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Original Article

Comparison of Oral Versus Intravenous Iron Therapy in Improving Hemoglobin Status in Patients of Chronic Kidney Disease

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ABSTRACT

Anemia (particularly iron deficiency) is an important concern in patients with chronic kidney disease (CKD) as it reflects the outcome of the disease. **Objective:** To compare the treatment efficacy of oral versus intravenous iron supplementation in improving the hemoglobin status of patients with chronic kidney disease not on hemodialysis or erythropoietin. **Methods:** Randomized controlled trial was carried out in Medicine Department of Pak Emirates Military Hospital, Rawalpindi from Jun 2023 to Dec 2023. Patients in Group I received intravenous iron sucrose 200 mg once a week diluted in 500 ml of 0.9% normal saline given over 60-90 minutes. Patients in Group O received oral iron supplementation in a dose of 325 mg (containing 65 mg of elemental iron) thrice a day taken one hour before taking their meals with a glass of water. The treatment was continued for 4 weeks. **Results:** Mean values of serum iron were 84.41±5.56 mcg/dl in Group I versus 84.67±5.43 mcg/dl in Group O before the start of therapy (p=0.726). Serum values for iron post-therapy were 143.40±6.01 mcg/dl in Group I versus 125.35±6.68 mcg/dl in Group O (p<0.001). Mean values for serum hemoglobin were 7.74±0.74 g/dl in Group I versus 7.61±0.82 g/dl in Group O before the start of therapy (p=0.256). Serum values of Hb post-therapy were 12.31±0.71 g/dl in Group I versus 9.91±0.82 g/dl in Group O (p<0.001). **Conclusions:** We conclude that Intravenous (IV) iron is superior to oral iron supplementation in improving iron stores and Hb levels in CKD patients not on dialysis and/or erythropoietin.

INTRODUCTION

The global prevalence of chronic kidney disease has been alarmingly high in the past two decades. The estimated prevalence of the general population suffering from chronic kidney disease has been >10% amounting to more than 850 million individuals suffering from the ailment worldwide in 2022 [1]. With such a high burden of disease, the number of cases is projected to increase by 2050, especially due to risk factors like malnutrition, hypertension, and diabetes mellitus on the rise as well [2]. In Pakistan, the prevalence among all age groups was 21.2% according to a recent study [3]. Anemia associated with iron deficiency is one of the hallmark features of the disease. The pathogenesis proposed is multifactorial and is attributed to deficiency in erythropoietin production, blood loss during hemodialysis, chronic inflammation, decreased absorption of iron and mechanism leading to relative and absolute deficiency of iron in the body [4]. Patients on hemodialysis are more prone to blood loss and iron deficiency and are advised intravenous iron supplemental as a mandatory treatment regime [5]. The

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successful treatment of CKD anemia is accomplished with recombinant human erythropoietin. Several studies have shown that in almost all erythropoietin-treated patients, iron supplementation is needed because iron deficiency may contribute to erythropoietin hypo-responsiveness [6, 7]. Various studies advocate IV therapy in a large number of chronic kidney disease patients not on dialysis or on erythropoietin also present with iron deficiency anemia. Intravenous iron supplemental is not warranted in all patients with mild to moderate disease and the allergic tendency of IV iron restricts its broad use in resource constrained setups requiring monitoring and admission for administration. The use of oral supplemental in these patients have been a matter of debate and whether it is more effective or on par in improving the hemoglobin status in patients with mild to moderate disease who are not on hemodialysis or erythropoietin. We aim to study this cheaper, cost-effective, and safe alternative and compare it to the intravenous formulations to see the increase and improvement in hemoglobin status post-therapy.

The study was conducted to compare the treatment efficacy of oral versus intravenous iron supplementation in improving the serum iron and hemoglobin status of patients with chronic kidney disease not on hemodialysis or erythropoietin.

