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Comparative Analysis Of Erythropoietin Alfa And Darbepoetin Alfa On Hemoglobin Levels In Chronic Kidney Disease Patients: An Observational Study In Iraq

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Abstract

Objective: The study compared the effectiveness of Darbepoetin alfa and Epoetin alfa in managing anemia in chronic kidney disease patients in Iraq.

Method: This was an observational study, conducted in Iraqi dialysis centers, ninety-three clinically stable adult patients on hemodialysis/peritoneal dialysis were enrolled in the study, with baseline hemoglobin levels below 10 g/dL Patients received either Darbepoetin (n=33) or Epoetin (n=60) free of cost, with monthly hemoglobin levels monitored over six months.

Results: The study indicated that the Darbepoetin group achieved a statistically significant higher mean hemoglobin level (9.44 ± 0.99 g/dL) at six months compared to the Epoetin group (8.90 ± 1.05 g/dL). However, the median increase in hemoglobin levels from the baseline was not statistically significant amongst the two groups. A notable finding was that Darbepoetin's significant benefit was primarily observed in male patients, with no significant difference in females.

Conclusion: This study provides unique real-world data from Iraq, offering insights into ESA effectiveness within a local context and highlighting the importance of considering patient characteristics, including gender, in anemia management strategies.

Key words: *Darbepoetin alfa, Epoetin alfa, comparative analysis, CKD, ESAs.*

1. INTRODUCTION

Anemia is amongst one of the most prevalent and vital complication of Chronic Kidney Disease (CKD), patients with anemia progress rapidly to End Stage Renal Disease (ESRD) (1-3). The main cause of anemia in CKD patients is reduced erythropoiesis, attributed to the low production of Erythropoietin (EPO) by the kidneys (4). EPO is responsible to stimulate Red Blood Cells (RBCs) in the bone marrow of a person, with the decline in kidney function production of EPO decreases (5). Iron deficiency amongst the major contributor to anemia in CKD patients, it should be treated prior to the EPO treatment (6). The main causes of Iron deficiency can be blood loss, impaired iron absorption or increase in Hepcidin levels (5). Systemic

inflammation, mostly present in CKD patients results in increased Hepcidin level, thus inhibiting release of iron and reduces iron absorption from the gut, causing anemia (5, 7). Systemic inflammation can also suppresses the erythropoiesis (5). The other factors contributing to anemia include, reduced RBCs lifespan, uremic toxins inhibiting bone marrow response to EPO, vitamin B12/folic acid deficiencies, and hyperparathyroidism (4, 8).

Management of anemia in CKD patients includes iron therapy, erythropoiesis stimulating agents (ESAs) and RBCs transfusion (9, 10). The treatment goal for anemia in CKD patients is to maintain the hemoglobin(Hb) levels mostly on lower side, in order to prevent complications e.g. heart failure, and reduced quality of life (1, 9, 11). ESAs like Erythropoietin alfa and Darbepoetin alfa are commonly used for the management of anemia in CKD patients (12). These agents stimulate erythropoiesis binding to the erythropoietin receptor on erythroid progenitor cells in the bone marrow, which activates intracellular signaling pathways, thus promoting and differentiating the progenitor cells into the RBCs, resulting in the increased production of RBCs (12-14). The main stimulus of Erythropoietin synthesis is tissued hypoxia (14). Erythropoietin Alfa was the first human erythropoietin used for management of anemia in patients with ESRD, and patients receiving cancer therapies (14). Darbepoetin Alfa was the first ESA to offer extended dose interval as compared to Epoetin alfa & beta (15). Both Epoetin and Darbepoetin are considered equally safe and effective (16), however some potential risks and tumor progression have raised concerns on the safety and efficacy of ESAs in some clinical trials (17).

The major difference between erythropoietin alfa and darbepoetin alfa is their half-life, Darbepotin alfa has three time higher half-life compared to erythropoietin alfa, therefore can be administered less frequently (18-21). This is because of an addition of N-linked carbohydrate groups, which reduces its affinity to EPO receptor and thus prolonging circulation time (18). Erythropoietin alfa is administered one to three times per week, while darbepoetin alfa can be administered weekly or once in two weeks to maintain hemoglobin levels (21).

