ORIGINAL ARTICLE

Does Iron Supplementations Improve Serum Iron and Parameters of Complete Blood Count in Chronic Renal Failure Patients Receiving Recombinant Human Erythropoietin?

SADAT MEMON[1], GUNESH KUMAR[2], JAMIL LAGHARI[3], SHAZIA BEGUM[4], KELASH KUMAR[5], REKHA[6]
[1,2]Assistant Professor, [3]Associate Professor, Department of Pharmacology & Therapeutics, Liaquat University of Medical & Health Sciences, Jamshoro
[4]Associate Professor & Chairperson, Department of Anatomy Peoples' University of Medical & Health Sciences, Nawabshah, SBA
[5]Senior Registrar, Department of Anesthesiology, Liaquat University of Medical & Health Sciences, Jamshoro
[6]Senior Medical Officer, Health Department, Government of Sindh
Correspondence to: Dr. Kelash Kumar, E-mail: drkelashmalhi@gmail.com, Cell: 03342611314

ABSTRACT

Objective: To evaluate the effect of oral and intravenous supplements of Iron on complete blood count and plasma iron in patients of chronic renal failure who are already on rHuEPO.

Study Design: Comparative prospective interventional study.

Place and Duration of Study: Department of Pharmacology and Therapeutics of LUMHS Jamshoro in collaboration to Department of Urology at Liaquat University Hospital (LUH) Jamshoro/Hyderabad from 1st April 2016 to 30th September 2016.

Methodology: Eighty patients were included and divided into two groups. Group A patients were given tablet ferrous sulphate 200 mg orally 3 times/day and rHuEPO 2000Internaational Units Subcutaneously twice/week and Group B patients were administered Inj. Iron Dextran I/V 2ml diluted in 200ml N/S twice/month and rHuEPO2000 International Units Subcutaneously twice/week. Serum iron levels were checked both in the beginning and end of study. Complete blood count was done on monthly interval for 6 months.

Results: The hemoglobin level in group A was 6.73± 0.20 g/dl and in B Group was 6.63±0.19 g/dL. The reticulocyte counts was 0.59± 0.05 % in group A while in group B, 0.72±0.06 % and showed that group B subjects showing considerable increase in comparison to group A subjects. In group A, mean serum Fe++ was 76.38±1.68 µg/dl and in group B was 73.28±1.72 µg/dl (P=0.20) and both groups A and B have significant rise in serum Fe++ levels.

Conclusion: The combination of intravenous iron and erythropoietin (rHuEPO) therapy significantly improved the complete blood count parameters and serum iron levels in chronic renal failure patients of Group B.

Key Words: Chronic kidney disease (CKD), Serum iron, Anemia, Complete blood count (CBC), Chronic renal failure (CRF), Human recombinant erythropoietin (rHuEPO)

INTRODUCTION

Anemia in chronic renal failure is defined as fall in one of the main component of red blood cells, i.e.in hemoglobin level or red blood cell percent in blood. As per World Health Organization, male or a postmenopausal female is anemic, if their hemoglobin is less than 13 gm/dl.[1]

Chronic renal failure related anemia and kidney's blood filtration capacity are closely related. Because when there is progression of chronic kidney disease, there will be additional loss of kidney function. Anemia which is related to chronic kidney disease will be further deteriorated when there is decrease in the renal glomerular filtration.[2,]

The main sign and symptoms anemia of CRF are breathlessness, poor concentration, tiredness, weakness and decrease in activity. There is difficulty in falling asleep, reduced sexual activity and immune system will be less active. Chronic renal failure associated anemia can further worsen the heart problems.[3,4]

At some point in the procedure of dialysis, the renal failure patients of dialysis lose large quantities of blood. Inside the dialysis machine there will be remnants of blood. Significant loss of blood can lead to the decrease in iron in CRF patients. So that is the main reason that if CRF patients will not receive proper iron supplements, they will suffer from deficiency of iron. Their iron stores will be vanished and they will develop CRF related anemia.[5,6] The diagnosis of CRF anemia can be made by determining the hemoglobin levels, reticulocyte count and RBC's hypochromicity.[7]

The response to treatment with supplements of iron will be there when there is decrease in iron stores within the human body or when adequate response of erythropoietin is present within the human body. If there is no significant improvement in the stores of Iron within the human body that means there is no response to the treatment with iron suppliments.[8,9] Kalantar-Zadeh et al[10] merely demonstrate the progress in levels of hemoglobin but they do not demonstrate enhancement in iron levels.