METHODS

This randomized controlled trial was carried out at the Department of Medicine, Pak Emirates Military Hospital, Rawalpindi from Jun 2023 to Dec 2023. Trail ID 73381, IRCT Id, IRCT20310030596 05N1 registered at https://irct.behdasht.gov.ir/trial/73381. Sample size was calculated keeping the confidence interval at 95%, power of test at 80% with mean difference observed for increase in serum iron being 41.88±5.69 mcg/dl in the IV iron supplementation group and 39.68±2.23 mcg/dl in the oral iron supplementation group after therapy [8]. Minimum sample size came out to be 89 for the IV group and 101 for the oral group keeping the population variance at 10,000. We initially included 250 patients for the RCT with 210 patients in the final study design after meeting inclusion criteria divided into two groups of IV versus oral iron supplemental group with 105 participants in each. Method of sampling was non-probability consecutive by lottery method. Ethical review board's permission was taken on 25 May 2023, IRB no A/28/ER/554/23. Inclusion criteria included that all male and female patients over the age of 18 years not on hemodialysis or erythropoietin diagnosed as anemia with a baseline Hb of less than 13 g/dl in males and less than 12 g/dl in females with established chronic kidney disease with a GFR (glomerular filtration rate) of less than 60ml/min for more than 90 days assessed using the CKD-EPI equation and/or hyper albuminuria with urine albumin ≥ 30 mg in 24 hours or urine albumin to creatinine ratio (ACR) ≥ 30 mg/g. Exclusion criteria included that patients on dialysis, erythropoietin or use of erythropoietin stimulating agents (ESAs) in the last 3 months, patients with advanced liver, cardiac or ESKD (end-stage kidney disease), drug allergies to iron and its supplemental form during therapy or previous known history or unwilling to be included in the study. The RCT included all the assessed participants for eligibility and meeting the inclusion criteria divided into the intravenous iron supplementation group (Group I) (n=105) and the oral iron supplementation group (Group O) (n=105) (Figure 1). Patients in Group I received intravenous iron sucrose 200 mg once a week diluted in 500 ml of 0.9% normal saline given over 60-90 minutes under observation in the medical ward. Allergy if any assessed by the doctor on duty was treated with prompt cessation of therapy and administration of IV hydrocortisone 200 mg stat and IV promethazine 25 mg stat and observed for 3 hours or till signs and symptoms settled. Patients in Group O received oral iron supplementation in a dose of 325 mg (containing 65 mg of elemental iron) thrice a day taken one hour before taking their meals with a glass of water. The treatment regime was started using the standard KDIGO (kidney disease: improving global outcomes) guidelines. Intolerable side effects including allergy and severe gastric upset were indications for cessation of therapy and exclusion from the trial group. The therapy was carried out for 4 weeks and patients were advised weekly follow-up for assessment. Samples taken at the end of the trial period were done with patients with 10 hours fast and 7 days after the completion of therapy. Primary variables observed were changes in the serum iron, Hb, transferrin and TIBC, that were measured through blood sample collected and analyzed through standard ROCHE analyzer for the samples taken. Secondary variables observed were the adverse effect profile seen with both treatment regimes. Demographic data were statistically described in terms of mean, standard deviations, frequencies, and percentages when appropriate. Independent sample t-test was used to study mean values between both groups. A p value of ≤ 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.0.

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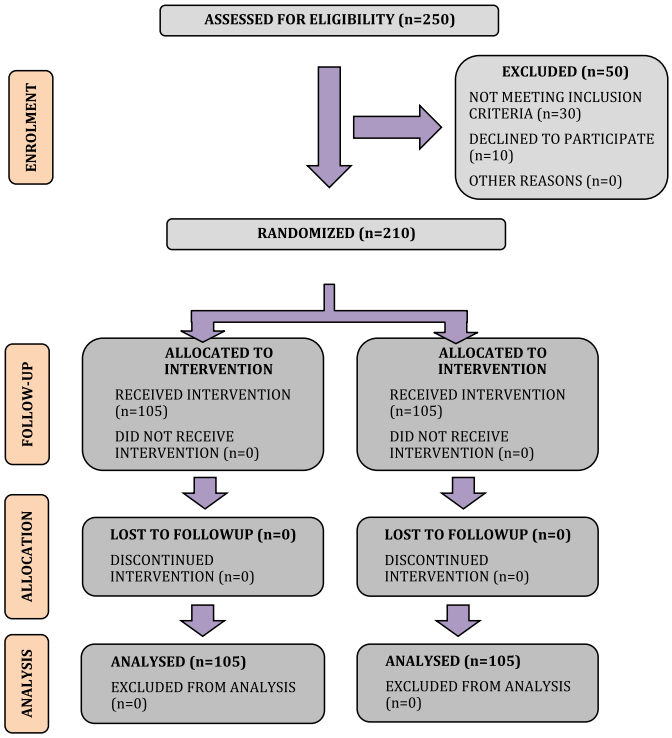

