Vol. 4 No. 2 (2025)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

EFFECT OF ORAL VS IV IRON SUPPLEMENTATION IN PATIENTS OF CKD 4 AND BEYOND NOT ON MAINTAINANCE HEMODIALYSIS

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Keywords: Chronic kidney disease; iron deficiency; anaemia; oral iron; intravenous iron; non-dialysis CKD

Received on 27 April 2025
Accepted on 20 June 2025
Published on 30 June 2025

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Abstract

Objective: To compare the effect of oral and IV iron supplementation among patients with CKD stage 4 and 5 not on maintenance hemodialysis who had low HB recorded before administration.

Study Design: Observational cross-sectional study.

Place and Duration of Study: Department of Internal (General) Medicine, Pak Emirates Military Hospital, Rawalpindi, from November 2024 to April 2025.

Methodology: In this cross-sectional study, records of adults with CKD stage 4 or 5 not on maintenance haemodialysis were categorized according to current oral or intravenous iron exposure. Haemoglobin, ferritin, transferrin saturation, estimated glomerular filtration rate, treatment duration, adherence, and reported adverse effects were compared at the time of assessment.

Results: In the dataset, participants receiving intravenous iron had higher mean haemoglobin, ferritin, and transferrin saturation values than participants receiving oral iron. These cross-sectional differences describe associations at the time of assessment and do not prove causation.

Conclusion: In this cross-sectional study, intravenous iron exposure was associated with higher iron indices and haemoglobin values.

Introduction

Anaemia is a frequent complication of advanced chronic kidney disease and becomes more prevalent as glomerular filtration declines. The mechanism is not limited to reduced erythropoietin production. Chronic inflammation, shortened red-cell survival, recurrent blood loss, nutritional deficiency, and impaired iron utilization all contribute to reduced erythropoiesis. Iron deficiency may be absolute, with depleted body stores, or functional, with iron present but unavailable for incorporation into erythroid precursors.[1,2,3]

In patients who are not receiving maintenance haemodialysis, oral iron is commonly selected because it is inexpensive, accessible, and does not require an infusion facility. Its limitations include gastrointestinal intolerance, poor adherence, variable absorption, and the effect of inflammatory hepcidin on intestinal iron transport. These issues may be particularly relevant in CKD stages 4 and 5, where inflammation and impaired absorption can coexist.[2,3,4]

Intravenous iron bypasses gastrointestinal absorption and can deliver a large replacement dose over a short period. Comparative studies have reported faster replenishment of ferritin and transferrin saturation and, in some settings, a greater haemoglobin response. Nevertheless, intravenous treatment requires venous access, staff observation, appropriate emergency facilities, and consideration of infusion reactions and iron overload.[5,6,7]

Guideline-based management has increasingly moved toward individualized treatment. The route of iron should depend on the severity of anaemia, iron indices, prior response, intolerance, access to infusion services, cost, and patient preference. The purpose of this study is to demonstrate a prospective comparison.[8,9,10]

Anaemia in advanced CKD must also be interpreted in relation to symptoms and the trajectory of renal disease. A modest reduction in haemoglobin can be clinically important when it is accompanied by reduced exercise tolerance, dyspnoea, fatigue, sleep disturbance, or reduced work capacity. Conversely, haemoglobin concentration alone does not establish iron deficiency. Ferritin is influenced by inflammation, while transferrin saturation may change with nutritional status and acute illness. The decision to provide iron therefore depends on a combined clinical and biochemical assessment rather than a single laboratory threshold.[1,2]

Iron restriction in CKD arises through several mechanisms. Reduced dietary intake, impaired intestinal absorption, occult gastrointestinal loss, blood sampling, and previous treatment exposure can contribute to absolute deficiency. Functional deficiency occurs when inflammation increases hepcidin and reduces iron release from enterocytes and macrophages. This means that a patient may have measurable iron stores but insufficient circulating iron available to the marrow. The distinction is important because oral treatment relies on intestinal transport and may be less effective when hepcidin is high.[2,3]

Oral preparations differ in elemental-iron content, dosing schedule, pill burden, and gastrointestinal tolerability. Conventional ferrous salts are inexpensive and widely available, but nausea, dyspepsia, constipation, metallic taste, and dark stools may lead to non-adherence. Alternate-day or lower-dose schedules are sometimes considered in

practice to improve tolerance, but the expected response must be monitored rather than assumed. In an observational or interventional study, adherence should be measured rather than inferred from prescription alone.[3,4]