Iron supplements therapy is intended to raise production of RBCs, to progress the F++ levels and to avoid the complications of CRF anemia. The aim of Intravenous iron treatment is to augment the hemoglobin levels and production of red blood cells in CRF patients.[11]

The recombinant human erythropoietin (rHuEPO) is developed by using recombinant DNA technology. It is similar to natural erythropoietin hormone structurally and functionally. The natural hormone, Erythropoietin is synthesized by renal system.[12-14] The recombinant DNA technology has a huge role in the chronic renal failure patients. Recombinant erythropoietin has impacted positive effects on the CRF patient's lives.[15] The treatment with I/V iron improves the stores of iron in body, increases the

bioavailability of iron and prevent the adverse effects that the oral iron supplements can produce.[16, 17]

MATERIALS AND METHODS

This comparative prospective interventional study was conducted at Department of Pharmacology and Therapeutics of LUMHS Jamshoro in collaboration to Department of Urology at Liaquat University Hospital (LUH) Jamshoro/Hyderabad from from 1st April 2016 to 30th September 2016 and comprised 80 chronic renal failure patients. They were divided in two groups; group A patients were given tablet ferrous sulphate 200 mg orally 3 times/day and rHuEPO 2000Internaational Units Subcutaneously twice/week and Group B patients were administered Inj. iron Dextran I/V 2ml diluted in 200ml N/S twice/month and rHuEPO2000 International Units Subcutaneously twice/week. Patient's age >25 years, chronic kidney disease already receiving rHuEPO injections, serum Hb5-8gm%, and PCV 15-24% were included. The patients of anemic due to any other condition, receiving androgen hormone treatment since a month, coronary artery disease, chronic infections disease e.g. hepatitis or TB etc and hypertensive were excluded.

Samples for blood investigations were taken by using disposable syringes. Samples were drawn by venipuncture from anterior cubital vein. Samples were transferred into T tube and centrifugation machine was used to separate the serum from blood cells. Roche/Hitachi Cobas C systems were used for investigations. The data was entered and analyzed through SPSS-16. For continuous variables student's t-test was applied and for categorical variables chi square test was applied. P value $p<0.05$ will be considered as significant.

RESULTS

The mean ages were 41.65±1.35 years of group A while 40.38±1.35 years of group B, statistical the no significant (P=0.50) difference between ages. The hemoglobin in group A was 6.73± 0.20 g/dL and in B Group was 6.63±0.19 g/dL (P=0.71). The subjects in B Group revealed a substantial rise in Hemoglobin in comparison to the subjects A group (P<0.05) from every month (Table 1).

The packed cell volume at baseline in groups A was 18.31± 0.48 g/dl and group B was as 18.13±0.47 g/dl (P=0.79). The subjects of group B demonstrated a significant rise in the packed cell volume in comparison to group A subjects (P<0.05) from second month till 6th month (Table 2).

Table 1: Comparison of hemoglobin levels (g/dL) in both groups

Duration	Group A (Mean±SEM)	Group B (Mean±SEM)	P value
Baseline (Day 0)	6.73±0.20	6.63±0.19	0.71[+]
1st month	6.76±0.21	7.58±0.20	0.006
2nd month	7.68±0.22	8.46±0.17	0.007
3rd month	8.93±0.14	8.92±0.19	0.006
4th month	9.40±0.15	9.83±0.20	0.008
5th month	10.26±0.08	10.74±0.26	0.008
6th month	11.24±0.11	11.98±0.84	0.0001

[+]Not significant

The reticulocyte counts was 0.59± 0.05 % in group A while in group B, 0.72±0.06 % (P=0.10) and showed that group B subjects showing considerable increase in comparison to group A subjects (Table 3).

In group A, mean serum Fe++ was 76.38±1.68 µg/dl and in group B was 73.28±1.72 µg/dl (P=0.20) and both groups A and B have significant rise in serum Fe++ levels. However, the patients of group B showed significant increase in serum Fe++ at 6th months (Table 4).

Table 2: Comparison of packed cell volume (g/dl) in both groups

Duration	Group A (Mean±SEM)	Group B (Mean±SEM)	P value
Baseline (Day 0)	18.31±0.48	18.13±0.47	0.79[+]
1st month	19.19±0.48	18.73±0.50	0.51[+]
2nd month	23.67±0.56	25.57±0.40	0.007
3rd month	26.98±0.32	29.54±0.16	0.0001
4th month	30.08±0.13	31.14±0.23	0.0001
5th month	31.14±0.23	33.93±0.31	0.0001
6th month	33.16±0.34	35.63±0.30	0.0001

[+]Not significant

Table 3: Comparison of reticulocyte count (%)

