 months and were reviewed by a consultant nephrologist. All parameters recorded at the initial assessment were checked and the dose of erythropoietin was adjusted accordingly. Outcome variable like hemoglobin was measured at 2, 4 and 6 months and reports were verified by consultant hematologist.

We decided on primary efficacy and safety end-points. The total number of patients achieving equal or more than hemoglobin levels of 12 mg/dL in the last month of treatment were labelled as the primary efficacy end-point. Safety end-points were severe anemia (Hb less than 6), lymphopenia with severe infection, and opportunistic infections. Patients who needed blood transfusion for any reason were excluded. All selected patients were kept devoid of iron therapy throughout

the 6 months of study and patients who had T-Saturation less than 25 were also excluded. Patients were monitored for side effects of ascorbic acid like nausea, vomiting, heartburn, and oxalosis on regular basis.

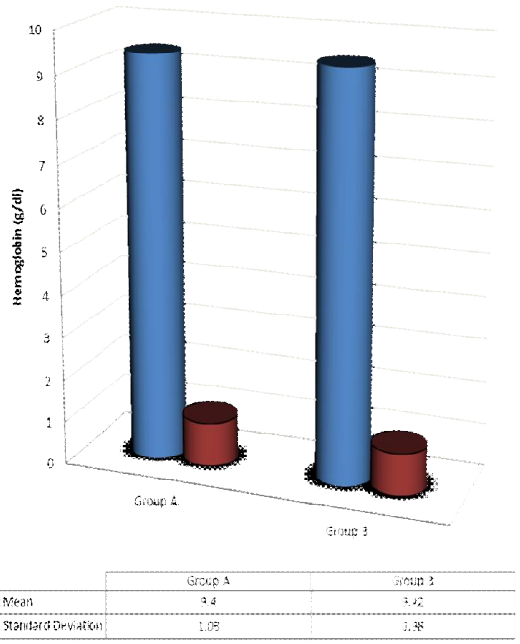
All data were recorded and analyzed in SPSS v 20.0. The percentages and frequencies were calculated for the categorical variables. For continuous variables mean and Standard deviation were calculated. The student's t-test was used for assessment of the significance of the difference between two groups for continuous variables (mean Hb). A p-value of < 0.05 was considered significant.

Results

Of the total 266 medical students enrolled in this research, most (53.75%) of our study participants were final-year MBBS students as depicted in Figure 1.

The mean age of the patients in group A was 48.49 ± 13.77 years and in group B was 49.31 ± 13.48 years. The majority of patients 25 (35.71%) were of 46 to 60 years of age. Out of the total 70 patients, 43(61.43%) patients were males and 27(38.57%) patients were females with a ratio of 1.6:1.

Figure 1 shows the mean pre-therapy hemoglobin in both groups with no significant difference among them (p-value = 0.901). The mean duration of disease was 4.64 ± 2.41 months. Majority of patients presented with stage 5 CKD i.e. 23 (32.86%) in both groups as shown in Figure 2. Mean post-therapy hemoglobin in Group A (erythropoietin alone) was 9.34 ± 1.06 g/dl while in Group B (erythropoietin plus ascorbic acid) was 10.37 ± 1.16 g/dl as shown in Figure 3 (p-value = 0.0002).



P-value 0.901.

Figure 1: Mean pre-therapy Hemoglobin in both groups

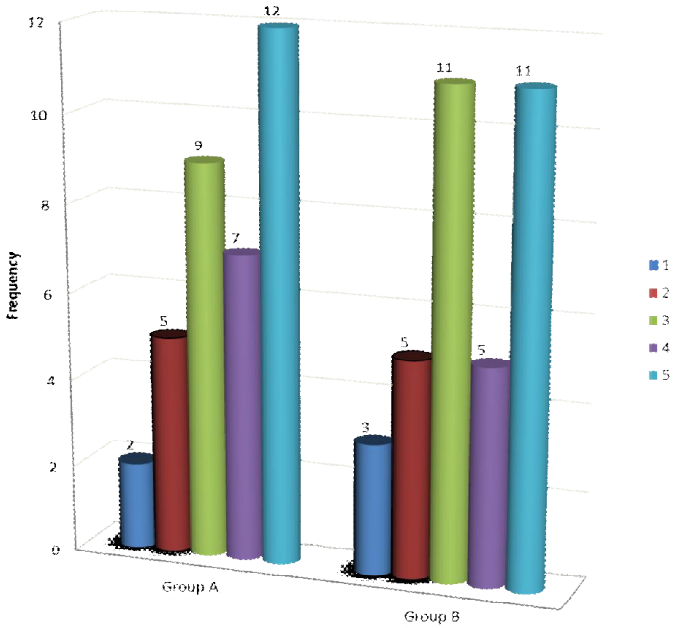
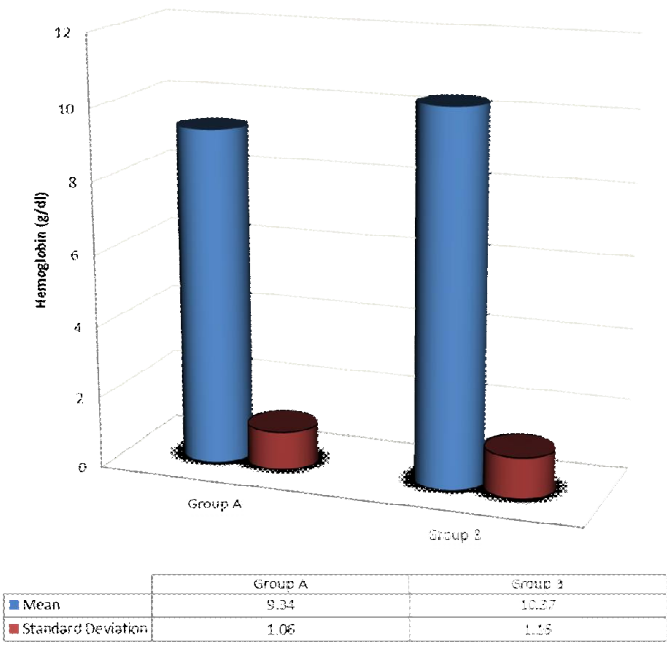


