## Original Article

# Interchanging Darbepoetin Alfa and Epoetin Alfa in Treatment of Anemia in Pediatric Patients on Regular Hemodialysis: It is possible.

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## ABSTRACT

**Introduction:** Anemia frequently occurs as a comorbidity in chronic kidney disease (CKD). In the management of anemia among patients undergoing hemodialysis, erythropoiesis-stimulating agents (ESAs) play a crucial role.

**Aim of the Study:** we aimed to explore the feasibility of using darbepoetin and epoetin alfa interchangeably with the same patient and to assess the differences in side effects associated with each ESA.

**Methods**: A crossover study was conducted at the Pediatric Dialysis Unit of Ain Shams University Children's Hospital, involving forty patients diagnosed with end-stage kidney disease (ESKD) who were receiving regular hemodialysis over an eight-month period. Patients with known blood disorders causing anemia, active blood loss, infections, uncontrolled hypertension, or serious allergic reactions to ESAs were excluded. The participants were randomly assigned into two equal groups. Each group was given one type of ESA for three months before switching to the other type for an additional three months. Blood samples were collected at both the beginning and end of each three-month treatment phase to measure hemoglobin levels, serum urea, serum creatinine, and iron profile indicators.

**Results**: The analysis revealed no significant differences in hemoglobin levels between the two drugs. The switch from one ESA to another did not result in any notable drop in hemoglobin levels. Additionally, no serious adverse effects such as convulsions, hypertension, or thrombosis were observed with either medication.

**Conclusion**: The findings suggest that it is feasible to interchange between darbepoetin and epoetin alfa in pediatric patients undergoing hemodialysis without compromising Hb level or risking grave side effects.

**Keywords**: Darbepoetin Alfa, Epoetin Alfa, Anemia, Pediatric, Hemodialysis

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## INTRODUCTION

Anemia is a prevalent comorbidity among individuals with chronic kidney disease (CKD), affecting a significant majority of these patients. Research indicates that approximately 75% of those with end-stage kidney disease experience anemia. This condition primarily arises from the reduced synthesis of erythropoietin by renal parenchymal cells. Erythropoiesis-stimulating agents (ESAs) are the cornerstone of anemia treatment in patients undergoing hemodialysis. The use of recombinant human erythropoietin (r-HuEPO) has proven effective for managing renal anemia, leading to increased red blood cell (RBC) mass, a reduced requirement for blood transfusions, and an improvement in anemia-related symptoms within this cohort [1]. Previous studies have shown that the presence of sialic acid in the carbohydrate structure of erythropoietin influences its serum half-life, hence epoetin (EPO) has a relatively brief circulating half-life [2]. In contrast, darbepoetin alfa (DPO), which features one amino acid modification, and two additional carbohydrate sites compared to EPO, has a more extended half-life. This characteristic has led to its widespread adoption as an alternative to Epoetin (EPO) for children diagnosed with CKD.

## METHODS

To investigate the effects of both medications on children with end-stage kidney disease undergoing regular hemodialysis, a two-period crossover study was conducted over eight months from October 2021 to May 2022 at the Pediatric Dialysis Unit of Children's Hospital Ain Shams University.

The study included forty patients aged between 6 and 17 years who had been on regular hemodialysis for at least three months. Exclusion criteria encompassed known blood disorders causing anemia, active blood loss, infections, uncontrolled hypertension, or serious allergic reactions to ESAs. Also, any additional chronic illness or comorbidity, other than ESKD, was ruled out before inclusion of participants.

Participants were divided into two groups of twenty; Group 1 received erythropoietin alpha (EPO) three times weekly (dose ranging from 150 to 300 IU/Kg/week) for three months before transitioning to darbepoetin (DPO) using a conversion ratio of 300:1[3]. Darbepoetin (DPO) was administered once weekly via either intravenous or subcutaneous routes (patients with Hb level<10 mg/dl received IV DPO because it is more effective compared to SC route which has longer duration of action). Conversely, Group 2 received ESAs in reverse order.

