MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.11.130.135

OPEN ACCESS

Key Words
Iron deficiency anaemia, haemoglobin deficiency, IV iron sucrose, chronic kidney disease, chronic renal disease

Corresponding Author
Megha R. Raju,
Department of General Medicine, Sree Mookambika Institute of Medical Sciences, Kanyakumari, Tamil Nadu, India

Author Designation
[1]Post Graduate
[2]Professor

Received: 20 August 2024
Accepted: 14 October 2024
Published: 16 October 2024

Citation: Megha R. Raju and R.V. Mookambika, 2024. Comparing the Effectiveness of Intravenous vs Oral Iron Therapy in Patients with Chronic Kidney Disease: Associated Anemia. Res. J. Med. Sci., 18: 130-135, doi: 10.36478/makrjms. 2024.11.130.135

Comparing the Effectiveness of Intravenous vs Oral Iron Therapy in Patients with Chronic Kidney Disease: Associated Anemia

[1]Megha R. Raju and [2]R.V. Mookambika
[1,2]Department of General Medicine, Sree Mookambika Institute of Medical Sciences, Kanyakumari, Tamil Nadu, India

ABSTRACT
Patients with chronic kidney disease (CKD) should be particularly concerned about anaemia, especially iron deficiency, as it is a reflection of the disease's prognosis. There are currently few guidelines for treating anaemia in these patients with intravenous iron (IV) therapy. In patients with chronic renal disease, this study compares oral and intravenous iron. In this prospective case-control research, patients with chronic renal disease who were hospitalized to the medicine department of Sree Mookambika Institute of Medical Sciences, Padanilam, Kulasekharam, Kanyakumari in India. 150 patients in all were split into two groups of 75, one of which received intravenous iron (IV iron sucrose) and the other oral iron (ferrous sulphate 325 mg tablets). In both categories, there were more males (57.6%, 64.7%) than girls (42.3%, 35.2%). In both the IV iron group (33) and the oral iron group (36), the majority of participants were between the ages of 41 and 60. In the IV and oral iron groups, 25.8%, 52.9%, 21.1% and 21.3% of the participants, respectively, had mild, moderate and severe hemoglobin deficiency. When it comes to the measure of iron deficiency anaemia, IV iron sucrose therapy has been shown to be more successful, well-tolerated and efficacious than oral iron treatment in individuals with chronic renal disease.

INTRODUCTION

Iron deficiency anaemia is found in all grades of chronic kidney disease but more in haemodialysis-dependent patients needing iron therapy. In haemodialysis-dependent chronic kidney disease, there are more favourable outcomes for injectable iron supplements over oral iron[1]. Clinical evidence had shown that the use of intravenous (IV) iron in patients with CKD is more effective than oral treatment, but in chronic kidney disease patients not on dialysis there is no widely accepted consensus on which route of iron administration should be used as first-line therapy. Moreover, the optimum route of giving iron to CKD patients is still controversial[1,2]. Key systems for the pathogenesis of pallor in chronic kidney disease include an overall lack of erythropoietin, iron inadequacy and malnutrition, expanded blood misfortune and abbreviated erythrocyte life expectancy. The successful treatment of CKD anaemia 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[2-6]. The utilization of intravenous (IV) iron can be restricted by anaphylactic responses due to dextran containing iron formulations[4,6]. The hepcidin-induced blockade of iron absorption in the gut explains the reduced efficacy of oral iron replacement in patients with CKD, often necessitating iron repletion therapies that bypass the gastrointestinal tract in patients with CKD. This has also led to interest in developing novel therapies that target factors stimulating hepcidin secretion and/or ferroportin, the topic of which is covered in several excellent reviews and other reports[7-11]. In addition, new hypoxia-inducible factor 1a prolyl hydroxylase inhibitors may target this pathway by reducing hepcidin concentrations, resulting in improved gastrointestinal iron absorption and reduced sequestration of iron in reticuloendothelial stores, both of which enhance iron availability for erythropoiesis[12].

Patients with CKD on hematolysis are given iron therapy as an alternative to erythropoietin-stimulating agents (ESAs)., whereas only 33% of CKD patients not on hematolysis receive ESA treatment[13]. Two multi center trials in the United States sought to determine the efficacy and feasibility of iron sucrose infusion in the treatment of dialysis-related frailty. No true drug-related unfavorable effects or intense contact reactions were seen in either of these cases. Both these two trials were limited in scope and both had subtle differences in iron upkeep regimes. To date, no large-scale, multi center, multi-portion analysis has been conducted to study the efficacy of any intravenous iron compound in a patient-administration environment expressed by various dosing regimens as rehashed dosages[6,13].

