MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.10.497.502

The Role of Primary Care in Managing Chronic Kidney Disease

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ABSTRACT
One of the main issues in public health, chronic kidney disease (CKD), has significant hazards and can have a negative impact on both an individual's and society's overall health. Few researches have examined the variables influencing community-level access to CKD care in kanyakumari district, Tamilnadu rural districts. In order to learn more about the opinions and experiences of important stakeholders and to determine the obstacles and possible enablers affecting primary care providers' ability to provide CKD care, a qualitative study was designed. The study looked at the percentage of patients with CKD who met a set of 12 quality indicators. Associations between divergence from these quality metrics were also examined in the study. Patients were excluded for enrollment if they had a history of known sensitivity to any component of ferrous sulfate or iron sucrose; chronic or serious infection, malig-nancy, or major surgery in the month prior to enrollment., parenteral iron within six months prior to enrollment., blood transfusion within the two months prior to enroll-ment., clinically significant bleeding within three months prior to enrollment., concomitant severe diseases of the liver, cardiovascular system, severe psychiatric disorders, or other conditions which, in the opinion of the investiga-tor, made participation unacceptable. Among patients in the intent-to-treat population, there were no significant differences at baseline between pa-tients in the IV iron group and those in the oral iron group in demographic descriptors, iron status, or severity of anemia. The patient and the doctor will ultimately decide whether to use IV or oral iron based on how important it is to consider factors like cost, convenience, compliance, safety and tolerability. The effective cost of iron therapy for treating CKD-associated anaemia takes into account both the iron agent's cost and any savings from using lower ESA dosages.

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Key Words
Chronic kidney, significant, qualitative, designed, enrollment, sensitivity

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Received: 20 August 2024
Accepted: 29 September 2024
Published: 5 October 2024

Citation: J. Gayathri and K.P. Selvarajan Chettiar, 2024. The Role of Primary Care in Managing Chronic Kidney Disease. Res. J. Med. Sci., 18: 497-502, doi: 10.36478/makrjms. 2024.10.497.502

INTRODUCTION

In HD-CKD, efficacy favors intravenous (IV) iron over oral iron supplements[1], safety favors use of IV iron sucrose or ferric gluconate over iron dextran at doses ranging from 25-125 mg[2] and diagnostic utility fa-vors the iron status tests transferrin saturation (TSAT), ferritin and content of hemoglobin in reticulocytes (CHr)[1,2].

Among patients with nondialysis-dependent CKD (ND-CKD), by contrast, evidence on key issues of iron efficacy, safety and test utility is missing, sparse, or incon-clusive. For example, three randomized, controlled trials (RCTs) comparing efficacy of IV iron to oral iron in ane-mia of ND-CKD have yielded contradictory results. The first showed that IV iron is not superior to oral iron[3]. The second showed that IV iron is superior to oral iron in raising Hb >11 g/dL but not in raising Hb >1 g/dL[4]. The third showed that IV iron is unequivocally superior to oral iron[5].

Oxidative stress plays an important role in the pathogenesis and progression of CKD[6,7]. Iron increases biological markers of oxidative stress[8] in cell cultures[9], animal models[10] and among end-stage renal disease patients treated with hemodialysis[11-13]. Among patients with CKD not on dialysis, IV iron can generate oxidative stress and downstream effects such as endothelial damage and kidney injury[14,15]. Thus, iron-induced injury may lead to an accelerated course of renal[7] and cardiovascular disease[16,17]. Research recommendations emphasize the need to evaluate the long-term risks of IV iron therapy among CKD patients[18].

Iron therapy in HD-CKD patients serves as an adjuvant to erythropoiesis-stimulating agents (ESAs), including epoetin alfa, epoetin beta, or darbepoetin. By contrast, in patients with ND-CKD, only a third of pa- tients receive ESA therapy[19]. Iron therapy in these patients may be undertaken as primary treatment of ane-mia. The important benefits of treating anemia in CKD, the cost of ESA therapy, the potential for iron therapy to lower or eliminate ESA doses and the possibility that concurrent ESA therapy exerts a differential effect on ef-ficacy of IV and oral iron agents, all emphasize the need for detailed comparative information on iron efficacy in ND-CKD patients.

Accordingly, we conducted an RCT comparing IV iron sucrose to oral ferrous sulfate in anemic ND-CKD pa-tients. We included patients with and without concurrent ESA therapy. We compared the efficacy of IV to oral iron, assessed the safety of iron sucrose given at 200 mg and 500 mg doses and evaluated the relationship between base-line iron indices and likelihood of response to IV iron challenge.