Figure 1: Phases of Randomized Controlled Trial

RESULTS

A total of 210 patients were analyzed in the study protocol divided into the IV iron group (Group I) (n=105) and the oral iron group (Group O)(n=105). Mean age of patients in Group I was 41.75±5.85 years versus 42.07±6.11 years in Group O (p=0.695). Mean weight was 63.70±4.04 kg in Group I versus 63.88±4.00 kg in Group O (p=0.745). Gender distribution revealed 86 (81.9%) males and 19 (18.1%) females in Group I versus 86 (81.9%) males and 19 (18.1%) females in Group O (table 1).

Table 1: Demographic Characteristics of Both Groups (n=210)

Variable	Group I (n=105)	Group O (n=105)
Age (Years)		
Mean±SD	41.75±5.85	42.07±6.11
Weight (Kg)		
Mean±SD	63.70±4.04	63.88±4.00
Gender		
Male	86 (81.9%)	86 (81.9%)
Female	19 (18.1%)	19 (18.1%)

Mean values of serum iron were 84.41±5.56 mcg/dl in Group I versus 84.67±5.43 mcg/dl in Group O before the start of therapy (p=0.726). Serum values for iron post-therapy were 143.40±6.01 mcg/dl in Group I versus 125.35±6.68 mcg/dl in Group O (p<0.001). Mean values for serum hemoglobin were 7.74±0.74 g/dl in Group I versus 7.61±0.82 g/dl in Group O before the start of therapy (p=0.256). Serum values of Hb post-therapy were 12.31±0.71 g/dl in Group I versus 9.91±0.82 g/dl in Group O (p<0.001). Mean serum ferritin levels before the start of therapy were 102.20±5.03 ng/ml in Group I versus 102.27±4.90 ng/ml in Group O (p=0.912). Same values measured post-therapy were 130.83±3.41 ng/ml in Group I versus 120.85±10.83 ng/ml in Group O (p<0.001). Mean serum transferrin levels measured were 232.61±12.92 mg/dl in Group I versus 231.98±12.50 mg/dl in Group O before the start of therapy (p=0.721). Post-therapy levels were 302.51±9.52 mg/dl in Group I versus 285.18±3.70 mg/dl in Group O (p<0.001). Mean TIBC values pre-therapy were 383.78±9.41 mcg/dl in Group I versus 383.86±9.52 in Group O (p=0.948). Values observed post-therapy were 349.93±9.84 in Group I versus 363.28±5.00 in Group O (p<0.001)(table 2).

Table 2: Comparison of Primary Variables between Both Groups (n=210)

Variable	Group I (n=105)	Group O (n=105)	p-Value
Mean Serum Iron (Mcg/Dl)			
Before Therapy	84.41±5.56	84.67±5.43	0.726
After Therapy	143.40±6.01	125.35±6.68	<0.001
Mean Hemoglobin (G/Dl)			
Before Therapy	7.74±0.74	7.61±0.82	0.256
After Therapy	12.31±0.71	9.91±0.82	<0.001
Mean Serum Ferritin (Ng/Ml)			
Before Therapy	102.20±5.03	102.27±4.90	0.912
After Therapy	130.83±3.41	120.85±10.83	<0.001
Mean Serum Transferrin (mg/dl)			
Before Therapy	232.61±12.92	231.98±12.50	0.721
After Therapy	302.51±9.52	285.18±3.70	<0.001
Mean Total Iron Binding Capacity (mcg/dl)			
Before Therapy	383.78±9.41	383.86±9.52	0.948
After Therapy	349.93±9.84	363.28±5.00	<0.001

Comparison of adverse effects profile showed that constipation was reported by 15 (14.3%) patients in Group I versus 40 (38.1%) patients in Group O. Diarrhea was reported by 06 (5.7%) patients in Group I versus 11 (10.5%) patients in Group O. Allergy to iron formulations was seen in 12 (11.4%) patients in Group I versus 05 (4.8%) patients in Group O. The frequency of nausea was equal in both groups with 03 (2.9%) patients reporting the complaint. Headache was not reported by any in Group I versus 05 (4.8%) patients in Group O. Hypotension was seen in 16 (15.2%) patients in Group I versus 00 (0%) patients in Group O (table 3).