MATERIALS AND METHODS

Patients above 16 years of age with a glomerular filtration rate of less than 60ml/min/1.73m^2 for more than three months duration, haemoglobin (Hb) <13.0 g/dL and <12.0g/dL in males and females respectively were included in the study. Patients were further categorized into mild anaemia (Hb 9.0-10.9g/dL), moderate anaemia (Hb 7.0-8.9g/dL) and severe anaemia (Hb less than 7.0 g/dL) according to the World Health Organization classification[6]. Patients with acute kidney injury, iron overload or iron use, drug aversion, past sensitivities, decompensated liver cirrhosis or active hepatitis (more than three times the upper average limit of alanine aminotransferase) and care by ESA within eight weeks before the screening visit were excluded from the study. According to the formula, 144 cases of chronic kidney disease was the sample size but we took 170 cases of chronic kidney disease, distributed equally into two groups of 85 cases, one where the participants received infusions of IV iron sucrose and another group where the participants received oral ferrous sulfate (325mg tablets). Eligible participants were randomized in a 1:1 ratio, the sequence of which was computer- generated by a statistician. Besides the complete blood count, their transferrin saturation (TS), serum ferritin, total iron binding capacity (TIBC) and Hb levels were measured. Patient with overnight fasting and who was not on iron supplements for a minimum of seven days were preferred prior to sample collection.

Dose: Patients were instructed to take ferrous sulfate 325 mg tablets (65 mg elemental iron) with water orally one hour before meals three times a day for 30 days. IV iron sucrose 200mg diluted with 200ml of 0.9% sodium chloride, infused over 30-60min. IV iron sucrose 200mg dose given once a week for four weeks.

Statistical Analysis: Data collected were tabulated in a Microsoft Excel sheet. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS v. 22.00 for Windows., IBM Corp., Armonk, NY). The difference between the two groups was performed by t-test with the p-value set at<0.05.

RESULTS AND DISCUSSIONS

Males (57.6%, 64.7%) were present in greater numbers than females (42.3%, 35.2%) in both groups. The majority of subjects belonged to 41-60 years of age in the IV iron group (33) as well as in the oral iron group (36). Mild, moderate and severe Hb was reported among 25.8%, 52.9%, 21.1% and 21.1%, 56.4% and

Table 1: Baseline Characteristics among the Study Subjects

Variables	IV Iron Group (N=85)	Oral Iron Group (N=85)
Male	49 (57.6%)	55 (64.7%)
Female	36 (42.3%)	30 (35.2%)
Age Group (in years)		
20-30	11 (12.9%)	12 (14.1%)
31-40	20 (23.5%)	13 (15.2%)
41-50	17 (20%)	22 (25.8%)
51-60	20 (23.5%)	18 (21.1%)
>60	17 (20%)	20 (23.5%)
Age (in years)±SD	48.51±14.91	50.41±15.76
Weight (in Kg)±SD	66.32±13.27	63.80±13.81
Severity of anaemia (Hb levels)		
Mild	22 (25.8%)	18 (21.1%)
Moderate	45 (52.9%)	48 (56.4%)
Severe	18 (21.1%)	19 (22.3%)

Table 2: Mean Hemoglobin in Both Groups After Oral and IV Infusions According to Anaemia Grades

Grades	IV Iron Group (N=85)Mean±SD		Oral Iron Group (N=85)Mean±SD	
	Before therapy	After therapy	Before therapy	After therapy
Mild anaemia	11.45±0.66	13.17±0.98	11.34±0.89	12.00±2.16
p-value	0.03*		0.08	
Moderate anaemia	8.20±2.00	11.03±2.37	8.53±0.83	9.32±0.81
p-value	<0.01*		0.17	
Severe anaemia	6.11±0.62	8.72±2.13	6.36±0.41	7.34±0.57
p-value	0.009*		0.05*	

Table 3: Serum iron, Serum Ferritin and Transferrin Saturation Comparison Before and After Infusion among the Groups