MATERIALS AND METHODS

Anemic patients with stage 3-5 ND-CKD who required iron supplementation, met all inclusion and exclusion criteria and had given informed consent were enrolled into the study at 35 study sites. We randomized patients into the study if they met the following criteria: hemoglobin (Hb) 11.0 g/dL, TSAT 25%, ferritin 300 ng/mL, either no ESA or no ESA dose change for eight weeks and no parenteral iron for six months. We permitted oral iron use prior to en-rollment. Subjects who were not immediately eligible for randomization underwent monthly laboratory examina-tion for up to 10 weeks, followed by randomization upon meeting eligibility criteria.

Patients in the IV iron treatment arm received intravenous iron sucrose (Venofer., American Regent, Inc., Shirley, NY, USA) 1000 mg in divided doses over 14 days, as either 500 mg IV infusions on study days 0 and 14 or 200 mg injections on five different days from day 0-day 14. Patients in the oral iron treatment arm received oral ferrous sulfate (CVS Corp., Woonsocket, RI, USA., Geri-Care Pharmaceuticals Corp., Brooklyn, NY, USA), 325 mg thrice daily, providing 195 mg ferrous iron per day, for 56 days. Clinical laboratory evaluation and safety assessment was performed every two weeks through day 56 and results were compared to baseline values.

Inclusion Criteria for Enrollment: Patients were eligible for enrollment if they were over the age of 18, able to give informed consent and evi-denced both anemia (Hb 11.5 g/dL) and chronic kidney disease stage 3-5.

Exclusion Criteria for Enrollment: Patients were excluded for enrollment if they had a history of known sensitivity to any component of ferrous sulfate or iron sucrose., chronic or serious infection, malig-nancy, or major surgery in the month prior to enrollment., parenteral iron within six months prior to enrollment., blood transfusion within the two months prior to enroll-ment., clinically significant bleeding within three months prior to enrollment., concomitant severe diseases of the liver, cardiovascular system, severe psychiatric disorders, or other conditions which, in the opinion of the investiga-tor, made participation unacceptable., pregnancy or lac-tation., current treatment for asthma., anticipated surgery requiring hospitalization during the study period other than vascular access or peritoneal catheter placement., anticipated dialysis or renal transplantation during the study., administration of an investigational drug within 30 days of enrollment., chronic alcoholism or drug abuse within the past six months and known hemochromato-sis or hemosiderosis.

Criteria for Premature Withdrawal: Premature withdrawal was required if renal replace- ment therapy (dialysis or transplantation) was initiated or an intervention for management of anemia was given. We defined an anemia intervention as either a red blood cell transfusion, an increase in epoetin or darbepoetin dose, or iron administration not included in the study pro-tocol.

Treatment: IV iron treatment arm patients received iron sucrose 1000 mg IV in divided doses over a 14-day period as either a 500 mg infusion in 250 mL 0.9% NaCl given over 3.5-4 hours on days 0 and 14 (approximately 2 mg/min), or a 200 mg injection undiluted over two to five minutes (approximately 40 mg/min) on five different occasions within the 14-day period beginning on day 0. Randomization method for assigning treatment group. We first identified subjects as ESA-treated or non-ESA-treated. We then independently stratified ESA-treated and non-ESA-treated subjects by gender and Hb level (9.0 g/dL, 9.1-10.0 g/dL and 10.1-11.0 g/dL). Within each resulting combination of strata, we then randomized subjects in a 1:1 ratio to study iron treatment groups A and B.

Determination of Efficacy and Safety: The primary measure of efficacy was an in-crease in Hb of at least 1.0 g/dL at any time between baseline and either the end of study or withdrawal. We determined sample size for this study based on the hy-pothesis that the response rate with a 1.0 g/dL increase in Hb over pretreatment levels was 40% in the iron su-crose arm and 15% in the oral iron arm. A minimum of 72 subjects was required in each arm to assess such a difference in response by means of Fisher exact test with a two-sided significance level of 0.05 and a power of 0.90. We assumed that 10% of subjects enrolled in the obser-vation phase would not meet criteria for randomization. Thus, we aimed to enroll approximately 160 subjects.

Statistical Analysis: The principal analysis of the primary end point was the unstratified compar-ison of the Hb response rate between the two study arms (IV iron sucrose versus oral iron) in the combined non-erythropoietin and erythropoietin-treated population, using a two-sided Fisher exact test at the 0.05 signif-icance level. Analysis of response by visit was evaluated using the Cochran-Mantel-Haenszel (CMH) test control-ling for center (not stratified by other factors). The null hypothesis of no difference between the treatment groups in proportion of Hb responders was rejected if the P value of association was 0.05. We used a logistic regression model to evaluate the effect of potential covariates on the odds of achieving the 1.0 g/dL Hb response at the day 56 visit based on the last observation carried forward method.

