Original Article
DOI: https://doi.org/10.70749/ijbr.v3i6.1839

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://ijbr.com.pk
ISSN: 2960-2793/ 2960-2807

Comparison of Oral Iron Alone with Oral Iron Plus Oral Ascorbic Acid in the Treatment of Anemia in Chronic Kidney Disease Patients

Hafiz Muhammad Sajid Anayat[1], Bilal Javaid[1], Ijaz Nabi[1], Salman Mehmood[1], Madiha Rauf[1], Saba Gulnaz[1], Tauqeer Haider[1]

[1]Department of Nephrology, Allied Hospital Faisalabad, Faisalabad Medical University, Faisalabad, Pakistan

ARTICLE INFO

Keywords: Chronic Kidney Disease, Anemia, Oral Iron, Ascorbic Acid, Hemoglobin, Non-Dialysis CKD.

Correspondence to: Hafiz Muhammad Sajid Anayat,
Department of Nephrology, Allied Hospital Faisalabad, Faisalabad Medical University, Faisalabad, Pakistan.
Email: sajidanayat90@gmail.com

Declaration

Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History

Received: 12-05-2025 Revised: 07-06-2025
Accepted: 23-06-2025 Published: 30-06-2025

ABSTRACT

Objectives: To compare mean hemoglobin concentration in chronic kidney disease patients with anemia treated with Iron alone and Iron plus oral Ascorbic Acid. **Methodology:** This study was conducted at the Department of Nephrology, Allied Hospital, Faisalabad during the period from from 8 January 2025 to 8 May 2025. A total of 60 patients were randomly assigned to two groups: Group A (oral iron only, n=30) and Group B (oral iron + oral ascorbic acid, n=30). Hemoglobin concentration was recorded at baseline and after 3 months. Subgroup analysis was performed by age, gender, BMI, and CKD etiology. **Results:** Baseline hemoglobin levels were comparable between both groups (p=0.427). After 3 months, Group B demonstrated a significantly higher increase in hemoglobin (10.96 ± 1.11 g/dL) compared to Group A (9.57 ± 1.06 g/dL), (p=<0.001). Stratified analysis showed greater hemoglobin improvement in the combination therapy group across all subgroups, especially among younger patients, females, and those with glomerulonephritis. **Conclusion:** The combination of oral iron with ascorbic acid is more effective than iron alone in improving hemoglobin levels in CKD-associated anemia. This simple, cost-effective strategy may be particularly valuable in low-resource settings.

INTRODUCTION

Globally, CKD affects about 10% of adults and results in millions of early fatalities.[1–2] Anemia is considered the most common complication linked with CKD.[3] It plays a major role in worsening disease progression, lowering life quality, and increasing health risks.[4] This anemia stems from several contributing mechanisms.[5] Prevalence rates rise with CKD progression, reaching 7% to 50% in advanced stages.[6–7]

The pathogenesis of anemia in CKD involves multiple mechanisms, among which iron deficiency anemia (IDA) is most prevalent. It is characterized by diminished erythropoiesis due to a lack of available iron. Globally, iron deficiency stands as the leading cause of anemia and is frequently reversible. WHO guidelines[8–9] emphasize its treatability, especially in the early stages. A diet rich in iron can correct pre-latent deficiency, but advanced IDA necessitates oral iron supplementation to restore iron stores and correct hematopoiesis. Commonly used agents include ferrous sulfate and ferric succinate. Ascorbic acid (vitamin C), aside from animal-derived food, is known to enhance non-heme iron absorption.[10] In dialysis patients, it boosts iron mobilization and heme synthesis by facilitating the release of iron from storage.[11]

In a study[11] on the role of intravenous iron and ascorbic acid for treatment of functional iron deficiency in patients under hemodialysis, the baseline Hb was 8.28 ± 0.37 g/dL and endpoint Hb level was 9.61 ± 0.41 g/dL after intravenous iron, while the baseline Hb level was 7.61 ± 0.22 g/dL and endpoint Hb was 11.97 ± 0.26 g/dL after intravenous iron plus ascorbic acid.

Anemia in CKD cases is strongly associated with increased morbidity and mortality. Therefore, correcting anemia in these patients is not only essential for prolonging survival but also for significantly improving their quality of life and physical activity tolerance. Erythropoietin therapy is a cornerstone of treatment; however, it is costly, and higher-than-recommended doses are linked with adverse outcomes. If ascorbic acid proves to be effective in managing renal anemia, it may help enhance treatment outcomes while reducing the required dose of

erythropoietin, making management both safer and more economical.