Variables	IV Iron group Mean±SD		Oral Iron group Mean±SD	
	Before therapy	After therapy	Before therapy	After therapy
Serum iron	92.59±30.93	133.46±49.74	89.38±29.91	128.96±53.38
p-value	0.005*		0.008*	
Serum ferritin	113.22±44.17	140.28±52.71	123.48±58.27	134.71±57.78
p-value	0.003*		0.003*	
Transferrin saturation	19.10±4.11	26.32±4.57	18.79±4.16	22.60±4.45
p-value	<0.01*		0.03*	
TIBC	396.64±36.71	346.12±32.25	398.56±24.36	372.03±24.36
p-value	0.004*		0.03*	

Table 4: Hemoglobin Comparison According to CKD Stage Pre- and Post-Infusion among the Groups

Stages	IV Iron		Oral Iron	
	Before Therapy	After Therapy	Before Therapy	After Therapy
Stage 3a	9.4±2.96	12.4±3.07	9.32±3.40	8.17±3.64
p-value	<0.01*	0.08		
Stage 3b	8.27±3.04	10.51±2.57	8.62±2.38	9.23±2.38
p-value	0.03*	0.23		
Stage 4	8.18±2.97	11.9±2.56	8.76±2.92	9.68±2.74
p-value	<0.01*	0.08		
Stage 5	7.37±2.17	9.53±2.24	8.54±2.74	9.30±2.54
p-value	0.02*	0.17		

Table 5: Comparison of Side Effects among Both the Groups.

Complications	IV Iron	Oral Iron
	N (%)	N (%)
Gastrointestinal disorders		
Constipation	15 (17.6%)	37 (43.5%)
Diarrhoea	5 (5.8%)	7 (8.2%)
Discoloured faeces	0	7 (8.2%)
Gastrointestinal haemorrhages	0	5 (5.8%)
Others		
Nausea	7 (8.2%)	8 (9.4%)
Headache	6 (7.0%)	5 (5.8%)
Myalgia	7 (8.2%)	0
Hypotension	5 (5.8%)	0
Infusion site reactions	7 (8.2%)	0

22.3% of the subjects in the IV and oral iron group respectively as shown in (Table 1). After IV and oral iron infusion, Hb levels increased in all the stages of anaemia. In moderate anaemia cases, before and after therapy, Hb levels increased from 8.20-11.05gm/dl in the IV group ($p<0.05$) while in the oral iron group, it increased from 8.53-9.32 ($p>0.05$). Before and after therapy in the IV group, Hb increased from 6.11-8.70 and 6.36-7.34 in the oral group among severe anaemia cases. When Hb levels were compared statistically before and after therapy in severe anaemia cases in the iron as well as oral group, it was found to be

statistically significant as shown in (Table 2). All the parameters viz. serum iron, serum ferritin and TS increased comparatively more in IV iron as compared to the oral iron group. Before therapy, the mean TIBC was 396.64 and 398.56 in the IV and oral iron groups respectively. After therapy, mean TIBC decreased to 346.10 and 372.03 in the IV and oral iron groups respectively. When the TIBC mean was compared statistically in IV iron and oral groups, it was found to be statistically significant as shown in (Table 3). (Table 4) shows the Hb comparison according to CKD stage pre and post-infusion among the groups. In the IV Iron group, a statistically significant increase was found in Hb after the therapy among all stages of kidney disease ($p<0.05$) while the same was not reported in the oral iron group. Gastrointestinal side effects were reported more among the oral iron group in comparison to the IV iron group while side effects like headache, myalgia, hypotension and infusion site reactions were found more in the IV group as shown in (Table 5).

Iron-deficient anaemic CKD patients have been recommended to take oral or IV iron supplements according to current National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines. Some studies have already demonstrated that the efficacy of oral iron is as good as that of IV iron[14,15]. However, promising results were shown in terms of IV iron, not only increasing the Hb level but also replenishing the iron stores[16,17]. We have observed that IV iron is much more efficacious in raising the Hb level as the primary endpoint compared to oral iron at the end of four weeks. There are reports on the treatment of anaemia with IV iron, but there is little comparable oral therapy evidence, as well as contradictory data[17,18]. In our study, after IV and oral iron infusion, Hb levels increased in all the stages of anaemia. In moderate anaemia cases, before and after four weeks of therapy, Hb levels increased from 7.21-10.04gm/dl in the IV group ($p<0.05$) while in the oral iron group, it increased from 7.54-8.33 ($p>0.05$). Before and after therapy in the IV group, Hb increased from 5.12-7.71 and 5.37-6.35 in the oral iron group among severe anaemia cases with a statistically significant difference. When overall mean Hb was compared, it was found to be statistically significant in the IV group. Charytan *et al.* observed important mean changes in baseline Hb values for each visit in all treatment groups in their study, with a mean change from baseline to day 43 of 1.0g/dl ($p=0.0001$) for IV iron and 0.7g/dl ($p=0.0001$) for oral iron, respectively. The mean change in Hb values from baseline to day 43 was higher for IV iron, but this discrepancy did not achieve statistical significance. In the oral group, the mean maximum Hb level was 10.7g/dl and in the IV group, 11.1g/dl[19].