There has been several comparatives studies, comparing the effectiveness and safety of ESAs in ESRD. A study comparing Epoetin beta and Epoetin alfa in ESRD hemodialysis patients, found no statistically significant difference in the mean hemoglobin level of the patients between the two groups (22). Another study compared Darbepoetin alfa to the recombinant human erythropoietin (rHuEPO) in 522 dialysis patients (15). The patients were randomized to continue rHuEPO or an equivalent dose of Darbepoetin alfa with low frequency, demonstrating rHEPO doses were 22% lower for subcutaneous(SC) route versus intravenous(IV) route, which was not the case with Darbepoetin needing similar doses for both routes of administration (15). In another study it was observed that hemoglobin variation was less frequent, and fewer dose changes were required in Darbepoetin group as compared to Epoetin group (23). Another study conducted in non-dialysis patients of CKD, both ESAs were equally effective in terms of patient outcomes (24).

In Iraq, dialysis centers follow the guidelines drafted by Iraqi Ministry of Health for the management of anemia, these are mostly adapted from the international guidelines (25, 26). The common practices include use of ESAs (Epoetin alfa and Darbepoetin alfa), with the doses adjusted based on hemoglobin levels 10-11.5 g/dL (26, 27). ESAs are available in major public sector hospitals in Iraq free of cost, but shortage can occur due to supply chain issues (28). The estimated cost of Epoetin alfa 4000 IU is around 30–60USD per vial, while for Darbepoetin alfa 50 mcg is around 80–150USD per syringe. Biosimilar alternates are also available in the market with upto 40% lower costs. Iron sucrose (Venofer®) is the most preferred IV iron supplementation, Ferric carboxymaltose (Ferinject®), is also used in privates centers but is more expensive,

while ferrous sulfate is used when IV Iron is not available (26). The target ferritin levels are set to be 200–500 ng/mL (26). Blood transfusion is avoided when possible, to prevent iron overload and alloimmunization, and is reserved for severe anemia i.e. Hb<7g/dL (26). The monthly monitoring of Hb per month, Iron studies (ferritin, transferrin saturation) every three months, and C-Reactive Protein(CPR) testing to rule out inflammation-induced anemia is recommended as per the guidelines (26, 27). The challenges in Iraqi dialysis centers include shortages of ESA and Iron supplements in public hospitals, high cost of treatment ESA & Iron in private clinic, lack of compliance to the protocols, and limited use of Roxadustat (HIF-PH inhibitor) due to unavailability (25, 28).

The treatment guidelines of ESAs in Iraq have been derived from the studies on populations with different genetic, environmental and healthcare systems. Genetic variations in Iraqi patients can influence the metabolism and response of both erythropoietin alfa and Darbepoetin. Patterns of nutritional deficiencies, dietary variations and environmental exposures can interact with anemia management. While prevalence of different comorbidities, access and medication adherence plus the economic factors can also influence the treatment outcomes. The only study on the ESAs in ESRD in the region was held in Qatar (29), but due to difference in the, healthcare systems, genetic profiles, and environmental factors the results cannot represent the Iraqi population. There is a clear need to carry out the comparative safety and efficacy studies of ERAs for the management of anemia in CKD patients in Iraq. Such research would help rationalize treatment strategies and patient outcomes in the country. This study will also compare the impact of the switch erythropoietin afla to Darbepoetin on hemoglobin levels, in CKD patients in Iraq, and also identify the factors influencing hemoglobin response and adherence to the treatment guidelines. The results of the study has potential to inform clinical decision making regarding ESA selection and anemia management strategies in CKD patients in Iraq.

2. METHODS

This study is a prospective, observational, multicenter study conducted at dialysis centers of Al-Ramadi and Al-Falluja Hospital, Iraq. Clinically stable adult CKD patients receiving hemodialysis and/or peritoneal dialysis for at least six months were enrolled. The enrolled patients were having baseline Hb levels < 10 g/dL and the patients were either on Erythropoietin alfa and Darbepotein alfa therapies, having serum ferritin ≥ 200 ng/mL and transferrin saturation levels of ≥ 20% at the baseline. The exclusion criteria of the study included patients having active bleeding or systemic hematological disorders, malignancies, congestive heart failure, uncontrolled hypertension, lactating or pregnant women, uncontrolled diabetes i.e HbA1C ≥ 10%, underlying liver disease, reported allergy to EPO & Darbepotein, or active infections.