A washout period lasting six weeks was implemented due to the overlapping effects observed between the two drugs; this duration represents the maximum clearance time for both medications [4]. Blood samples were collected after this washout phase and again at the conclusion of each drug's testing period over three months. The six-week washout period was excluded from the study's results; however, ESA administration continued throughout this time due to its essentiality. We intended to exclude any patient during the study once major bleeding, undergoing surgery or systemic infection became an

issue, yet this did not happen, probably due to the short period of the study.

All participants underwent comprehensive interviews covering demographics such as age and gender, along with details regarding their renal failure etiology, dialysis history, and medication usage. Laboratory tests included complete blood counts at both the beginning and end of each drug's testing phase for all participants in both groups alongside assessments for serum ferritin, serum iron levels, and total iron binding capacity (TIBC). The target hemoglobin level was set between 11.0 and 12.0 g/dl.

All patients received hemodialysis thrice weekly; thirteen patients alternated between hemodialysis and hemodiafiltration (HDF), maintaining an average ratio of 2:1 [5] while twenty-seven patients solely underwent hemodialysis sessions due to limitations related to HDF filter availability and patient intravenous access flow rates. Dialysis treatments were conducted using Gambro Artis and Cordiax 5008S machines.

During drug administration, potential complications were monitored closely; these included hypertension, vascular access thrombosis (affecting arteriovenous fistulae or central venous catheters), headaches, abdominal discomforts such as nausea or vomiting, diarrhea, myalgia or arthralgia, oedema as well as any allergic reactions like skin rashes, cold like symptoms or laryngeal edema. Assessment of pure red cell aplasia (PRCA) was noticed by regular monitoring of Hb results.

Informed consent was obtained from all participants in simple Arabic language prior to their enrollment in the study. The confidentiality of data was ensured throughout the study.

Ethical approval from the Research Ethics Committee of Faculty of Medicine, Ain Shams University was obtained.

**Statistical analysis**

It was performed using the Statistical Package for Social Sciences (SPSS), version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. A confidence interval of 95% was established, with a margin of error accepted at 5%. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

Forty patients were included in the study, 60% were males, age ranged between 6-17 (12.038±3.317), duration of dialysis ranged from 1-9 years (3.438±1.805). The effects of each drug on different measured parameters are shown in **Table 1 and 2**. Targeted Hb, in both EPO and DPO, was reached in 9 patients which is 22.5% of total cases and was not reached in 25 patients which is about 62.5% with percentage of concordance of 85%, Statistical analysis by chi-square tests showed high significance by measure of agreement test P value was 0.000 with high significance net result. That proved that both drugs give the same effect with nearly negligible difference **Table 3**.

The different modalities of hemodialysis (HD or mixed modality of at least once a week on-line hemodiafiltration) did not show significant effect on different parameters while on either treatment. No serious side effects as convulsions, hypertension, or thrombosis were noticed, other common

side effects of DPO were found as injection site pain with 22.5% in patients who receives it by SC route, cough in 7.5%, edema of the four limbs in 2.5% and diarrhea in 2.5% of cases. While during EPO administration some side effects were noticed such as headache 25%, diarrhea 12.5%, and nausea 15%. **Figure 1**

**Table 1:** The change in different parameters after EPO treatment

| Time / Parameter | Start EPO | End EPO | P value |
|---|---|---|---|
| Hb (gm/dl) | 6-12.5 (9.535±1.553) | 6.5-12.4 (9.615±1.643) | 0.666 |
| Serum iron (ug/dl) | 21-191.3 (92.168±41.674) | 28-179 (88.015±38.739) | 0.37 |
| Ferritin (ng/ml) | 56.7-5140 (1293.9±1184.6) | 46-5440 (1236±1118) | 0.454 |
| TIBC (ug/dl) | 120-440 (219.86±54.791) | 109-411 (218±61.701) | 0.805 |
| Serum Creatinine (mg/dl) | 5.2-15 (8.5±1.9) | 3.5-11.9 (8.5±2.2) | 0.981 |
| Urea (mg/dl) | 92-250 (164.4±35.58) | 72-264 (151.4±44) | 0.07 |

