



Comparative effectiveness of erythropoietin alpha and beta in hemodialysis patients: a single-center prospective observational study

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ABSTRACT

Background and objectives: Anemia is a prevalent complication endured by patients with chronic renal disease. Renal anemia also leads to the development of cardio-vascular complications. Epoetin alpha and beta are recombinant human erythropoietin prioritized for managing anemia in hemodialysis patients. The current study aimed to compare the therapeutic efficacy of both erythropoietin alpha and erythropoietin beta in treating renal anemia.

Materials and methods: This prospective observational study was conducted in a Renal Dialysis Centre at a tertiary care Hospital of Karachi, Pakistan for a period of 3 months. The two erythropoietin products used were human recombinant erythropoietin alpha (Tropin®) and erythropoietin beta (Recormon®). Both groups were age-matched, BMI, eGFR, gender, and comorbidities like diabetes and hypertension were indifferent. The comparative analysis was performed after the completion of 3 months.

Results: A total of 94 participants were included in the analysis, 54 in group A and 40 in group B. Mean albumin, urea, creatinine, ferritin, iron, and transferrin saturation at inclusion were statistically insignificant, TIBC was higher in group A ($p = 0.005$) and CRP levels were slightly higher in group B ($p = 0.050$). There was significant improvement in Hb level ($p = 0.025$), PCV ($p = 0.001$), and RBC count ($p = 0.007$) in group B. While in group A, there was significantly increased MCV ($p = 0.005$) and MCHC ($p = 0.002$). In intention to treat analysis, 22.2% of subjects in group A and 40.0% in group B reached desired Hb levels of ≥ 11 g/l after 3 months.

Conclusion: In our assessment of hemodialysis patients, erythropoietin beta was found more effective than erythropoietin alpha.

ARTICLE HISTORY

Received 30 August 2021

Accepted 17 September 2021

KEYWORDS

CKD; ESRD; anemia; erythropoietin; hemoglobin; dialysis

1. Introduction

Anemia is a prevalent complication endured by patients with chronic renal disease [1,2]. Nephrogenic anemia usually occurs as a consequence of inadequacy and deficiency of erythropoietin synthesis in response to low hemoglobin (Hb) [1,2]. Incidence and progression of anemia are increased in individuals with worsening disease, and it is observed to be two to three times more prevalent among individuals suffering from diabetes mellitus when compared to different populations [2]. Renal anemia also leads to the development of cardio-vascular diseases i.e., left ventricular hypertrophy, heart failure and mortality associated with cardiac issues [3,4]. Erythropoiesis stimulating agents (ESA's) have been utilized for the treatment of nephrogenic anemia since the 1980s [1–5]. Erythropoietin is a crucial growth factor required for recruitment, proliferation, and survival of erythroid progenitor cells [1]. It is a hematopoietic factor synthesized in peritubular interstitial cells lining cortex of kidney [2]. Erythropoietin is released mainly as a consequence of hypoxia [1]. In

patients suffering from end-stage renal disease, the release of erythropoietin is insufficient with need of oxygen due to erosion of normal renal microvasculature detecting oxygen, increased peritubular oxygen pressure required for release of erythropoietin, conversion of peritubular interstitial cells into matrix generating fibroblasts, aggregation of pro-inflammatory cytokines hindering erythropoietin production and autonomic sympathetic dysregulation [3]. Erythropoietin stimulating agents are categorized in two broad categories i.e., short-acting (epoetin alpha, epoetin beta, epoetin delta, epoetin omega and epoetin theta) and long-acting (Darbepoetin alpha, Continuous erythropoietin receptor activator (CERA), Peginesatide) [1].

