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Intravenous iron plus erythropoietin versus erythropoietin alone for treatment of anaemia in patients of end stage renal disease: A comparative prospective unblinded trial

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Abstract---Objective: To determine the efficacy of intravenous iron along with erythropoietin for treatment of anemia in patients of chronic kidney disease undergoing maintenance haemodialysis. Study Design: Randomized comparative prospective, unblinded study. Study Place: Divisional Headquarter Teaching Hospital Mirpur Azad Kashmir. Duration Of Study: 06 Months, from June 2021 to December 2021. Methodology: This study was conducted in Divisional Headquarter Teaching Hospital Mirpur AJK and it included 107 patients with metabolically stable chronic kidney disease with hemoglobin of 8-11 g/dl. Patients were randomly assigned into 2 groups,, "EPO group" which received subcutaneous erythropoietin only with each hemodialysis session and the "Iron group" which received erythropoietin with each session of hemodialysis and 200mg of intravenous iron once a month with up or down titration every monthly according to hemoglobin and transfer in saturation level in serum. Standard CKD measurement was same in both groups. Serum hemoglobin and serum transferrin saturation was measured at the start of the treatment. Both groups were followed every monthly for efficacy and side effect profile and assessed at 3 months with serum hemoglobin and seum transferrin saturation level. Results: Results of the study indicate the addition of intravenous iron along with erythrpoietin in the management of CKD patient for correction of

anaemia has advantage over using erythropoietin alone as it has significantly (p-value<0.05) increased hemoglobin and serum transferrin saturation levels in cases over a period of 03 months on maintainence hemodialysis as compared to patients in control group. It has also decreased iron deficiency anaemia related complications such as cardiovascular patients and has reduced the dose requirement of erythropoietin as secondary outcome of the study.

Keywords---intravenous iron, maintainence hemodialysis, seum ferritin level, erythropoietin, hemoglobin, iron deficiency anaemia, chronic kidney disease.

Introduction

One of the common complications in patients of end stage renal disease is iron deficiency anaemia, enhancing the risk of cardiovascular events and mortality rate[1]. In CKD patients anemia is considered when hemoglobin level is less than 12g/dl.[2] Anaemia occurs more rapidly when the Glomerular Filtration Rate (GFR) is less than 25-30ml/min1.73m^2.[3] Severe anaemia in CKD patients results in multiple complications such as high output cardiac failure,angina and hypoxia leading to shortness of breath. [4] In order to avoid these complications it is important to properly manage anemia and keep hemoglobin levels as well as iron stores within recommended range i.e 11-12g/dl and TSAT 20-50% respectively. [5] Recombinant erythropoiesis stimulating agents are widely used to overcome anemia in CKD patients and they do improve quality of life and hemoglobin level, however the treatment is related to side effects as well[6]. Many of the studies indicate that treating anemia in CKD with increased doses of erythropoietin can significantly increase risk of cardiovascular events as well as mortality rate. [7] Therefore, nowadays addition of intravenous iron in early treatment is considered an important step in order to reduce the dosage of erythropoietin and reducing the complications associated with these erythropoiesis stimulating agents. [8] Keeping in view the complications of high dose of erythropoietin, we conducted a study aiming to see the effect of intravenous iron on maintaing normal Hemoglobin level and its effect on the required weekly dose of erythropoietin in ESRD patients on maintainence hemodialysis. The occurrence of cardiovascular events was also assessed in these patients following 6 month period.

Methodology

This study was conducted during June 2021 to December 2021 in Divisional Headquarter Teaching Hospital Mirpur AJK. It was a comparative prospective unblinded trial to compare the efficacy of intravenous iron alongwith subcutaneous erythropoietin versus erythropoietin alone in patients of chronic kidney disease who were on maintainence hemodialysis. A sample size of one hundred and seven patients was calculated to compare effects of intravenous iron alongwith erythropoietin and subcutaneous erythropoietin alone with 90% confidence interval and ± 8% margin of error for population proportion value p=0.5, using the formula Z21-@/s 1-P/E2P with the help of WHO calculator.