**Table 2:** The change in different parameters after DPO treatment

| Time / Parameter | Start DPO | End DPO | P value |
|---|---|---|---|
| Hb(gm/dl) | 6.5-12.1 (9.6±1.6) | 6-12.5 (9.7±1.7) | 0.496 |
| Serum iron (ug/dl) | 31-190 (85.2±41.4) | 34.9-226 (86.5±43.2) | 0.752 |
| Ferritin (ng/ml) | 106-4200 (1078.5±951.5) | 111-3765 (1166.2±979.4) | 0.237 |
| TIBC (ug/dl) | 68-389 (209±60.7) | 90-343 (213±51.9) | 0.625 |
| Serum Creatinine (mg/dl) | 4.9-14.4 (8.425±2.416) | 4.7-12 (8.173±1.912) | 0.433 |
| Urea (mg/dl) | 80-344 (156.1±53) | 72-226 (148.2±39.1) | 0.378 |

**Table 3:** Hb target with each treatment

| Target End DPO | Target End EPO | | | | | | Chi-Square |
|---|---|---|---|---|---|---|---|
| | Yes | | No | | Total | | |
| | N | % | N | % | N | % | P-value |
| Yes | 9 | 22.5 | 4 | 10 | 13 | 32.5 | <0.000 |
| No | 2 | 5 | 25 | 62.5 | 27 | 67.5 | |
| Total | 11 | 27.5 | 29 | 72.5 | 40 | 100 | |