Epoetin alpha and beta are recombinant human erythropoietin that are generated by utilizing Chinese hamster ovary (CHO) cells transfected with authentic human EPO gene [1,3]. Erythropoietin alpha is a prioritized choice for managing anemia in hemodialysis patients for last two decades [6,7]. Its utilization minimizes the compulsion of blood transfusions,

mitigates symptoms of anemia, improves life expectancy, declines morbidity associated with cardiovascular factors and boost the quality of life [6,8]. In patients with chronic kidney disease undergoing hemodialysis and simultaneously suffering from nephrogenic anemia, epoetin alpha, and beta are administered intravenously three times a week; while in patients undergoing pre-dialysis, peritoneal dialysis and transplantation, they are administered one to three times a week [9]. Half-life of epoetin depends on the route of administration with epoetin alpha having 6.8 and 19.4 h while epoetin beta has 8.8 and 24.2 h when administered intravenous and subcutaneous, respectively [4]. Dosage of erythropoietin is 2000–5000 IU after the session of hemodialysis, and target is to achieve increase in Hb levels of 0.5–1.5 g/dl in period of 4 weeks and a 2–4% increase in hematocrit level within 2–4 weeks [10]. In accordance with biochemical and pharmacological aspects of epoetin, volume distribution of epoetin beta in both intravenous and steady state is increased in comparison to epoetin alpha while terminal elimination half-life of epoetin beta is 20% longer than epoetin alpha [4,9,10]. Epoetin beta when compared with epoetin alpha has delayed subcutaneous absorption [4]. Half-life of epoetin beta is greater than half-life of epoetin alpha when administered with subcutaneous route [9].

The aim of this study is to compare therapeutic efficacy of both erythropoietin alpha and erythropoietin beta in treating anemia associated with chronic kidney disease in our study population with the desired hemoglobin levels of ≥ 11 g/l.

2. Methods

This prospective observational study was conducted in a Renal Dialysis Centre at a tertiary care Hospital of Karachi, Pakistan. There are more than 200 patients registered for regular hemodialysis at this centre. The ethical review committee approved the study protocol and informed consent was taken from each participant before enrolling in the study. The two most frequently used erythropoietin products for all dialysis patients in our unit were human recombinant erythropoietin alpha (Tropin®) and human recombinant erythropoietin beta (Recormon®). Patients on any other forms of erythropoietin including long-acting erythropoiesis stimulating agent Mircera® were excluded from the study. The dosage administered subcutaneously was 6000 IU thrice weekly for alpha and 5000 IU twice weekly for beta erythropoietin in most of the individuals. The patients were diagnosed with CKD stage 5 with a minimum of 6 months of regular hemodialysis,

Hb < 10 g/dl with saturation iron reservoirs transferrin saturation $> 20\%$ and ferritin levels > 200 ng/ml.

The inclusion criteria for our study were hemoglobin levels less than 10 g/dl, frequency of hemodialysis thrice weekly, duration of hemodialysis onset at least 6 months prior to inclusion, Serum iron and ferritin levels above lower limits described before, and C-reactive protein (CRP) levels below upper limit throughout the course of the study. Those patients who had hospitalization within the past 3 months prior to the study, required blood transfusion, had an active infection, depleted iron stores, elevated inflammatory markers, presence of malignant disease, or were not anemic were excluded from the study as shown in Figure 1. We recorded baseline hemoglobin concentration (Hb), packed cell volume (PCV), red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Data were observed for 3 months, and comparisons were made after the completion of 3 months of continuous administration in each group. The groups were matched for their baseline characteristics (age, gender, comorbidities, and other laboratory criteria).

Data were expressed as mean and standard deviation or frequency and percentage. The comparison for each patient before and after the completion of treatment at 3 months was performed using paired sample t-test, and a value of $p < 0.05$ was considered significant (Statistical Package for Social Sciences, Version 25.0). The comparison of baseline data was performed by either using independent sample t-test, Chi-square, or Fisher's Exact test as indicated.

3. Results

The two study groups were identified as those receiving erythropoietin alpha (group A) and beta (group B), respectively. A total of 94 participants were included in the analysis, 54 in group A and 40 in group B. Baseline characteristics of both groups were age-matched ($p = 0.120$), gender ($p = 0.506$) and comorbidities like diabetes ($p = 0.950$), hypertension ($p = 0.315$), mean BMI ($p = 0.548$) and eGFR ($p = 0.708$) were indifferent in both groups. The propensity score for all these covariates were calculated as 0.41 ± 0.06 in group A and 0.43 ± 0.08 in group B, respectively, with a mean difference of -0.02 . Mean albumin, urea, creatinine, ferritin, iron, and transferrin saturation at inclusion were statistically insignificant at study commencement, however, total iron-binding capacity (TIBC) was higher in group A ($p = 0.005$) and CRP levels were slightly higher in group B ($p = 0.050$) as shown in Table 1.