Patients of any gender with age ≥ 18 to≤ 70 years and having iron deficiency anaemia defined as hb ≤11.0 g/dl, or transferrin saturation(TSAT) <20 %,with stable chronic kidney disease secondary to any underlying condition who were on maintainence hemodialysis twice or thrice weekly were included in this study. Patients having unstable CKD or with cardiovascular compromise or who had cardiovascular event during study period, patients with Hb <6.0 g/dl ,TASAT > 50%, s. ferritin level>500ug/1 or having allergy to IV Iron preparation were excluded from final analysis. Patients having active infection, malignant condition, active metabolic/endocrinological disease or having Anti-HCV or HbsAg were not included in the study population. Permission from Institutional Ethics Review Board (IERB)was taken before starting study and written informed consent was taken from all study participants before enroling them to study. Study was conducted on the basis of Intention-To-Treat (ITT) sample. All study participants were prepared of ITT sample if they enrolled for study and were examined for study.

Study participents were randomly assigned into two groups using head or tail method, those receiving only subcutaneous recombinant erythropoietin for correction of anemia were labelled as “EPO group” and those receiving IV iron twice a month along with subcutaneous recombinant erythropoietin were labelled as “Iron group”. Both groups were receiving subcutaneous erythropoietin twice weekly one hour after hemodialysis session and dose was adjusted by nephrologist. The case group was also receiving 200 mg of intravenous iron once monthly. Patients hemoglobin level and transferrin saturation was monitored monthly to adjust dose of erythropoietin by nephrologist in order to keep hemoglobin level between 9-11mg/dl.

Data analysis was done by using stastical package for social sciences (spss version23) programme. Student t-test was used to compare the efficacy of intravenous iron in “iron” group i.e patients who received both intravenous iron and subcutaneouss recomibinant erythropoietin at the time of admission and after 3 months of period. Difference between “EPO group” and “Iron group” was considered significant if *p*-value was <0.05.

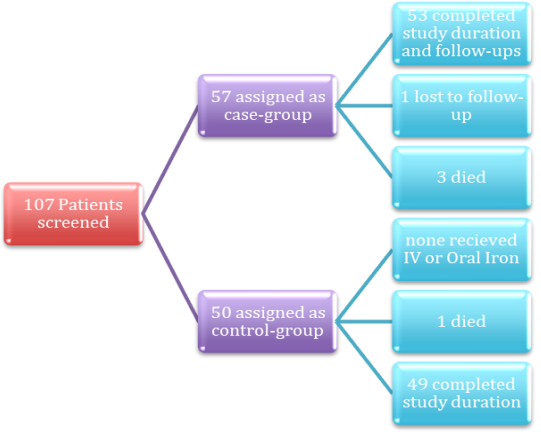

Fig 1.1. Study profile

Results

Our study population consisted of 107 patients based on inclusion and exclusion criteria and were assigned randomly into two groups.57 patients were assigned in iron group, however 53 patients could complete the study duration. One patient lost the follow up and 3 patients expired during the study period.Similarly 50 patients were assigned in iron group; 49 patients completed the duration and 1 patient died. fig 1.1

The mean age of patients in iron group was 52.43±10.69 and of EPO group was 50.75±12.76. Ratio of male to female in iron group was 50.9% and 49.1% respectively while in EPO group 57.1% were male and 42.9% were female. Conditions leading to end stage renal disease are noted down in table-1.Most common cause seen was DM(39.6% in iron group and 34.7% in EPO group) and HTN being the second most common cause(24.5% in iron group and 22.4% in EPO group).

Table I
Baseline Characteristics in ITT Population

BASELINE CHARACTERISTICS	EPO GROUP (Erytropoietin alone)	IRON GROUP (IV Iron+Erytropoietin)
Patients (n)	49	53
Age (mean±SD)	50.75±12.76	52.43±10.69
Gender(%mean) • Male • Female	 57.1 42.9	 50.9 49.1
CAUSES % (n)		
Diabetes	34.7%(17)	39.6%(21)
Hypertension	22.4%(11)	24.5%(13)
DM+HTN	16.3%(8)	13.2%(7)
Hakeem medications	4.1%(2)	1.9%(1)
Glomerulonephritis	4.1%(2)	3.8%(2)
Nephrolithiasis	6.1%(3)	1.9%(1)
Nephrolithiasis+HTN	2%(1)	5.7%(3)
BPH + HTN	6.1%(3)	5.7%(3)

The efficacy of intravenous iron was assessed after 3 months.There was significant difference in transferin saturation levels and hemoglobin levels between iron group and EPO group at end of 3 months after receiving treatment. Effect of intravenous iron alongwith subcutaneous recombinant erythropoietin on increasing transferin saturation and hemoglobin was more in the iron group as compared to the group which received erythropoietin alone, however the p- value was not statistically significant for hemoglobin. Results are noted down in table II below.