Patients in Erythropoietin alfa group were administered the doses of 4000 IU/mg twice to three times a week. While patients in the Darbepoetin alfa group were administered the doses between 20 to 40 IU/mg every other week. Both the groups were given provided the treatment free of cost by the hospitals. The demographic information, medical history, CKD stage, comorbidities and dialysis schedule along with the safety assessments, including serum chemistry, complete blood count, Hepatitis and HIV screening were collected for each patient at the baseline of the study using the patient medical chart. Monthly Hb levels, patient laboratory tests were monitored and recorded over six months for each patient. The dose and frequencies of ESAs, and other relevant medication treatments i.e. Iron replacement therapy, vitamin D were monitored. Patients were monitored for any sign or documentation of adverse events. Patient medical charts were used to confirm the administration dose and frequency of ESAs and Iron supplementation.

The sample size was calculated to detect clinically meaningful difference in the mean hemoglobin levels of Darbepotein and Epoetin group, assuming two sided significance level (α) of 0.05 and the statistical power of 80% (0.80), and standard deviation of 1.0 g/dL, estimated sample size of 30 patients per group was calculated in order to detect a mean difference of 0.5 g/dL. According to the anticipated drop-out rate of 10%, the sample size was estimated to be 33 in each group. A convenient sampling was done depending on the availability of patients in the dialysis centers, and a total of 93 patients were enrolled in the study. The data was collected for the patients from October 2024 till June 2025.

The ethical approval of the study was obtained by the ethical review committee of the Al-Farahidi University (Ref no: 3-2652025) and relevant approvals were obtained from both the hospitals. A written Informed consent was obtained from each participant prior to the enrollment. The results were tabulated, compared and the statistical analysis was conducted using IBM SPSS statistics 27.

3. RESULTS

In this study a total of 93 patients were enrolled meeting the eligibility criteria of the study, divided into Darbepoetin (n=33) and Epoetin (n=60) treatment groups. Baseline characteristics were comparable between groups with minor variations. Both the groups were predominated with males i.e. 61.3% while the percentage of females accounted in the study was 38.7%. The Darbepoetin group was older (mean age: 60.61 ± 13.94 years) compared to the Epoetin group (52.78 ± 14.11 years). A total of 54.5% (18/33) of Darbepoetin patients were ≥65 years compared to 21.6% (13/60) in the Epoetin group. Patients in the Darbepoetin group had higher mean weight (81.94 ± 19.54 kg) than Epoetin patients (74.43 ± 17.39 kg). The baseline Hb was observed to be slightly higher in the Darbepoetin group (8.84 ± 0.79 g/dL) versus the Epoetin group (8.41 ± 1.01 g/dL) (Table-1).

Table 1: Baseline characteristics of patients

Patient characteristics	Darbepoetin (n=33)	Epoetin (n=60)	Total (n=93)
Sex, n (%)	33 (100%)	60 (100%)	93 (100%)
Male	21 (63.6%)	36 (59%)	57 (61.29%)
Female	12 (36.4%)	24 (41%)	36 (38.71%)
Age (years) mean ± SD	60.61 ± 13.94	52.78 ± 14.11	55.56 ± 14.47
<65, N (%)	15 (45.45%)	47 (78.3%)	62 (66.67%)
>=65. N (%)	18 (54.54%)	13 (21.67%)	31 (33,33%)
Weight (kg) mean ± SD	81.94 ± 19.54	74.43 ± 17.39	77.10 ± 18.44
Hemoglobin level(g/dL) mean ± SD	8.84 ± 0.79	8.41 ± 1.08	8.56 ± 1.01

Table 2: The Comparison of the mean Hemoglobin level (g/dL) at the end of six months.

Group	n	Mean ± SD Hb(g/dL)	Mean difference (95% CI)	t (df)	p-value	Cohen's d [95% CI]
Darbepoetin	33	9.44 ± 0.99	0.53 [0.08,0.98]	2.394 (91)	0.019	0.52 [0.09,0.95]
Epotein	60	8.90 ± 1.05				
Notes: Levene's test : F = 0.078, p = 0.781(equal variance assumed); Effect size: Cohen's d with pooled standard deviation						

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Comparing the means of the Hb at the end of six months, an independent samples t-test showed a statistically significant difference in means hemoglobin levels between Darbepoetin and Eoptein groups t = 2.394, df = 91, p = 0.019. Participants receiving Darbepoetin had higher MeanHb (M=9.44g/dL, SD = 0.99) compared to those receiving Epotein (M = 8.90 g/dL, SD 1.05), with a mean difference of 0.53 g/dL (95% CI [0.08,0.98]). The effect size was moderate (Cohen's d = 0.52, 95% CI [0.09,0.95]). Homegeneity of variances was confirmed via Levene's test (F=0.078, p = 0.0781).