RESULTS AND DISCUSSIONS

Among patients in the intent-to-treat population, there were no significant differences at baseline between patients in the IV iron group and those in the oral iron group in demographic descriptors, iron status, or severity of anemia (Table 1).

Table 1. Baseline Demographic and Laboratory Values among Intent-to-Treat Patients in IV Iron and Oral Iron Treatment Groups

Baseline Results	Treatment Group		
	IV iron (N = 89)	Oral iron (N = 92)	P-value
Demographics			
Age years	63.4	64.8	0.2342
Race Caucasian/black/other	48/33/8	44/41/7	0.5577
Gender Male/Female	31/58	31/61	1.0000
Epoetin or darbepoetin User/Nonuser	37/52	36/56	0.7492
Weight kg	86.7	84.5	0.3066
Laboratory			
Hb g/dL	11.1	11.2	0.5518
TSAT%	17.3	17.6	0.9194
Ferritin ng/mL	93.5	104.9	0.9395
TSAT <20% and Ferritin<100 ng/mL N	35	38	0.8720
Estimated GFR mL/min/1.73 m2	31.3	29.4	0.8258

In the IV iron group compared to the oral iron group, the proportion of patients who achieved the primary end point, a rise in Hb 1.0 g/dL, was greater (45.2% vs. 29.1%, P 0.0346) and the mean increase in Hb was higher by day 42 (0.8 vs 0.5 g/dL, P 0.0298). Factors associated with superior IV iron efficacy com-pared to oral iron efficacy included baseline ferritin >100 ng/mL, baseline Hb 10 g/dL, GFR 45 mL/min, use of ESA with Hb 10 g/dL, non-use of ESA with GFR 45 mL/min, age 65 years and male gender (Table 2).

Table 2. Baseline Value or Condition Associated with Differential Primary end Point Response to IV Compared to Oral iron (Hb=1.0 g/dL)

Baseline value or condition	IV iron N/total%	Oral iron N/total%	IV vs. oral P-value
Overall	40/89 (44.9%)	28/92 (30.4%)	0.0347
Ferritin			
<100 ng/mL	26/54 (48.1%)	21/51 (41.1%)	0.4197
≤100 ng/mL	19/35 (54.2%)	12/41 (29.2%)	0.0180
Hb			
>10 g/dL	28/60 (46.6%)	22/61 (36.0%)	0.2088
≤10 g/dL	16/29 (55.1%)	8/34 (23.5%)	0.0478
GFR			
>45 mL/min/1.73m2	7/20 (35%)	10/20 (50%)	0.2194
≤45 mL/min/1.73m2	40/77 (51.9%)	20/75 (26.6%)	0.0039
ESA use and GFR<45 mL/min/1.73m2			
No ESA use	21/45 (46.6%)	8/48 (16.6%)	0.0126
ESA use	19/32 (59.3%)	11/38 (28.9%)	0.0935
ESA use and baseline			
Hb 10 g/dL No ESA use	6/19 (31.5%)	6/22 (27.2%)	0.7298
ESA use	10/17 (58.8%)	4/16 (25.0%)	0.0159
Age years			
<65	16/47 (34.0%)	15/45 (33.3%)	0.7607
>65	22/44 (50.0%)	12/49 (24.4%)	0.008
Gender			
Male	15/32 (46.8%)	6/32 (18.7%)	0.0080
Female	26/59 (44.0%)	23/62 (37.0%)	0.4145

Our results show that IV iron is su-perior to oral iron in replenishing iron stores, improving adequacy of iron for erythropoiesis, raising the mean Hb to above 11 g/dL and achieving the primary therapeutic end point, a Hb rise of 1 g/dL from baseline. Differences in experimental design probably explain differences between our findings and those of two pre-vious RCTs comparing IV iron to oral iron therapy in ND-CKD. The first study found no difference between the effects of IV iron compared to oral iron therapy on the rise in Hb after initiating ESA therapy[20]. That trial was designed and powered as a nonsuperiority trial. Com-pared to the current trial, the previous trial enrolled few patients using ESA therapy prior to enrollment (N 2), the total study population was much smaller (N 45 randomized, 32 completed), the initial IV iron doses were smaller (300 mg) and were repeated monthly (6 months) and ESA therapy was not fixed but rather was initiated in all study patients at a sizeable dose (2000 U epoetin alfa subcutaneously twice weekly) simultaneous with iron therapy. Although TSAT was not measured, the base-line median percent hypochromic red cells (PHRBC) was normal in both groups, suggesting that iron was adequate for erythropoiesis at baseline. Small sample size, small doses of IV iron given over a long period of time, initiation of ESA in previously untreated patients and iron sufficiency atbaseline all tend to minimize the discernable effects of iron treatment and therefore, favor nonsupe-riority of IV compared to oral iron.