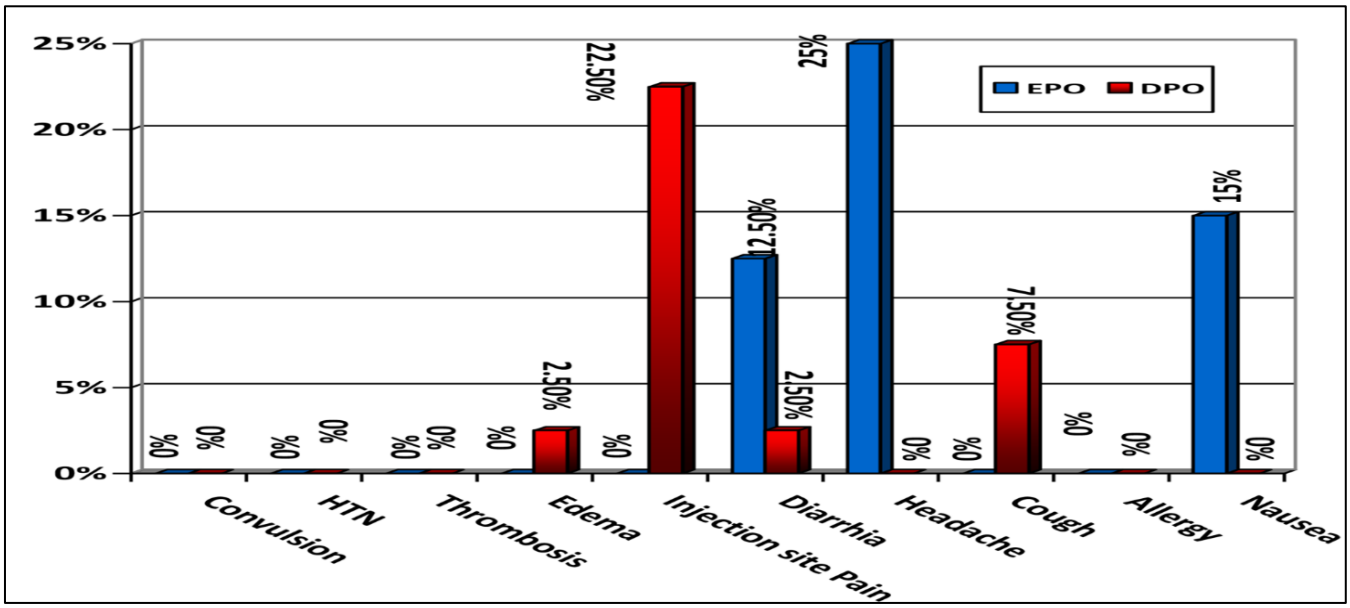


**Figure 1:** Side effects with both drugs

## DISCUSSION

Recently, darbepoetin alpha (DPO) has gained popularity as a treatment for anemia in children with chronic kidney disease (CKD) due to its longer half-life. However, the limited availability of this medication has necessitated the interchange of two forms of erythropoiesis-stimulating agents (ESAs) within the same patient population, depending on which drug is accessible. Epoetin alfa (EPO) and darbepoetin alfa (DPO) are commonly used interchangeably for managing anemia in patients suffering from advanced CKD and end-stage kidney disease. Notably, there has been no specific research directly comparing the risks and outcomes associated with EPO versus DPO [4].

Our study was designed as a two-period crossover trial to demonstrate that darbepoetin alpha and epoetin alpha can be effectively used interchangeably to treat renal anemia in Egyptian children undergoing hemodialysis. Additionally, we sought to investigate any differences in side effects between the two ESAs. In our findings, after treatment with EPO, there was no significant change in mean hemoglobin levels (from 9.5 mg/dl to 9.6 mg/dl), with a p-value of 0.666. Similarly, after treatment with DPO, mean hemoglobin levels changed insignificantly from 9.64 mg/dl to 9.77 mg/dl, yielding a p-value of 0.496. These results contrast with those from previous studies. One reported a significant increase in hemoglobin levels at the end of six months for both r-HuEPO and DPO (P = 0.01 for r-HuEPO; P = 0.02 for DPO). Hb did not differ between patients on and not on dialysis in both groups at the end of the study (P > 0.05) [6] another study stated similar results [7].

In another study involving seven children aged between 3 and 16 years with chronic kidney disease who received DPO for durations ranging from 5 to 34 months, all patients had baseline hemoglobin levels below 12.5 g/dl. Among these patients, two had previously been treated with another ESA; both switched patients and those naïve to ESA therapy responded positively to darbepoetin alfa treatment, with 86% achieving a target hemoglobin level of at least 11.8 g/dl [8].

The discrepancies between our results and those of other studies may arise from our cohort being comprised solely of patients already on ESAs prior to the study's initiation and exclusively including individuals on regular hemodialysis rather than earlier stages of CKD. Additionally, we cannot dismiss the possibility of resistance to ESAs among our participants due to their prolonged exposure to these treatments combined with our relatively short follow-up period.

Regarding iron profiles during treatment with both DPO and EPO, no significant changes were observed; during EPO administration, p-values for ferritin, serum iron, total iron-binding capacity (TIBC), and transferrin saturation were recorded as 0.265, 0.177, 0.190, and 0.265 respectively; while during DPO treatment these values were noted as follows: serum ferritin at p=0.92; serum iron at p=0.872; TIBC at p=0.625; transferrin saturation at p=0.882.

In terms of achieving targeted hemoglobin levels during treatments with both EPO and DPO, nine patients (22.5% of total cases) reached this goal while it was not achieved by 25 patients (62.5%), resulting in a concordance rate of 85% (p-value = 0). These findings align with another study on pediatric patients where no significant difference in hemoglobin

levels was found between groups receiving either recombinant human erythropoietin or darbepoetin alpha [6].

Furthermore, a study involving pediatric patients who transitioned from intravenous EPO to intravenous DPO while continuing hemodialysis for at least two years also reported no significant changes in hemoglobin levels over time [3]. Conversely, a multicenter prospective study conducted in Japan indicated that pediatric patients receiving subcutaneous r-HuEPO who were switched to DPO experienced an increase in mean hemoglobin levels from 9.9 ± 1.0 to 11.1 ± 1.0 g/dL at 8 weeks following the start of DPO treatment. The target Hb was achieved in 88 % of these patients, and 60 % maintained this target at the end of the study [9].