Table 3: Comparison of Change in Hg after 6 months between groups

Treatment grou	n	Median chang in Hb (g/dL)	IQR (g/dL)	Mann-Whitney U	p-value	Effect size
Darbepo	33	0.5	-0.65 to 1.45	U= 949.000	0.742	0.034
Epotein	60	0.4	-0.40 to 1.38	P value = 0.742		

The median change in hemoglobin after six months did not differ significantly between the two treatment groups. The Darbeop group showed a medican increase of 0.50g/dL (IQR: -0.65 to 1.45) while the Epotein group showed a median increase of 0.40g/dL (IQR: -0.65 to 1.45). A Mann-Whitney U test suggested no statistically significant difference in hemoglobin improvements between two groups (U = 949.000, p value = 0.742). The negligible effect size (r=0.034) indicates no clinically menaingfull difference between the therapies. Table-3. Both treatments showed modest hemoglobin improvement, (0.40 to 0.50 g/dL median change) after six months, Darbepoetin group had wider variability (IQR 2.10 vs 1.78 g/dL). Notably, 25% of patients in the groups experience hemoglobin declines: Darbepo 25% declined >0.65 g/dL, Epotin 25% declined >0.40g/dL, suggesting a subgroup of non-responder in both arms. Figure1: Box plot of Hemoglobin change from baseline to 6 months shows Darbepoetin group median change = 0.50 g/dL compared to Epotein group 0.40 g/dL. Overlapping interquartile ranges and similar distributions confirm no significant difference between the groups.

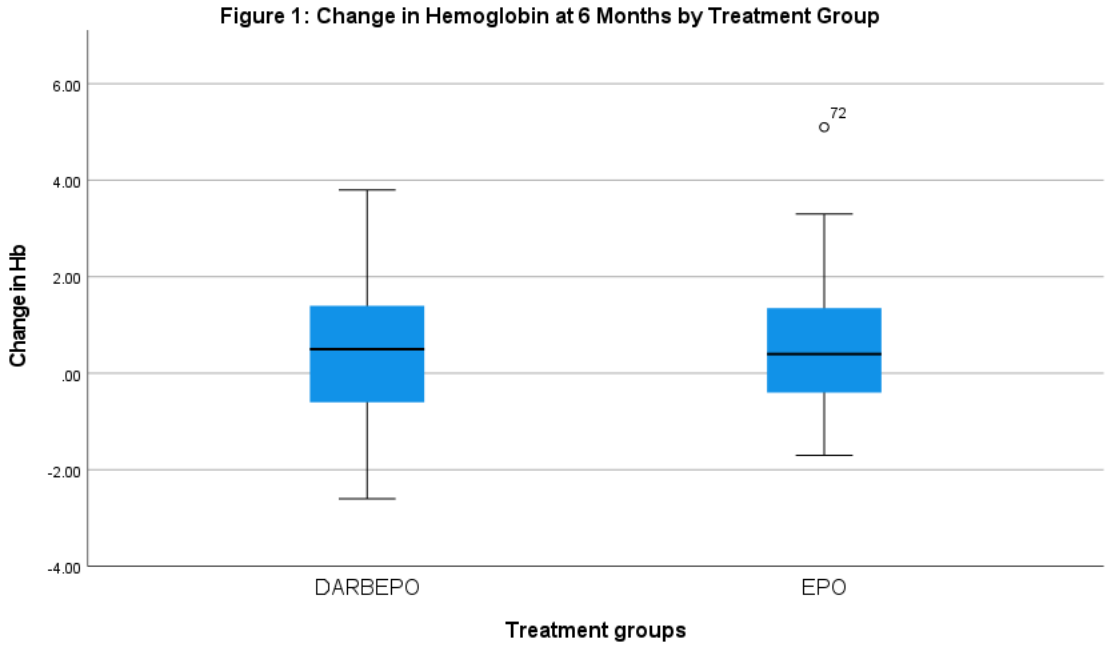

Table 4: Darbepotein alfa vs Epoetin alfa for treating anemia mean Hb for six months