The patients were observed after 3 months of initiation of erythropoietin preparations and found

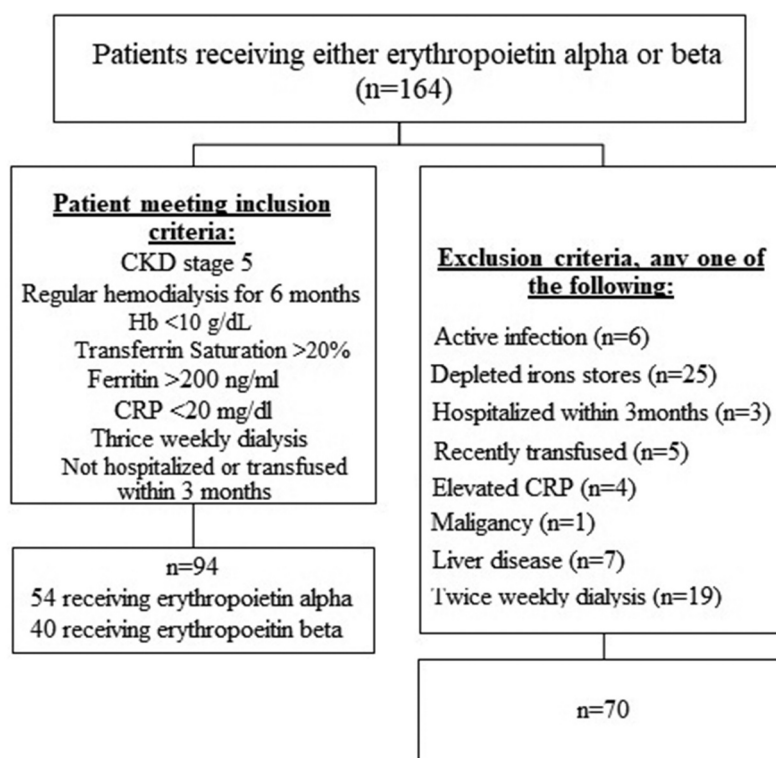


Figure 1. Methodology flow diagram of inclusion and exclusion criteria.

significant improvement in Hb level ($p = 0.025$), PCV ($p = 0.001$), and RBC count ($p = 0.007$) in group B. While in group A, there was significant increased MCV ($p = 0.005$) and MCHC ($p = 0.002$). However, the rest of the parameters remain insignificant in group A. The mean increase in Hb levels was 9.80 ± 1.20 to 10.25 ± 1.10 g/l in group A, and 9.66 ± 1.49 to 10.63 ± 1.52 g/l in group B. A mean increase in PCV of 0.425% was observed in group A as compared to 1.758% in group B as shown in Table 2. When compared mean difference in both groups, PCV was found nearly significant in group B ($p = 0.051$), while rest of the parameters were insignificant as shown in Figure 2. So, the highest

effect of erythropoietin beta was to increase hematocrit levels in our study population. In intention to treat analysis, 22.2% of the subjects in group A (12 out of 54), and 40.0% of the subjects in group B (16 out of 40) reached the desired Hb levels of ≥ 11 g/l after 3 months.

4. Discussion

Amendments in the state of anemia are one of the crucial steps in the treatment of patients with end-stage renal disease irrespective of preterminal or terminal stage of chronic kidney disease [2]. This study was regulated to compare the efficacy of both

Table 1. Baseline characteristics of the studied population ($n = 94$).