Duration	Group A (Mean±SEM)	Group B (Mean±SEM)	P value
Baseline (Day 0)	0.59±0.05	0.72±0.06	0.10[+]
1st month	0.71±0.07	0.88±0.06	0.078[+]
2nd month	0.91±0.07	1.06±0.04	0.042
3rd month	0.97±0.07	1.31±0.03	0.0001
4th month	1.04±0.60	1.33±0.13	0.0001
5th month	1.05±0.62	1.36±0.23	0.0001
6th month	1.27±0.06	1.43±0.04	0.0001

[+]Not significant

Table 4: Comparison of serum iron (µg/dl)

Duration	Group A (Mean±SEM)	Group B (Mean±SEM)	P value
Baseline (Day 0)	76.38±1.68	73.28±1.72	0.20[+]
6th month	105.43±3.26	138.63±0.91	0.0001

[+]Not significant

DISCUSSION

Anemia associated with CRF is a common symptom of this ailment. Our study was conducted to demonstrate the effectiveness of oral and intravenous iron preparation and to evaluate their special effects on complete blood count and serum iron levels. The patients of 2nd group exposed a maximum rise in hemoglobin in comparison with 1st Group (P<0.05) since 2nd month of the study. Toblli et al [18] demonstrated a significant increase in hemoglobin levels from baseline 6.70 to 7.6 grams/dl at 2nd month (P=0.001), their study is accordingly with our study. Although, other studies Gull et al[19] and Rehman et al[20] have stated the less increase in hemoglobin levels in their patients. They stated that the decrease rise in hemoglobin's because of the inclusion of terminal stage kidney disease patients in their study, increase bleeding, severe in BUN and serum creatinine levels and deprived drug compliance in their CRF patients.

Agrawal et al[21] had stated that intensities of hemoglobin can be enhanced with oral and intravenous iron supplements both. But there is slow improvement with oral iron in comparison to intravenous iron. Their study is in agreement with our findings.

The packed cell volume were 18.31±0.48 % in group A and 18.13±0.47 % in group B (P=0.79). The patients in

group B showed considerable rise in the packed cell volume (%) in comparison to the group A (P<0.05) from second month forward (Table 2). The PCV finding of research belonging to us, are in balance with other studies[18,19] which had reported that PCV at baseline as 19.5 and 16.8% correspondingly, were increased to 23.6 and 22.76% correspondingly at 2nd month onwards. Tobli et al[18] stated a significant increase in levels of PCV 41.9% at baseline which are in divergence with our research.

The baseline reticulocyte counts were 0.59±0.05 % in group A while in group B, 0.72±0.06 % (P=0.10). There was significant improvement in subjects of group B reticulocyte count from second month. The earlier studies are in agreement to our research.[22,23]

Waziri et al[24] had suggested the prominent rise in rticulocyte count from second month. Their study is in agreement to our research. However, research findings of Qunibi et. al[25] are in dissimilarity with our findings.

The patient of 2nd group subjects revealed utmost rise in serum iron (Fe++) levels. The serum iron in patients of group B was raised to 138.63±0.91 mg/dl in comparison to group A 105.43±3.26 mg/dl (P=0.0001). The findings of serum Fe++ are in agreement with previous studies of Pisani et al[26] and Agarwal et al.[27] However Rathaus[28] and Ponikowski et al[29] had stated questionable results of serum iron which are not in agreement to the present study. MacDougall et al[30] had said that the treatment with I/V iron is an highest method to quickly reload the serum iron levels inpatients of chronic kidney disease.

CONCLUSION

The treatment with I/V iron and erythropoietin considerably expands the complete blood count parameters and plasma F++ (iron) levels in patients of chronic renal failure of Group B.