Subgroup	N	Darbepoetin group n(mean±SD)	Epoetin group n(mean ±SD)	Mean Deference [CI 95%]	Treatment p-value	Group p-value	Effect size (Cohen's d)
Overall	93	33 (9.44 ± 0.99)	60 (8.90 ± 1.05)	0.53 [0.02,1.04]	0.042		0.52
Sex						0.367	
Male	57	21 (9.60±0.99)	36(8.92±1.02)	0.68[0.08,1.28]	0.027		0.67
Female	36	12 (9.15±0.97)	24(8.88±1.11)	0.27[-0.50,1.04]	0.487		0.25
Age						0.664	
<65years	31	18 (9.60±0.72)	13 (9.35 ± 0.54)	0.25[-0.23, 0.74]	0.297		0.38
≥65years	62	15 (9.24±1.24)	47 (8.78±1.12)	0.46[-0.22,1.14]	0.182		0.40
Treatment p-value from independent samples t-test; Group p-value for treatment by subgroup interaction from two way ANOVA, Effect size: Cohen's d with pooled standard deviation							

As shown in Table 4, Darbepoetin significantly increased mean hemoglobin levels compared to Epoetin over six months (mean difference: +0.53 g/dL, 95% CI [0.02,1.04], p-value = 0.042, Cohen's d = 0.52). Subgroup analyses revealed this effect was driven primarily by male patients (+0.68 g/dL, p-value = 0.027, Cohen's d = 0.67), with no significant benefit in females (p-value= 0.664). Though both younger (<65years) and older (≥65years) patients showed non-significant trends favoring Darbepoetin (mean differences: +0.25 g/dL and +0.46 g/dL, respectively). Variance was heterogenous across age groups (Levene's p value = 0.011), suggesting adjusted analysis.

4. DISCUSSION

The studies comparing the efficacy and safety of ESAs, are common in international literature, with the wide variety of trials to large observational cohorts (30-32). There has been no prior studies comparing directly the ESAs in CKD patients in Iraq, therefore this study is one of its kind with a sample size of 93 patients. This study found comparable baseline characteristics between the two groups i.e. Darbepoetin (N=33) and Epoetin (N=60) groups, with notable variations. The study population in this study was predominantly male (61.3%) (Table 1). Patients in Darbeopoetin group were older i.e. on an average 60.61 ± 13.94 years compared to 52.78 ± 14.11 years to Epoetin group, an Iraqi study comparing different ESAs in hemodialysis enrolled 100 patients with mean age of 45.66 years (33). A higher proportion (54.5%) of Darbepoetin patients were ≥65 years old compared to Epoetin group (21.6%) (Table 1). The contrasts of having older patient population, suggests difference in the demographics of CKD patients in different Iraqi dialysis centers or over time. The older cohort in this study might reflect increasing prevalence of CKD in older populations in Iraq. The Darbepoetin group in this study showed slightly higher baseline hemoglobin levels (8.84 ± 0.79g/dL) compared to Epoetin group (8.41 ± 1.08 g/dL) (Table 1). A prospective randomized comparative study in Qatar compared three ESAs, in hemodialysis patients, but did not give provide the detailed specific beaseline demographics of the groups (29). The details description of the groups in this study contributes to the regional understanding by focusing specifically on the Iraqi context.

The results of this study suggested that the Darbepoetin group achieved a statistically significant higher mean Hb level of 9.44 ± 0.99 g/dL compared to the Epoetin group with 8.90 ± 1.05 g/dL at six months, with a mean difference of 0.53 g/dL (p = 0.019), and (Cohen's d = 0.52) (Table 2), suggesting a clinically relevant difference in the final mean hemoglobin levels between the two group of patients, these results are noticeably

different from international studies exploring the comparative efficacy of both the agents suggesting not a significant difference in hemoglobin levels between the groups (23). Another recent Phase III trial from China concluded that Darbepoetin was not inferior to Epoetin alfa in maintaining Hb levels of the patients within the target range of 10.0–12.0 g/dL (30). Similarly another randomized trial found that Darbepoetin maintained hemoglobin as effective as recombinant human Epoetin (rHuEPO) (34). A comparative study from Qatar confirmed the efficacy of different ESAs including both Darbepoetin and Epoetin in hemodialysis patients, while this study did not provide specific meand HB difference directly comparable as in this study (29).

This study significantly contributes to the emerging comparative ESA research within Iraq by directly comparing Darepoetin and Epoetin with in Iraq patient cohort, addresses a critical gap and provides direct comparative analysis. An Iraqi study conducted by Alaa Kareem Dhayef in 2017 compared the anemia response to Epoetin Alfa and Beta in patients with CKD on hemodialysis (33). The information generated in this study is vital for informing treatment choices relevant to the Iraqi healthcare environment. The finding of higher mean Hb levels with Darbepoetin is a significant contribution, especially within the context of many international studies that suggest equivalence. This result is particularly crucial for the Iraqi and regional literature, providing much-needed comparative data that can directly inform clinical decisions and contribute to more tailored anemia management strategies in your local population.