Variables	Group A (erythropoietin alpha), $n = 54$	Group B (erythropoietin beta), $n = 40$	p-value
Age (in years)	56.70 ± 10.53	53.37 ± 9.64	0.120
Males	36 (60.0)	24 (40.0)	0.506
Females	18 (52.9)	16 (47.1)	
Hypertension	50 (92.6)	34 (85.0)	0.315
Diabetes	28 (51.9)	21 (52.5)	0.950
eGFR (mL/min/1.73 m ²)	7.72 ± 3.21	7.96 ± 2.84	0.708
BMI (kg/m ²)	26.19 ± 4.79	25.55 ± 5.48	0.548
Albumin (g/l)	3.54 ± 0.52	3.65 ± 0.45	0.286
Urea (mg/dl)	103.95 ± 41.82	106.79 ± 38.39	0.737
Creatinine (mg/dl)	7.89 ± 2.36	7.29 ± 2.38	0.228
Ferritin (ng/ml)	328.45 ± 181.79	285.90 ± 190.06	0.274
TIBC (μg/dl)	221.50 ± 34.60	196.70 ± 49.53	0.005
Serum iron (μg/dl)	87.40 ± 50.19	85.56 ± 63.21	0.880
T-sat (%)	42.00 ± 8.46	45.22 ± 7.40	0.058
CRP (mg/dl)	5.42 ± 6.95	8.76 ± 9.25	0.050

Data presented as mean and standard deviation or frequency and percentage. P-value calculated by independent sample t-test, chi-square and Fisher's exact test (as appropriate).

eGFR: estimated glomerular filtration rate; BMI: body mass index; TIBC: total iron binding capacity; T-sat: transferrin saturation; CRP: c-reactive protein; n: number of individuals.

Table 2. Mean difference in hemoglobin levels before and after study duration among the groups.

Variables	Group A (erythropoietin alpha), n = 54			Group B (erythropoietin beta), n = 40		
	Before therapy	After therapy	Mean difference	Before therapy	After therapy	Mean difference
Hemoglobin (g/l)	9.80 ± 1.20	10.25 ± 1.10	+0.452	9.66 ± 1.49	10.63 ± 1.52	+0.975
p-value		0.213	-		0.025*	-
MCV (fl)	87.38 ± 9.66	89.90 ± 9.30	+2.523	88.06 ± 8.60	90.75 ± 8.42	+2.687
p-value		0.005*	-		0.090	-
PCV (%)	33.37 ± 2.12	33.79 ± 1.52	+0.425	32.97 ± 1.81	34.73 ± 2.01	+1.758
p-value		0.057	-		0.001*	-
MCH (pg)	27.47 ± 5.73	28.42 ± 3.37	+0.952	28.18 ± 2.44	28.31 ± 2.55	+0.125
p-value		0.301	-		0.662	-
MCHC (g/dl)	31.14 ± 1.37	32.19 ± 1.58	+1.047	31.06 ± 1.31	31.62 ± 2.09	+0.562
p-value		0.002*	-		0.233	-
RBC count ($\times 10^6$ /uL)	3.46 ± 0.81	3.64 ± 0.68	+0.176	3.43 ± 0.69	3.81 ± 0.67	+0.375
p-value		0.215	-		0.007*	-

Data presented as mean and standard deviation; All p-values computed via paired sample t-test.

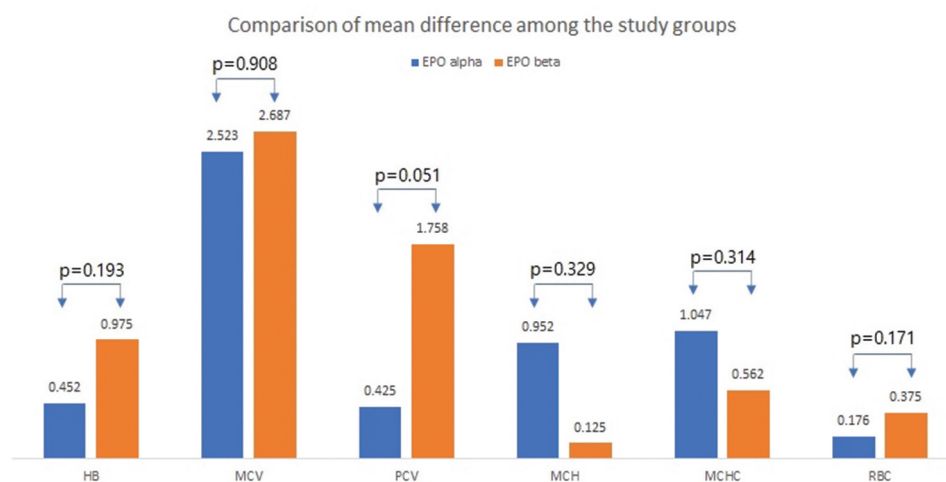
* indicates significant values of less than 0.05 (two-tailed).