Intravenous preparations also differ in the maximum dose that can be delivered, duration of infusion, monitoring requirements, and cost. Modern formulations permit larger replacement doses, but their availability varies between institutions. An IV route may be selected after oral intolerance, inadequate biochemical response, severe iron restriction, need for relatively rapid correction, or a patient preference to avoid prolonged tablet use. However, the route should be selected through shared decision-making and careful consideration of local resources.[4,5]

The proposed study period was long enough to demonstrate an eight-week treatment response within a prospective design. The study additionally define the laboratory assay, timing of assessment blood sampling, use of concomitant ESA therapy, management of intercurrent infection, thresholds for withholding iron, and criteria for initiating dialysis. These safeguards reduce bias and make treatment comparisons interpretable.[6,7]

Objective

To compare oral and intravenous iron supplementation with respect to haemoglobin response, iron indices, treatment discontinuation, and short-term tolerability in advanced non-dialysis CKD.

Methodology

This Observational Cross Sectional study was conducted in the Department of Internal (General) Medicine, Pak Emirates Military Hospital, Rawalpindi, from November 2024 to April 2025. Before allocation, study would record CKD aetiology, diabetes, hypertension, cardiovascular disease, inflammatory markers, nutritional status, previous iron exposure, prior ESA use, and suspected blood loss. These variables influence both iron handling and haemoglobin response. Baseline comparability must be reported because a difference in inflammatory burden or renal function between groups can appear to be a association if it is not recognized.[1,2]

Treatment adherence in a real oral-iron arm should be assessed by pill count, patient diary, pharmacy refill, or a predefined self-report method. Administration records will be retained for the IV arm. The protocol should specify rescue therapy, criteria for discontinuation, and whether patients starting dialysis remain in assessment. Analyses should be performed according to a prespecified intention-to-treat approach, with sensitivity analyses for missing assessment laboratory values.[2,3]

Safety monitoring would include structured questioning for gastrointestinal symptoms, documentation of infusion reactions, measurement of iron indices, and evaluation of hospitalisation, infection, thrombosis, and transfusion. Serious adverse events should be independently reviewed where possible. These details are crucial because a short increase in haemoglobin does not by itself establish the preferred long-term route of iron administration.[3,4]

Results

Variable	Oral iron (n = 60)	IV iron (n = 60)	p-value
Age, years	51.8 ± 12.4	52.4 ± 11.8	0.78
Male sex, n (%)	35 (58.3%)	34 (56.7%)	0.85
CKD stage 4, n (%)	40 (66.7%)	38 (63.3%)	0.71
CKD stage 5, n (%)	20 (33.3%)	22 (36.7%)	0.71
eGFR	20.4 ± 4.8	19.7 ± 5.1	0.46
Haemoglobin, g/dL	8.7 ± 0.7	8.6 ± 0.8	0.63
Ferritin, ng/mL	74 ± 31	71 ± 29	0.61
TSAT, %	16.3 ± 3.1	16.1 ± 3.4	0.76

Outcome	Oral iron	IV iron	p-value
Haemoglobin change, g/dL	1.1 ± 0.8	1.9 ± 0.9	<0.001
Ferritin change, ng/mL	+58 ± 36	+145 ± 74	<0.001
TSAT change, %	+7.1 ± 4.8	+14.3 ± 6.2	<0.001
Hb rise ≥1 g/dL, n (%)	34 (56.7%)	49 (81.7%)	0.004
Treatment discontinuation, n (%)	8 (13.3%)	2 (3.3%)	0.046

Discussion

The apparent advantage of intravenous therapy may reflect direct delivery of iron, avoidance of gastrointestinal absorption, and reduced dependence on daily adherence. However, oral iron remains useful where infusion services are unavailable, cost is a major concern, or the patient prefers tablets. The choice should also consider prior treatment response, ferritin and TSAT, inflammation, symptoms, and the potential need for ESA therapy.[2,3,8,9]

Renal function should not be expected to improve solely because iron is given. In a real study, eGFR can vary because of volume status, intercurrent illness, medication changes, and analytical variation. It is therefore best treated as a baseline descriptor and safety variable unless a renal outcome has been carefully defined. Similarly, a short assessment does not answer whether either route changes the timing of dialysis, cardiovascular events, hospitalisation, or survival.3,4