METHODOLOGY

The present randomized controlled trial took place at the Department of Nephrology, Allied Hospital, Faisalabad, spanning from 8 January 2025 to 8 May 2025. following ethical clearance from both the Institutional Review Board and the College of Physicians and Surgeons Pakistan (CPSP). Participants were recruited only after being thoroughly informed about the study objectives, potential risks, and their rights. Written informed consent was obtained from each participant. All collected clinical and personal data were kept confidential in accordance with ethical research standards.

A total of 60 patients with CKD and anemia undergoing maintenance hemodialysis for more than three months were enrolled using non-probability consecutive sampling. The sample size was calculated using the WHO sample size calculator with a 5% level of significance, 90% power, an anticipated mean hemoglobin (Hb) concentration of 9.61 ± 0.41 g/dL in the iron-only group (Group A), and 11.97 ± 0.26 g/dL in the iron plus ascorbic acid group (Group B). Each group included 30 patients. Inclusion criteria were adults aged 18 to 70 years of either gender, diagnosed with CKD, undergoing hemodialysis for more than three months, and having a hemoglobin level of less than 10 g/dL. Patients were excluded if they had received a kidney transplant, had blood transfusions within the past three months, had hyperparathyroidism, or had contraindications to erythropoietin or oral ascorbic acid.

Baseline evaluation included detailed history, clinical examination, and collection of a 5 mL blood sample to assess hemoglobin concentration. Participants were randomly assigned to two groups using the lottery method. Group A received oral iron therapy alone (ferrous succinate 100 mg tablet every 8 hours), while Group B received the same iron therapy in combination with oral vitamin C (200 mg per dose, i.e., 100 mg tablet every 8 hours). Both regimens were administered for three months. Participants were followed regularly through contact numbers provided and were monitored by a consultant nephrologist throughout the treatment period. The primary outcome was the change in hemoglobin concentration (g/dL) from baseline after three months of therapy.

Data entry and statistical analysis were performed using SPSS version 25. Continuous variables such as age, body weight, height, body mass index, estimated glomerular filtration rate, and hemoglobin concentration were summarized using mean and standard deviation. Categorical variables including gender and etiology of CKD (e.g., diabetes mellitus, hypertension, glomerulonephritis) were presented as frequencies and percentages. The primary comparison of mean hemoglobin levels between the two groups was performed using the independent sample t-test. Stratification was conducted for effect modifiers such as age, gender, BMI, and CKD etiology, followed by post-stratification application of the independent sample t-test. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Table 1 presents the demographic and baseline characteristics of the study population, which included 60 chronic kidney disease (CKD) patients with anemia, equally divided into two groups: those treated with iron alone and those treated with iron plus ascorbic acid. The age distribution showed that 46.7% of patients were aged 18–40 years, while 53.3% were between 41–70 years, with slightly younger patients in the iron-alone group. Regarding BMI, 43.3% of patients had a BMI between 18–25 kg/m^2, and 56.7% were in the 26–35 kg/m^2 category, with equal proportions in both groups. The most common causes of CKD were diabetes mellitus (33.3%), hypertension (33.3%), and glomerulonephritis (33.3%), with a fairly balanced distribution across groups. The gender distribution showed a slight female predominance (51.7%), and the mean age and BMI for the overall sample were 43.23 ± 15.59 years and 26.41 ± 4.64 kg/m^2, respectively.

Table 1

Demographic and Baseline Characteristics (n = 60)

Variable	Category	Iron Alone (n=30)	Iron + Ascorbic Acid (n=30)	Total (n=60)
Age Group	18–40 years	16 (53.3%)	12 (40.0%)	28 (46.7%)
	41–70 years	14 (46.7%)	18 (60.0%)	32 (53.3%)
BMI Group	18–25 kg/m^2	13 (43.3%)	13 (43.3%)	26 (43.3%)
	26–35 kg/m^2	17 (56.7%)	17 (56.7%)	34 (56.7%)
CKD Cause	Diabetes Mellitus	11 (36.7%)	9 (30.0%)	20 (33.3%)
	Hypertension	10 (33.3%)	10 (33.3%)	20 (33.3%)
	Glomerulonephritis	9 (30.0%)	11 (36.7%)	20 (33.3%)
Gender	Male	14 (46.7%)	15 (50.0%)	29 (48.3%)
	Female	16 (53.3%)	15 (50.0%)	31 (51.7%)
Mean ± SD	Age (years)		43.23 ± 15.59	
	BMI (kg/m^2)		26.41 ± 4.64	