MCV: mean corpuscular volume; PCV: packed cell volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; n: number of individuals.

epoetin alpha and epoetin beta in treating anemia associated with chronic kidney disease. The mean age of patients included in previously conducted trials ranged from 45 to 64 years with increased gender affinity towards male gender [2,5,10]. Multiple articles compared the therapeutic efficacy of both epoetin alpha and epoetin beta in maintaining hemoglobin levels (Hb) at a targeted range of 10–12 g/dl within 3–4 months of availing treatment [2,5,10]. Miscellaneous studies conducted in this accord reported no statistically prominent difference in hematocrit (PCV) levels among patients administered both epoetin alpha and epoetin beta to cure anemia of chronic kidney disease [2,5,10]. The study regulated by Azmandian et al, reported a statistically significant difference between epoetin alpha (Eprex) and epoetin beta (Cinnapoetin) in maintaining hemoglobin levels of 11 g/dl, supporting Cinnapoetin [5]. No difference was observed between both drugs in maintaining hemoglobin levels > or equal to 11 g/dl, while decreased frequency was recorded in regard to Cinnapoetin achieving levels of 13 g/dl [5].

Another study conducted in a similar pattern reported a prominent increase in hemoglobin levels when administered with epoetin alpha as compared to epoetin alpha in patients with chronic kidney disease [10].

The study conducted among the inhabitants of Bosnia and Herzegovina reported no difference between both drugs in maintaining hemoglobin levels (Hb) of 10–12 g/dl in patients with chronic kidney disease [2]. No variance was recorded in terms of dosage and the way of administration among both epoetins in maintaining standard levels of hemoglobin was observed [2,5,10]. While another study conducted by Loughnan et al, quoted that increased doses of epoetin alpha are required to maintain hemoglobin levels at 12 g/dl [11]. Azmandian et al, reported no discrepancies in the levels of ferritin, CRP, transferrin levels in patients of chronic kidney disease administered with both epoetins [5], while another study quoted similar findings with only difference recorded in levels of total iron-binding capacity [2]. Increased frequency of comorbidities (prominently

**Figure 2.** Comparisons of mean differences of studied parameters in both groups before and after completion of therapy.

hypertension) and at least one adverse effect was recorded in patients receiving epoetin beta [5,10].

To summarize, there are four previous studies primarily comparing the efficacy of both alpha and beta erythropoietin, among which one favored alpha preparation [10]. Oka et al, favored beta preparation [4], while two other trials failed to find any significant difference [5,11]. In our study, we found beta erythropoietin more favorable in our population. However, there are a few limitations of the current study. This is a prospective observational study, and there can be many confounding factors that may influence our results such as sociodemographic factors and the quality of life. Our study participants were not randomized, but they had comparable age, gender, and comorbidities. To assert a significant association, a randomized controlled trial is required, which is planned as a follow-up study in our center to characterize more about what signifies the effect of a particular erythropoietin preparation in our study population. The results of the current study cannot be generalized due to being designed as an observational protocol, however it adds to the current data to help make the choice of initiating erythropoietin therapy in this population.

5. Conclusion

In our preliminary assessment of hemodialysis patients, erythropoietin beta was found more effective than erythropoietin alpha in our study population. Although, it was a short-term observation with only 3 months of study duration, a follow-up randomized controlled study is warranted to signify these findings in a longer period of time with both external and internal validity. Also, it would be able to identify the factors involved in our renal disease population that lead to such a significant response to different preparations of erythropoietin.

Disclosure statement

The authors declare that they have no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Funding

No funding required in the study. The work was not supported by any sponsors.

Data availability

Data can be made available upon reasonable request from the corresponding author.

Ethical statement

Ethical considerations were fulfilled before the commencement of the study.

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