In a study by Adhikary et al. mean Hb increment was more in the IV iron group than in the oral iron group. Around 60% of patients in the IV iron group had an increase in the Hb level of more than 1gm/dl while only 20% of the oral iron group had this increase[20]. In our study, all the parameters like serum iron, serum ferritin and TS increased comparatively more in IV group as compared to the oral iron group. These results were in accordance with the study done by Charytan *et al.* They showed that the IV iron array had a critical mean rise in ferritin estimates with a mean shift of 288.0 ng/ml ($p=0.0001$) from normal to day 43[20]. Agarwal *et al.* analyzed seventy-five patients (intravenous iron n =36, oral iron n=39) and showed that the change from baseline in Hb was similar in the two groups., however, the increase in Hb was significant with intravenous iron. In comparison to oral iron, intravenous iron achieved greater improvements in ferritin[21].

iron supplementation has been shown to improve clinical outcomes in individuals with moderate to severe heart failure accompanied by reduced ejection fraction[22]. The reasons for this are not clear, because the benefits of iron supplementation are independent of any concomitant rise in hemoglobin, suggesting that iron replacement alone may be important for enhancing cardiac structure and function, perhaps by improving mitochondrial dysfunction[23]. Given the common coexistence of heart failure and CKD (often referred to as cardiorenal syndrome), it is reasonable to speculate that iron therapy may also improve outcomes in individuals with CKD and heart failure. Although no clinical trials have formally tested this hypothesis, a prior study of individuals with CKD receiving ferric citrate for treatment of iron deficiency anemia showed that ferric citrate was just as effective in improving iron stores and hemoglobin in patients with heart failure as those without heart failure. These data support the use of i.v. iron infusions or ferric citrate in a clinical trial testing the efficacy of iron repletion in improving clinical outcomes in individuals with CKD and heart failure. Among the most controversial aspects of iron therapy in CKD is the question of whether i.v. iron supplementation results in adverse events that potentially outweigh any benefits from raising hemoglobin. This is partly related to adverse reactions to high-molecular weight iron dextran-one of the first i.v. iron preparations available in clinical practice-characterized by anaphylactoid reactions, including respiratory arrest in its most severe form.31 Although relatively rare, the potential for severe hypersensitivity reactions resulted in a black box warning and the requirement of a test dose to ensure safety. With the introduction of safer i.v. iron preparations, iron dextran has largely been supplanted by second and third-generation iron products. Nonetheless, less severe hypersensitivity reactions, such as dizziness and hypotension, can still occur with current iron agents and there remains real concern

that the release of free iron with i.v. infusion may cause tissue damage via oxidative stress or increase susceptibility to infection[23]. Studies have both supported and refuted these concerns, with the balance of evidence suggesting that exposure to i.v. iron does not result in any greater risk of severe adverse reactions compared with oral iron or placebo[23].

CONCLUSIONS

It has been suggested that iron be used to treat CKD-related anaemia while taking into consideration the mode of administration and treatment plan. In addition, a variety of practical considerations such as the degree of anaemia, the objectives of treatment, the stage of chronic kidney disease and the type of dialysis must be made. According to the KDIGO guideline, there is little evidence to support the use of IV iron versus oral iron in CKD patients., nonetheless, results from several trials evaluating the effectiveness of IV iron have been published, including this article. For individuals with chronic renal disease, IV iron may be the recommended first line of treatment if doctors wish to raise hemoglobin levels or postpone alternative anaemia care.