In this study the median change in hemoglobin over six months did not demonstrate a statistically significant difference between the two groups i.e. Darbepoetin group (median increase of 0.50 g/dL) and the Epoetin group (median increase of 0.40 g/dL), although there was a significant difference in final mean hemoglobin (Table 3). This observation suggests that increase from baseline was potentially due to the influence of baseline hemoglobin differences between the groups. A key goal of ESAs is to maintain hemoglobin within a defined target (e.g. 10-12 g/dL), studies and trials have frequently reported the patient achieving these targets at the end of the study period (30, 31). This focus on maintenance rather than increase mean that change from baseline might be considered less critical compared to the final stable hemoglobin levels. Another study comparing the dose equivalence and stability of both the agents concluded that when managed appropriately, both the drugs lead to stable hemoglobin levels within target ranges, with similar efficacy (35). Another study explicitly states that ESAs including Darbepoetin and Epoetin are equally effective in treating anemia in renal hemodialysis patient and does not influence Hb variability (36). In our study the lack of significant difference in change of Hb might be influenced by baseline difference in Hb. If the Darbepoetin group started with a slightly higher baseline Hb, even a similar increase (0.50 g/dL vs. 0.40 g/dL) can result in a higher final mean Hb. This is normally observed in observational studies where perfect randomization and baseline comparability cannot always be assured (Table 3).

The evidence from Iraq and broader region regarding change from baseline Hb with Darbepoetin versus Epoetin is limited, as most studies focus on the effectives in maintain Hb. Our study provides a deeper insight reporting both final mean Hb and change from baselines in Iraqi population. Given the nature of the study where patient populations may have varied baseline charaterstics due to factors like access to care, treatment history, and overall health status, observing these difference is a reasonable outcome. The finding of our study highlights the importance of considering baseline patient characteristics while evaluating treatment effectiveness

In this study the subgroup analysis revealed a significant benefit of Darbepoetin in male patients, (0.68 g/dL, $p = 0.027$), compared to a non-significant difference in female patients (0.27 g/dL; $p = 0.487$), is a critical

finding (Table 4). This observation aligns with international literature suggesting sex-specific difference in responisiveness of ESAs, couple of studies reported that women often require higher erythropoietin doses to acheive the same hemoglobin targets as men, or they show lower hematocrits even on higher doses of EPO (37, 38). This suggests a fundamental difference in how genders respond to ESA therapies. Our finding that Darbepoetin showed more significant benefits in males compared to females aligns with the gender modulated ESA response, highlighting the importance of considering sex as a factor in ESA treatment.

The results of this study showed no significant age-dependent superiority of one drug over the other, while the response to treatment may be more variable in certain age groups. The studies have suggested that older adults with CKD present challenges in anemia management, mainly associated with factors like multiple morbidities, inflammation and nutritional status etc (39-41). In our study the similar response across age groups suggests that there underlying factors could be contributing to differing responses and highlights the need for further investigation in larger cohorts.

The significant strength of this study is that there are limited studies in the region comparing the effectiveness of ESAs. Secondly in this study we conducted the head to head comparison of the two ESAs in a local cohort providing practical insights for the clinical decision making. A detailed subgroup analysis was carried out and the study assessed the important clinical outcomes like mean hemoglobin levels and change from baseline as direct indicator of effectives. Despite the study providing valuable insights into the ESAs use in Iraq, there were several limitations including, observation design of the study, with limited sample size and only six months follow-up time of the patients. Also only minor variations between the baseline characteristics of the groups were observed. Finally the discrepancy between mean final Hb and median change in Hb over six months warrants careful interpretation.

5. CONCLUSION

This observational study concluded in Iraq comparing Darbepoetin and Epoetin alfa in CKD patients, is a unique first of its kind providing data for clinical decision making in the management of anemia in Iraq, The study found that Darbepoetin led to significantly higher mean hemoglobin levels at six months compared to Epoetin. However, the median change in hemoglobin from baseline did not differ significantly between the groups, suggesting that while Darbepoetin achieved higher absolute levels, the rate of increase from baseline was similar, possibly influenced by initial baseline differences. Furthermore sex-specific response, with Darbepoetin was observed in male patients, aligning with international literature on gender-modulated ESA responsiveness. Despite limitations inherent in its observational design, sample size, and follow-up duration, the research highlights the importance of considering baseline patient characteristics and gender in evaluating treatment effectiveness of ESAs.

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