In our study, DPO was well tolerated and comparable to EPO except for that DPO injection pain was much more intense than EPO injection in subcutaneous route, in the DPO group injection site pain was noticed in 22.5% of patients, this met an agreement with another study where patients received, blindly, injections of equivalent doses of DPO or EPO at 4-week intervals. Patients, parents and nurses performing the injections weren't informed of the drug injected. Pain perception was recorded by patients, parents and nurses immediately and 30 min after injection, the patients perceived immediate injection pain more intensely with DPO than with EPO (5.4 ± 1 vs 2.3 ± 0.6, $P < 0.05$). This was confirmed by parents (5.3 ± 1 vs 2.0 ± 0.9, $P < 0.05$) and nurses (4.4 ± 1 vs 2.2 ± 0.6, $P < 0.05$) [10].

However, some side effects were noticed with both drugs but none of them was serious enough to stop the administration of any of the drugs. We found that during DPO treatment, cough happened in 7.5%, edema of the four limbs in 2.5% and diarrhea was noticed in 2.5% of cases and that goes with the common side effects reported by FDA. While during EPO treatment, Diarrhea occurred in 12.5%, Headache in 25% and Nausea in 17.5%, no serious side effects as HTN, Thrombosis or Convulsions were reported during administration of both drugs. These results are like another study where no disturbing adverse event was recorded. Side effects as uncontrolled hypertension or asymptomatic thrombocytosis were not reported by the patients. Four of the children had mild hypertension as a part of the manifestation of chronic renal failure [8].

## LIMITATIONS OF THE STUDY

We consider the relatively short period of study as a limitation.

## RECOMMENDATIONS

The interchange of different ESAs in ESKD pediatric patients is possible without any significant drop in hemoglobin levels and this opens the door for more flexible and convenient treatment protocols especially in developing countries where the supply of such medications can be challenging at times

## CONCLUSION

The interchange between DPO and EPO is possible without pointing out any significant drop in hemoglobin or dreading any serious side effects. This switch can be very useful in Pediatric

hemodialysis units especially in developing countries where the switch might be inevitable if in short of supplies.

**ABBREVIATIONS**

| | |
|---|---|
| **CKD** | Chronic Kidney Disease |
| **DPO** | Darbepoetin Alpha |
| **EPO** | Erythropoietin alpha |
| **ESAs** | Erythropoiesis stimulating agents |
| **ESKD** | End-stage kidney disease |
| **Hb** | Hemoglobin |
| **HD** | Hemodialysis |
| **IV** | Intravenous |
| **NKF-K/DOQI** | National Kidney Foundation's Kidney Disease, Quality Initiative |
| **rHuEPO** | Recombinant human erythropoietin |
| **SC** | Subcutaneous |
| **SD** | Standard deviation |
| **SPSS** | Statistical package for social sciences |
| **TIBC** | Total iron-binding capacity |
| **TSTAT** | Transferrin saturation |

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## AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.
All authors have contributed to authorship, have read, and approved the manuscript.

**Conception and design of study:** M.E.A, I.Z.EH, R M.S

**Acquisition of data:** N.E.I

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**Approval of the version of the manuscript to be published:** All Authors

## STATEMENTS

**Ethics approval and consent to participate.**
This study was approved by Ethics Committee of Faculty of medicine, Ain Shams University, with the ethics code Ethical approval was obtained from the Research Ethics Committee of Faculty of Medicine, Ain Shams University (FMASU REC) (Assurance no. MS234/2020). Also, written informed consent was obtained from the parent of the participating children.

**Consent for publication**
The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

**Availability of data and material**
"Available for your request, anytime"

**Conflict of interest**
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