REFERENCES

1. World Health Organization. Nutritional anemia's: Report of a WHO scientific group. 1968.
2. Jelkmann W. Regulation of erythropoietin production. J Physiol 2011;589:1251-8.
3. Johansen KL, Finkelstein FO, Revicki DA, Gitlin M, Evans C, Mayne TJ. Systematic review and meta-analysis of exercise tolerance and physical functioning in dialysis patients treated with erythropoiesis-stimulating agents. Am J Kidney Dis 2010; 55:535-48.
4. Patel TV, Singh AL. Anemia in chronic kidney disease: new advances. Heart Fail Clin 2010; 6:347-57.
5. Fishbane S, Maesaka JK. Iron Management in End-Stage Renal Disease. Am J Kidney Dis 1997; 29:319-33.
6. Besarab B. Anemia and iron management. Semin Dial 2011;24:498-503.
7. Tessitore N, Girelli D, Campostrini N. Hepcidin is not useful as a biomarker for iron needs in haemodialysis patients on maintenance erythropoiesis-stimulating agents. Nephrol Dial Transplant 2010; 25: 3996–4002.
8. Fishbane S, Shapiro W, Dutka P. A randomized trial of iron deficiency testing strategies in hemodialysis patients. Kidney Int 2001; 60: 2406–2411.
9. Macdougall IC, Tucker B, Thompson J. A randomized controlled study of iron supplementation in patients treated with erythropoietin. Kidney Int 1996; 50: 1694–1699.
10. Kalantar-Zadeh K, Regidor DL, McAllister CJ. Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol 2005; 16: 3070–3080.
11. Stancu S, Barsan L, Stanciu A. Can the response to iron therapy be predicted in anemic nondialysis patients with chronic kidney disease? Clin J Am Soc Nephrol 2010; 5: 409–416.
12. Ji P. Pericytes: new EPO-producing cells in the brain. *Blood* 2016; 128 (21): 2483–5.
13. Miskowiak KW, Vinberg M, Christensen EM, Jens D Bukh JD, Catherine J Harmer CJ, Ehrenreich H, Kessing LV. Recombinant Human Erythropoietin for Treating Treatment-Resistant Depression: A Double-Blind, Randomized, Placebo-Controlled Phase 2 Trial. Neuropsycho-pharmacology 2014; 39: 1399–1408.
14. Can C, Emre S, Bilge I, Yilmaz A, Sirin A. Comparison of recombinant human erythropoietin and darbepoetinalpha in children. Pediatrics Int`l2013; 55: 296–9.
15. Kapitsinou PP, Liu Q, Unger TL, Rha J, Davidoff O, Keith B, Epstein JA, Moores SL, Erickson-Miller CL, Haase VH. Hepatic HIF-2 regulates erythropoietin responses to hypoxia in renal anemia. Blood 2010; 116:3039-48.
16. Agarwal R, Rizkala AR, Bastani B. A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. Am J Nephrol 2006; 26: 445–454.
17. Iain C. Macdougall, Andreas H. Bock, Fernando Carrera et al. a randomized trial of intravenous ferriccarboxymaltose versus oral iron in patients with chronic kidneydisease and iron deficiency anaemia. Nephrol Dial Transplant (2014) 29: 2075–2084.
18. Toblli JE, Di Gennaro F. Switching Patients with Non-Dialysis Chronic Kidney Disease from Oral Iron to Intravenous Ferric Carboxymaltose: Effects on Erythropoiesis-Stimulating Agent Requirements, Costs, Hemoglobin and Iron Status. PLoS ONE 2015; 10(4): e0125528.
19. Bailie GR, Larkina M, Goodkin DA. Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality. Kidney Int 2015; 87: 162–168.
20. Rehman IU, Idrees MK, Shoukat I. Outcome of End-Stage Renal Disease Patientswith Advanced Uremia and Acidemia. J Coll Physicians Surg Pak 2016; 26 (1): 31-35.
21. Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int 2015; 88: 905–914.
22. Drueke TB, Massy ZA. Oral or intravenous iron for anemia correction in chronic kidney disease? Kid Int`l2015: 88, 673–675.
23. Nabela Enam, Kavita Kakkad, Akshay Amin, Carole Lever. Management of hypertension in the hemodialysis population: a review of the literature. Journal of Community Hospital. Internal Medicine Perspectives 2014, 4: 240-55.
24. Waziri B, Mabayoje M, Bello B. Comparison of intravenous low molecular weight iron dextran and intravenous iron sucrose for the correction of anaemia in pre-dialysis chronic kidney disease patients: a randomized single-centre study in Nigeria. Clin Kid J 2016: 1–6.
25. Qunibi WY, Martinez C, Smith M. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. Nephrol Dial Transplant 2011; 26: 1599–1607
26. Pisani A, Riccio E, Sabbatini M. Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial. Nephrol Dial Transplant 2015; 30: 645–652.
27. Agarwal R, Leehey DJ, Olsen SM. Proteinuria induced by parenteral iron in chronic kidney disease—a comparative randomized controlled trial. Clin J Am Nephrol 2011; 6: 114–121
28. Rathaus M. C-reactive protein in the assessment of iron status in patients on hemodialysis. G Ital Nefrol 2009; 26: 338–346
29. Ponikowski P, Filippatos G, Colet JC. The impact of intravenous ferric carboxymaltose on renal function: an analysis of the FAIR-HF study. Eur J Heart Fail 2015; 17: 329–339.
30. MacDougall IC, Geisser P. Use of Intravenous Iron Supplementation in Chronic Kidney Disease: An Update. Iran J Kid Dis 2013;7:9-22.