REFERENCES

1. Kumar, S., R. Joshi and V. Joge, 2013. Do clinical symptoms and signs predict reduced renal function among hospitalized adults? Ann. Med. Health Sci. Res., 3: 492-497.
2. Parag A. , B. Anand, K. Sunil and A. Sourya 2020. Clinical profile of Uremic polyneuropathy in Chronic Kidney Disease patients. Medical Science. 24: 951-951.
3. Notice., 2012. Kidney Int Suppl (2011). 2: 10.1038/kisup.2012.37.
4. Auerbach, M. and H. Ballard, 2010. Clinical Use of Intravenous Iron: Administration, Efficacy and Safety. Hematology, 2010: 338-347.
5. Cappellini, M.D. and I. Motta, 2015. Anemia in Clinical Practice-Definition and Classification: Does Hemoglobin Change With Aging? Seminars Hematol., 52: 261-269.
6. Vikrant, S. and A. Parashar, 2015. The safety and efficacy of high dose ferric carboxymaltose in patients with chronic kidney disease: A single center study. Indian J. Nephrology, 25: 213-221.
7. Wang, C.Y. and J.L. Babitt, 2016. Hepcidin regulation in the anemia of inflammation. Curr. Opin. Hematol., 23: 189-197.
8. Xu, Y., V.M. Alfaro-Magallanes and J.L. Babitt, 2021. Physiological and pathophysiological mechanisms of hepcidin regulation: Clinical implications for iron disorders. Br. J. Haematology, 193: 882-893.
9. van Eijk, L.T., A.S.E. John, F. Schwoebel, L. Summo and S. Vauléon *et al.,* 2014. Effect of the antihepcidin Spiegelmer lexaptepid on inflammation-induced decrease in serum iron in humans. Blood, 124:2643-2646.
10. Hohlbaum, A.M., H. Gille, S. Trentmann, M. Kolodziejczyk and B. Rattenstetter *et al.*, 2018. Sustained plasma hepcidin suppression and iron elevation by Anticalin-derived hepcidin antagonist in cynomolgus monkey. Br. J. Pharmacol., 175: 1054-1065.
11. Sheetz, M., P. Barrington, S. Callies, P.H. Berg and J. McColm *et al.*, 2019. Targeting the hepcidin–ferroportin pathway in anaemia of chronic kidney disease. Br. J. Clin. Pharmacol., 85: 935-948.
12. Sugahara, M., T. Tanaka and M. Nangaku, 2017. Prolyl hydroxylase domain inhibitors as a novel therapeutic approach against anemia in chronic kidney disease. Kidney Int., 92: 306-312.
13. Sharma, G., R. Saxena and N. Gulati, 2018. Iron-deficiency Anemia and Chronic Kidney Disease: An Overview. World J. Anemia, 2: 85-89.
14. Silverberg, D.S., D. Wexler and M. Blum, et al., 2003. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. Nephrology Dialysis Transplant., 18: 141-146.
15. Silverberg, D.S., D. Wexler, M. Blum, G. Keren and D. Sheps *et al.,* 2000. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J. Am. Coll. Cardiol., 35: 1737-1744.
16. Stoves, J., H. Inglis and C.G. Newstead, 2001. A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. Nephrology Dialysis Transplant., 16: 967-974.
17. Agarwal, R., A.R. Rizkala, B. Bastani, M.O. Kaskas, D.J. Leehey and A. Besarab, 2006. A Randomized Controlled Trial of Oral versus Intravenous Iron in Chronic Kidney Disease. Am. J. Nephrology, 26: 445-456.
18. Charytan, D.M., A.B. Pai, C.T. Chan, D.W. Coyne, A.M. Hung, C.P. Kovesdy and S. Fishbane, 2015. Considerations and Challenges in Defining Optimal Iron Utilization in Hemodialysis. J. Am. Soc. Nephrology, 261238-1247.
19. Charytan, C., W. Qunibi and G.R. Bailie, 2005. Comparison of Intravenous Iron Sucrose to Oral Iron in the Treatment of Anemic Patients with Chronic Kidney Disease Not on Dialysis. Nephron Clin. Pract., 100: 55-62.

20. Adhikary, L. and S. Acharya, 2011. Efficacy of IV Iron Compared to Oral Iron for Increment of Haemoglobin Level in Anemic Chronic Kidney Disease Patients. J. Nepal Med. Assoc., 51: 133-136.
21. Agarwal, R., J.W. Kusek and M.K. Pappas, 2015. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int., 88: 905-914.
22. McDonagh, T. and I.C. Macdougall, 2015. Iron therapy for the treatment of iron deficiency in chronic heart failure: Intravenous or oral? Eur. J. Heart Fail., 17: 248-262.
23. Nuhu, F., A.M. Seymour and S. Bhandari, 2019. Impact of Intravenous Iron on Oxidative Stress and Mitochondrial Function in Experimental Chronic Kidney Disease. Antioxidants, Vol. 8 .10.3390/antiox81004980.