Table 2 compares the mean hemoglobin (Hb) levels before and after treatment between the two study groups. The baseline (pre-treatment) Hb levels were similar between the iron-alone group (8.32 ± 0.99 g/dL) and the iron plus ascorbic acid group (8.11 ± 1.00 g/dL), with no statistically significant difference (p = 0.427). However, a marked and statistically significant increase in post-treatment Hb levels was observed in the ascorbic acid group (10.96 ± 1.11 g/dL) compared to the iron-alone group (9.57 ± 1.06 g/dL), with a p-value of less than 0.001, indicating a significant therapeutic benefit from the combined treatment.

Table 2

Comparison of Pre- and Post-Treatment Hemoglobin Between Groups

Variable	Group	Mean ± SD	p-value[a]
Pre Hb (g/dL)	Iron Alone	8.32 ± 0.99	0.427
	Iron + Ascorbic Acid	8.11 ± 1.00	
Post Hb (g/dL)	Iron Alone	9.57 ± 1.06	<0.001
	Iron + Ascorbic Acid	10.96 ± 1.11	

Table 3 provides a stratified comparison of post-treatment hemoglobin levels based on age, gender, and BMI. Among patients aged 18–40 years, the iron plus ascorbic acid group had significantly higher Hb levels (11.13 ± 1.18 g/dL) than the iron-alone group (9.88 ± 1.12 g/dL; p = 0.008). Similarly, in the 41–70 years group, a significant

difference was observed (10.85 ± 1.08 vs. 9.22 ± 0.90 g/dL; p < 0.001). Male patients also showed a substantial Hb increase with combined therapy (11.06 ± 1.09 g/dL vs. 8.94 ± 0.99 g/dL; p < 0.001), while female patients had a more modest yet borderline significant difference (p = 0.050). Stratification by BMI revealed significantly better outcomes in both BMI groups, with higher post-treatment Hb levels in the ascorbic acid group for BMI 18–25 kg/m^2 (p = 0.020) and BMI 26–35 kg/m^2 (p < 0.001).

Table 3
Post-Treatment Hb Comparison Stratified by Demographics

Stratification	Subgroup	Mean Post-Hb (Iron Alone)	Mean Post-Hb (Iron + Vit C)	p-value
Age Group	18–40 years	9.88 ± 1.12	11.13 ± 1.18	0.008
	41–70 years	9.22 ± 0.90	10.85 ± 1.08	<0.001
Gender	Male	8.94 ± 0.99	11.06 ± 1.09	<0.001
	Female	10.13 ± 0.79	10.86 ± 1.17	0.050
BMI Group	18–25 kg/m^2	9.57 ± 0.92	10.45 ± 0.87	0.020
	26–35 kg/m^2	9.58 ± 1.19	11.35 ± 1.14	<0.001

Table 4 focuses on post-treatment Hb levels stratified by underlying CKD etiology. In patients with diabetes mellitus, the post-treatment Hb was higher in the ascorbic acid group (10.91 ± 1.08 g/dL) compared to the iron-alone group (9.94 ± 1.02 g/dL), though the difference narrowly missed statistical significance (p = 0.053). For hypertensive CKD patients, the combination therapy significantly improved Hb levels (p = 0.032). Notably, in patients with glomerulonephritis, the increase in hemoglobin was highly significant (11.05 ± 1.04 vs. 9.11 ± 0.85 g/dL; p < 0.001), suggesting a particularly strong benefit of adding ascorbic acid in this subgroup.

Table 4
Post-Treatment Hb Comparison Stratified by CKD Cause

CKD Cause	Mean Post-Hb (Iron Alone)	Mean Post-Hb (Iron + Vit C)	p-value
Diabetes Mellitus	9.94 ± 1.02	10.91 ± 1.08	0.053
Hypertension	9.59 ± 1.21	10.91 ± 1.32	0.032
Glomerulonephritis	9.11 ± 0.85	11.05 ± 1.04	<0.001

DISCUSSION

This randomized controlled trial aimed to compare the efficacy of oral iron supplementation alone versus in combination with ascorbic acid in the treatment of anemia among non-dialysis chronic kidney disease (CKD) patients. The findings demonstrated a statistically significant improvement in mean hemoglobin concentration in the group receiving iron combined with ascorbic acid, compared to the group receiving iron alone. Moreover, this beneficial effect of combination therapy was consistently observed across various subgroups, including different age brackets, genders, body mass index ranges, and etiological classifications of CKD.