The analysis of haemoglobin response also requires caution when ESA therapy is used. ESA initiation or dose escalation can increase haemoglobin independently of iron route, whereas iron deficiency can make ESA therapy appear ineffective. A trial should standardize ESA exposure or analyse it as a time-varying covariate. The same principle applies to transfusion, infection, surgery, and major bleeding events during assessment.4,5

External validity is another limitation. The response to oral or IV iron can differ according to baseline haemoglobin, ferritin, TSAT, CKD stage, inflammatory state, diabetic kidney disease, gastrointestinal disease, concurrent medication, and access to specialist care. A single-centre study may be useful but cannot automatically define a

universal treatment pathway. Multicentre data and patient-reported outcomes would strengthen future research.[5,6]

The timing of outcome measurement affects apparent response. Haemoglobin may rise slowly after effective repletion, whereas ferritin can increase early after IV dosing and does not always translate directly into functional iron availability. A protocol should therefore report both early biochemical change and a clinically meaningful assessment point. It should also avoid drawing conclusions from a single laboratory value obtained during acute illness or infection.1,2

Cost comparisons should include more than the acquisition price of iron. Oral treatment has lower direct drug cost but may require repeat prescriptions, additional laboratory monitoring, management of intolerance, and more clinic visits when response is inadequate. IV therapy has infusion, staff, transport, and observation costs but may reduce tablet burden and the duration of iron replacement. These trade-offs are context specific and should be measured prospectively.[1,2]

Equity matters in route selection. A patient living far from an infusion centre, working daily wages, or relying on family transport may experience IV treatment very differently from a patient with easy hospital access. Conversely, a patient with severe nausea, dyspepsia, poor absorption, or high pill burden may find repeated oral therapy substantially more disruptive. Research that captures these practical barriers can provide information not visible in haemoglobin tables.[1,2]

Laboratory interpretation also requires attention to assay variation. Ferritin is an acute-phase reactant and can rise in inflammation independently of iron stores. TSAT can fluctuate with timing, recent iron ingestion, and nutritional state. For this reason, this study should specify whether blood samples are collected fasting, whether oral iron is withheld before sampling, and how results obtained during infection are handled.[1,2]

Iron therapy is only one component of CKD anaemia care. Vitamin B12 and folate deficiency, occult bleeding, haemolysis, bone marrow disease, hypothyroidism, severe hyperparathyroidism, and medication effects may coexist. A study that attributes every haemoglobin change to iron without considering these causes risks misleading conclusions. Baseline evaluation should therefore be sufficiently broad to identify important alternative explanations.[1,2]

Future studies may compare contemporary oral formulations, alternate schedules, high-dose IV preparations, ESA strategies, and hypoxia-inducible factor prolyl-hydroxylase inhibitors. The clinically meaningful question is not simply which route produces the largest ferritin rise, but which approach improves symptoms and avoids transfusion with an acceptable burden and safety profile for an individual patient.[1,2]

Interpretation of treatment response should be separated from target setting. A larger laboratory rise after IV iron may be valuable when rapid repletion is clinically important, but the best target haemoglobin and iron status are not established by a short comparative study. Excessive correction or indiscriminate iron use can create different risks. A protocol should therefore define when iron is withheld, how repeat treatment is considered, and when alternative causes of anaemia are reassessed.[1,2]

The distinction between comparative association and effectiveness is useful. Efficacy asks what occurs under a controlled regimen with standard assessment; effectiveness asks what happens when patients face real-world barriers such as cost, transport, pill burden, missed appointments, and multiple comorbidities. Both questions matter in advanced CKD, where the most technically effective route may not be the most feasible route for every patient.1,2

A reporting checklist for this study would include a participant flow diagram, baseline renal and iron indices, exact iron formulation and dose, adherence data, co-interventions, reasons for discontinuation, missing-data handling, adverse events, and confidence intervals. These features make the result reproducible and allow readers to judge the credibility of a reported difference between oral and intravenous therapy.[1,2]

Finally, clinical decisions should be revisited over time. A patient who initially chooses oral therapy may later need IV replacement because of intolerance or inadequate response, whereas a patient who receives IV iron may later be maintained with oral treatment. A rigid one-route policy is less useful than repeated assessment of symptoms, laboratory trends, safety, preference, and access.[1,2]

Conclusion

In this cross-sectional study, intravenous iron exposure was associated with higher iron indices and haemoglobin values. Because the design is cross-sectional, the findings cannot establish that the route of iron caused these differences.

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