We showed that compared with oral iron-based therapy, IV iron therapy was associated with greater risk of infections and cardiovascular complications. Although assignment to the IV iron treatment group resulted in greater increments in both transferrin saturation and serum ferritin concentration, suggesting a better repletion of iron stores, there was little difference in mean hemoglobin increments in the long term. Overall, there was an increase in proteinuria noted, but between-group differences over time in baseline proteinuria were not observed. These findings confirm no increase in basal level of proteinuria over several weeks among patients receiving IV iron[21]. The adverse events observed in our randomized trial are biologically plausible. Iron promotes growth of even common bacteria such as Staphylococcus epidermidis[22]. In addition, the inflammatory response to infection is enhanced[23,24] and phagocytic function of neutrophils has been shown to be impaired by iron[25]. Compared with oral iron, a greater iron saturation and a higher serum ferritin concentration were seen in the IV iron group that may increase the likelihood for the generation of free iron. Free iron induces the generation of the hydroxyl ion via the Haber-Weiss Fenton reaction, quenching of nitric oxide and endothelial dysfunction and may accelerate atherosclerosis[26]. Repeated administration of iron sucrose results in proteinuria after infusion[21]., if this results in impaired sodium handling by the kidney, it may explain excess heart failure hospitalizations seen in our study.

Our findings may not be generalizable to patients with kidney failure requiring hemodialysis or those with heart failure. As an example, among patients with heart failure randomized to either ferric carboxymaltose or placebo and followed for 6 months, cardiovascular disorders (sum of cardiac, vascular and neuro disorders) were incident in 11.6/100 PY in the iron group and 25.6/100 PY in the placebo group. This is in sharp contrast to 52.5 events/100 PY in the IV iron group and 33.5/100 PY in the oral group in our study. Infections were seen with an incidence of 1.4/100 PY in the iron group and none in the placebo group that again is in contrast to 36.6 events/100 PY in the IV iron group and 25.8/100 PY in the oral group in our study. In another study, of the heart failure patients with iron deficiency with or without anemia, 86% came from Russia, Ukraine and Poland. Participants were randomized to ferric carboxymaltose or placebo and followed for 1 year and they had serious adverse event rate of approximately one-quarter of that reported in our study.29 Because compared with the general population, patients with CKD are at elevated risk for cardiovascular and infectious illnesses, IV iron may exacerbate this risk.

Our study does not exclude the possibility that greater efficacy can be achieved either by increasing the IV iron dose or by extending the period of oral iron supplemen-tation. Among patients given 1000 mg iron sucrose in divided IV doses, we found that the mean posttreatment TSAT was 25.1% and that 16 out of 79 patients achieved a mean TSAT 30%. Conceivably, since iron efficacy de-pends on delivering adequate iron for erythropoiesis and adequacy of iron delivery depends, in turn, on the level of TSAT, adjusting IV iron doses to achieve a target thresh-old TSAT (for example, 30%), rather than limiting the IV iron dose to 1000 mg, may lead to a greater increase in Hb than we observed.

We suspect that, just as IV iron efficacy may be constrained by underdosing, oral iron efficacy may be limited by short treatment duration. Among patients receiving oral iron, we found that the peak Hb response occurs early, well before completion of a 56-day study period. However, the continued albeit very slow rise of ferritin over 56 days among oral iron treated patients leaves open the possibility that longer periods of oral iron therapy could lead to later increases in Hb. On the other hand, a longer treatment

period might engender greater nonad herence with oral therapy, a significant problem even in the current 56-day trial.

CONCLUSION

The patient and the doctor will ultimately decide whether to use IV or oral iron based on how important it is to consider factors like cost, convenience, compliance, safety and tolerability. The effective cost of iron therapy for treating CKD-associated anaemia takes into account both the iron agent's cost and any savings from using lower ESA dosages. We have demonstrated that IV iron sucrose therapy is safe, well-tolerated and more efficacious than oral iron treatment using a fixed-ESA-dose trial design. To evaluate how well IV iron works in reducing ESA requirements compared to oral iron, more research examining increased IV iron doses, extended treatment intervals and flexible ESA dosing will be required.

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