Table 3: Comparison of Adverse Effect Profile between Both Groups (n=210)

Variable	Group I (n=105)	Group O (n=105)
Constipation	15 (14.3%)	40 (38.1%)
Diarrhea	06 (5.7%)	11 (10.5%)
Allergy	12 (11.4%)	05 (4.8%)
Nausea	03 (2.9%)	03 (2.9%)
Headache	00 (0%)	05 (4.8%)
Hypotension	16 (15.2%)	00 (0%)

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DISCUSSION

The study was carried out at our demographic setup to assess the efficacy of intravenous versus oral iron supplements to improve the iron levels and hemoglobin status in patients with chronic kidney disease. The prevalence of chronic kidney disease in Pakistan is increasing at an astonishing rate and the need for prolonged therapy for the primary disease as well as optimization required for the added complications is a major resource burden on our crippled health care system [9]. Anemia is one of the major complications associated with the disease and a landmark study by Obrador *et al.*, concluded that more than 68% patients with chronic kidney disease develop anemia during the disease process [10]. Even though aggressive strategies are required for correction of anemia in advanced cases and specially with patients on dialysis, those with mild to moderate disease can be treated effectively for anemia with oral or intravenous supplements. Whether one form proffers any advantage over the other was the aim since oral formulations if proven to be effective than IV form do not require detention and monitoring for their administration decreasing the hospital burden and resources. Not only correcting the anemia improve the physical status of the patients, but it also results in better cardiovascular stability and decreasing the complications associated with low Hb and cardiovascular compromise [11, 12]. Our study concluded that iron levels were improved in both the oral and the iron supplementation groups but there was a statistically significant improvement in the intravenous versus the oral form when the endpoint of the study was reached. The IV therapy group showed marked clinical improvement in the four weeks of therapy. The same was concluded by Gutierrez *et al* [13]. who observed marked improvement with the IV iron formulation in patients with chronic end stage kidney disease. Bazeley *et al.*, concluded that IV iron should be the preferred route in patients unless the therapy needs to be stopped due to allergic reaction or adverse effects not tolerable to the patient [14]. They also concluded that oral iron therapy should be the second line alternative in all cases unless indicated. Similar results were given by study done by Das *et al* [15]. When comparing the improvement in the hemoglobin status of the participants in both groups, a similar trend was seen where a statistically significant improvement was seen in the intravenous iron group as compared to the oral group. Our study included patients with mild and moderate amnesia and the mean rise was significantly high in the intravenous iron group at the end of four weeks of therapy. These findings were consistent with results of studies carried out by Riccio *et al.*, [16] and Lopes *et al* [17]. Another study by Ganz *et al.*, proposed that even with the added risk of infection with the IV route especially in severely debilitated patients, if used judiciously, the intravenous route should be the preferred method as the chances of infection are minimal [18]. When comparing the adverse effect profile, it is where the intravenous route offers a good advantage to patients than those on oral therapy. Gastrointestinal side effects associated with therapy were seen in around half of patients in the oral group in our study. Constipation remained the chief complaint followed by diarrhea, but none were severe enough to warrant discontinuation of therapy in our patients, but studies have concluded that patients become non-compliant to therapy following gastric side effects and they need to be monitored for effective results. These findings were consistent with those done by Emma *et al.*, [19] and Elstrott *et al* [20].

CONCLUSIONS

Our findings concluded that IV iron therapy was superior to oral iron supplementation in improving iron stores and Hb levels in CKD patients not on dialysis and/or erythropoietin.

Authors Contribution

Conceptualization: HN
Methodology: FR, UT, MFH, ZA
Formal analysis: HN, ZA
Writing-review and editing: ANC

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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