Table II
Independent samples test statistics

GROUPS	NUMBER	HEMOGLOBIN (MEAN)	STANDARD DEVIATION	TSAT (MEAN %)	STANDARD DEVIATION
At start of treatment					
EPO group (rEPO alone)	49	9.49	0.85	17.73	2.42
Iron group (IV Iron+rEpo)	53	9.09	0.86	17.98	2.77
At 03 months of treatment					
EPO group (rEPO alone)	49	9.45	0.82	20.26	5.55
Iron group (IV Iron+rEpo)	53	9.53	0.86	22.41	4.67
P-Value		0.63		0.038	

Discussion

Iron deficiency anaemia results in reduced oxygen supply to tissues leading to poor quality of life[9]. It also worsens the outcome of conditions such as heart failure,renal failure and malignancies[10]. Studies have reported that anaemia is not solely responsive to erythropoiesis stimulating agents in patients of chronic kidney disease[11]. According to guidelines by Kidney Disease Outcomes Quality Initiative (KDOQI) 2007, the proportion of patients who could achieve desired target level of hemoglobin by receiving erythropoiesis stimulating agents alone were less than 30%[12]. Therefore, the use of intravenous iron during the early stages of renal failure is recommended so that the unpleasing effects of erythropoiesis stimulating agents could be lessened in patients undergoing maintainence haemodialysis.[13]

The aim of current study was to evaluate the efficacy of intravenous iron for treatment of anaemia in patients of chronic kidney disease undergoing maintainence haemodialysis. The results of our study show that desired hemoglobin levels could be achieved early if intravenous iron is given along with subcutaneous recombinant erythropoietin compared to erythropoiesis stimulating agents alone in treating anaemia of end stage renal disease patients undergoing hemodialysis. Also the required weekly dose of recombinant erytrhopoietin was reduced in patients who were receiveing intravenous iron along with subcutaneous erythropoietin to maintain hemoglobin level in a range of 9-11g/dl.

A transferin saturation of < 20% is indicative of iron deficiency anaemia and is an independent risk factor in predicting the outcomes and mortality in patients undergoing maintainence hemodialysis[14]. In our recent study tansferin saturation was also increased more in study group receiving intravenous iron alongwith subcutaneous erythropoietin when it was followed after 3 months from start of treatment (table-II). Transferin saturation was positively related to levels of serum iron and total iron binding capacity and negatively related to the required dosage of eryhropoietin to some extent, however if the study period could be of longer

duration with a large sample size the results could be more significant. Several studies have been conducted nationally and internationally at larger levels who have evaluated the role of intravenous iron in reducing the required dosage of erythropoietin. One such study performed in United Kingdom recruiting 2000 patients on hemodialysis indicated that in patients who were receiving intravenous iron along with erythropoietin, the required dose of erythropoietin was significantly reduced[15]. Another study conducted by Sadat Memon et al at Liaqat University of Medical and Health Sciences showed that when intravenous iron was added with erythropoietin for treatment of anamia in patients on hemodialysis it was more effective as compared to erythrpoietin alone or oral iron in improving anemia[16].

Conclusion

It was observed in our study that intravenous iron pays an important part in improving anaemia and achieving target hemoglobin range of 10-12g/dl in patients of chronic kidney disease undergoing maintainence hemodialysis. It also reduced the required dosage of subcutaneous recombinant erythropietin to maintain target Hemoglobin range i.e 10-12g/dl. However further multicenter studies with larger population sample are needed to be done to evaluate the efficacy of intravenous iron on serum iron and transfer in saturation for longer period of time. These larger studies would definitely provide a way to understand the positive and negative impacts of repeated intravenous iron infusions and to make these as standard practice in our hospitals.

Limitation of study

Small sample size. Short duration of study. Constraint of study to the population of Mirpur division. Study outcomes were examined by the authors themselves and they were not blinded to the treatment groups and were directly involved in the treatment of patients.

Strength of study

Most of the patients completed the study. Loss to follow up was minimum as the patients taken for study were registered with dialysis centre of the hospital where study was done.

Conflict of interest

None

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