Anemia in CKD is typically driven by a combination of reduced erythropoietin production, impaired iron absorption, functional iron deficiency due to inflammation, and elevated hepcidin levels.[12] The addition of ascorbic acid may overcome some of these barriers by enhancing intestinal iron absorption through its reducing properties and by mobilizing iron from tissue stores.[13] Our findings align with this pathophysiological understanding and provide clinical evidence supporting its benefit.

These results are consistent with previous trials, such as the one conducted by Qaisar et al[14] which showed significantly improved hemoglobin levels in CKD patients treated with erythropoietin plus ascorbic acid compared to erythropoietin alone. Similarly, Al-Za'abi et al[15] also demonstrated enhanced efficacy when combining ascorbic acid with erythropoietin therapy. The benefit of combination therapy in our subgroups, especially among younger patients and those with glomerulonephritis, corresponds with findings by Di Lullo et al[16] who reported that Ferric Sodium EDTA combined with vitamin C and micronutrients improved hematologic outcomes in CKD patients unresponsive to standard oral iron.

Furthermore, Guedes et al[17] highlighted patient barriers to anemia management in CKD, such as treatment adherence and access to intravenous therapies, and advocated for patient-friendly oral regimens like the one tested in our study. This approach is particularly valuable in low-resource settings where intravenous iron and ESAs are often unavailable or unaffordable.[18] Recent evidence by Syed-Ahmed and Narasubramanian underscored the contribution of inflammation to iron resistance and anemia in CKD, a problem that vitamin C may help mitigate via its antioxidant and anti-inflammatory effects.[19] Sharma et al[20] also emphasized the need for safe, scalable interventions in CKD anemia care, particularly in underserved populations.

Although the findings of this study are encouraging, several limitations must be acknowledged and considered: The study duration was relatively short (3 months), limiting the evaluation of long-term efficacy and sustainability of hemoglobin improvement. Iron indices such as serum ferritin, transferrin saturation, and hepcidin were not assessed, which restricts understanding of iron metabolism dynamics. Gastrointestinal tolerability, compliance rates, and quality of life improvements were not measured. The study did not evaluate inflammatory markers or vitamin C serum levels, which could have elucidated mechanistic pathways. The single-center design may limit the generalizability of findings to broader populations.

Future studies should incorporate larger, multicenter cohorts with longer follow-up to validate the sustained benefits of combination therapy. Evaluation of iron indices (ferritin, TSAT), inflammatory markers (CRP, IL-6), and oxidative stress parameters should be included to better understand underlying mechanisms. Randomized trials comparing oral iron + vitamin C versus intravenous iron or ESAs could help guide clinical decision-making. Patient-reported outcomes, including adherence, gastrointestinal side effects, and quality of life, should be studied to ensure treatment acceptability. Ascorbic acid therapy could be explored in earlier CKD stages or in patients with ESA hyporesponsiveness.

CONCLUSION

The addition of oral ascorbic acid to iron therapy significantly improved hemoglobin levels in patients with anemia associated with CKD. This combination appears to be a safe, accessible, and cost-effective alternative to

intravenous therapies and may be particularly beneficial in resource-limited settings. These findings advocate for its broader use as part of individualized anemia management in CKD.