Figure 2: Distribution of patients according to the stage of chronic kidney disease



P-value = 0.0002 which is statistically significant.

Figure 3: Comparison of Post-therapy mean hemoglobin in both groups

Discussion

The CKD burden worldwide is increasing enormously and a 19.6% increase in prevalence has been reported from 2005 to 2015 based on data collected from different studies.[7] Aggregated results from different studies conducted in the USA and Europe showed a significant rise in CKD prevalence, however, sometimes there is marked disparity among the countries like 3.3% in Norway and 17.3% in north Germany.[7]

The introduction of erythropoietin in clinical practice about 30 years back dramatically changed the management of anemia which is associated with CKD. Renal anemia is found in more than half of the patients diagnosed with stages 4 and 5 of CKD.[8] Before the EPO therapy, patients dependent on dialysis were profoundly anemic usually having hemoglobin between 6 g/dl to 7g/dl; blood transfusion and iron therapy being only available treatments. The use of erythropoietin to maintain hemoglobin levels between 10 and 12.0 g/dl is recommended[9], however, erythropoietin use is not without risks. It should be avoided in patients with active malignancy and may be used with caution in patients with a previous history of stroke and neoplasia.[9]

The use of ascorbic acid in renal anemia has been a matter of debate in the last decade. The study which was conducted by Salih Karahan et al found that baseline ascorbic acid levels were lower in kidney patients and administration of ascorbic acid profoundly decreased central blood pressure and increased antioxidant potential of the patients.[10]

In a study conducted at Mazandaran University of Medical Sciences, Sari, Iran, the author showed significant mean hemoglobin rise in a group of patients who received intravenous ascorbic acid with each hemodialysis session along with erythropoietin (before 8.5 ± 1.2; after 9.6 ± 1.4) whereas mean hemoglobin in patients who received only erythropoietin did not show such improvement (before 8.5 ± 1.1; after 8.4 ± 1.3).[11]

In our study, we wanted to see the effect of ascorbic acid on anemia of kidney patients who were not on dialysis yet. The majority of the patients 25 (35.71%) in our study were between 46 to 60 years of age. The patients were treated for iron deficiency anemia (if any) before inclusion into the study. No patient was receiving any iron supplementation throughout the study to decrease the bias. Mean pre-therapy hemoglobin in Group A (erythropoietin alone) was 9.40 ± 1.03 g/dl while in Group B (erythropoietin plus ascorbic acid) was 9.42 ± 0.98 g/dl and mean post-therapy hemoglobin in Group A (erythropoietin alone) was 9.34 ± 1.06 g/dl while in Group B (erythropoietin plus ascorbic acid) was 10.37 ± 1.16 g/dl with a p-value of 0.0002 which was statistically significant. Patients on ascorbic acid responded comparatively better to EPO probably because of its antioxidant properties and ability to counterbalance radical species. Ascorbic acid may also play an important role in iron metabolism and its application in red blood cell formation so the total dose of EPO consumed to achieve the same hemoglobin may be reduced as well. Interestingly oral ascorbic acid was tolerated well by the patients and no side effects were noted.

Similar findings were elaborated by Jalalzadeh M et al in his study where he found that after 3 months of treatment, Hb levels increased from 10.11g/dl to 12.19 g/dl ($P < 0.001$; 95% confidence interval [CI] 2.7-1.4) in patients who were treated with erythropoietin plus ascorbic acid for correction of their anemia.[12] Sharkawy M. et al likewise showed a significant increase in mean values of hemoglobin levels in the erythropoietin plus ascorbic acid group from 7.85 ± 0.96 to 9.26 ± 1.17 ($p<0.001$) in comparison to the erythropoietin group.[13]

In another recent study which was conducted in a small group of hemodialysis patients, there was a 33% decrease in EPO requirement in patients who were treated with 250 mg of ascorbic acid daily for 3 months along with erythropoietin. Hb levels increase significantly from 10.1 ± 0.6 mg/dl to 10.7 ± 0.6 mg/dL (P = 0.03) and there were no particular side effects of ascorbic acid noted.[14]

Conclusion

This study concluded that standard dose erythropoietin plus oral ascorbic acid is more effective for anemia correction in chronic kidney disease patients and results are encouraging when compared with erythropoietin alone. Ascorbic acid is cheap and available freely in Pakistan So, we recommend that ascorbic acid along with erythropoietin can be used as first-line therapy in order to achieve better outcomes at lower EPO doses.

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