REFERENCES

1. Hanna RM, Streja E, Kalantar-Zadeh K. Burden of anemia in chronic kidney disease: beyond erythropoietin. Adv Ther. 2021; 38(1):52–75. https://doi.org/10.1007/s12325-020-01524-6
2. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022 Apr;12(1):7-11. https://doi.org/10.1016/j.kisu.2021.11.003.
3. Hain D, Bednarski D, Cahill M, Dix A, Foote B, Haras MS, Pace R, Gutiérrez OM. Iron-deficiency anemia in CKD: a narrative review for the kidney care team. Kidney Medicine. 2023 Aug 1;5(8):100677. https://doi.org/10.1016/j.xkme.2023.100677
4. Selim MFM, Lotfy EEM, Mohamed LAE, Zahran MH. Assessment of erythropoietin efficacy and dosing in hemodialysis patients. Eur J Mol Clin Med. 2021; 8(3):e2461–9. https://doi.org/10.21608/ejhm.2020.108894
5. Pottel H, Martin L, Broseta JJ, Cases A. Anemia in chronic kidney disease: from pathophysiology and current treatments, to future agents. Front Med. 2021; 8:e642296. https://doi.org/10.3389/fmed.2021.642296
6. Wong MM, Tu C, Li Y, Perlman RL, Pecoits-Filho R, Lopes AA, et al. Anemia and iron deficiency among chronic kidney disease Stages 3–5ND patients in the Chronic Kidney Disease Outcomes and Practice Patterns Study: often unmeasured, variably treated. Clin Kidney J. 2020; 13(4):613–24. https://doi.org/10.1093/ckj/sfz091
7. Zaawari A, Tejaswini KL, Davina GD, Singanaveni A. Prevalence of anemia among chronic kidney disease patients in India: a single-centre study. Int J Basic Clin Pharmacol. 2022 Sep;11(404):2319-003. https://doi.org/10.18203/2319-2003.ijbcp20222135
8. Deng J, Ramelli L, Li PY, Eshaghpour A, Schünemann GE, Crowther MA. Efficacy of Vitamin C with iron supplementation in iron deficiency anemia patients: a systematic review and meta-analysis. Blood. 2023 Nov 28;142:1097. https://doi.org/10.1182/blood-2023-174801
9. Ukey UU, Sharma SK, Chitre DS, Waghmare PR, Dabir AJ, Desai R, et al. Effect of oral vitamin C administration along with iron supplementation for treating anemia among adolescent girls – protocol for systematic review and meta-analysis. J Family Med Prim Care. 2024;13:537–41. https://doi.org/10.4103/jfmpc.jfmpc_660_23
10. Selim MF, Lotfy EE, Mohamed LA, Zahran MH. Assessment of erythropoietin efficacy in treatment of anemia in pre-dialysis chronic kidney disease patients. Egypt J Hosp Med. 2020; 80(3):1138–43. https://doi.org/10.21608/ejhm.2020.108894
11. Osman MY, Osman HM, Khalil IS, Sharaf IA, Mahmoud R. Parenteral use of iron and ascorbic acid (Vitamin C) in haemodialysis patients. Bull High Inst Public Health. 2007; 37(1):179–88. https://doi.org/10.21608/jhiph.2007.22309
12. Badura K, Janc J, Wąsik J, et al. Anemia of Chronic Kidney Disease—A Narrative Review of Its Pathophysiology, Diagnosis, and Management. Biomedicines. 2024;12(1191). https://doi.org/10.3390/biomedicines12061191
13. Hoving V, Donker AE, Schols SEM, et al. How I treat iron-refractory iron deficiency anaemia—An expert opinion-based treatment guidance. Br J Haematol. 2025;206(2):1067–1076. https://doi.org/10.1111/bjh.20030
14. Qaisar MA, Abideen ZU, Yameen M, et al. Comparison of Erythropoietin Alone with Erythropoietin Plus Oral Ascorbic Acid in Treatment of Anemia in Chronic Kidney Disease Patients. J Rawal Med Coll. 2021;25(2):181–185. https://doi.org/10.37939/jrmc.v25i2.1501
15. Al-Za'abi M, Al Balushi A, Al-Busaidi M, et al. Comparison of Erythropoietin alone with Erythropoietin plus ascorbic acid in the treatment of anemia in patients with chronic kidney disease. Saudi J Kidney Dis Transpl. 2014;25(6):1231–1235.
16. Di Lullo L, Marchitto N, Curcio A, et al. The best therapeutic option for oral treatment of secondary anaemia in chronic kidney disease. Nephrol Renal Dis. 2021;6:1–6. https://doi.org/10.15761/nrd.1000184
17. Guedes M, Robinson BM, Obrador GT, et al. Management of Anemia in Nondialysis Chronic Kidney Disease: Current Recommendations, Real-World Practice, and Patient Perspectives. Kidney360. 2020;1(8):855–862. https://doi.org/10.34067/kid.0001442020
18. Nawaz H, Rehman FU, Talal U, et al. Comparison of Oral Versus Intravenous Iron Therapy in Improving Hemoglobin Status in Patients of Chronic Kidney Disease. Pak J Health Sci. 2024;5(4). https://doi.org/10.54393/pjhs.v5i04.1377
19. Syed-Ahmed M, Narasubramanian S. Iron deficiency in chronic kidney disease: a narrative review of current and emerging therapies. Kidney Med. 2023;5(5):100581.
20. Sharma A, Rathore SS, Madaan H, et al. Anaemia of Chronic Kidney Disease: A Review. Int J Adv Res. 2020;8(2):505–510.