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Causes of Erythropoiesis-Stimulating Agent Resistant Anemia in Children with Chronic Kidney Disease at a Tertiary Hospital

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Abstract

Background and Aim: Routine clinical and laboratory assessments facilitate the diagnosis of erythropoietin (EPO) resistant anemia. Resistance to EPO rarely occurs in children with chronic kidney disease (CKD). It may be caused by several factors, such as poor compliance, hyperparathyroidism, malnutrition, inadequate dosages, and medication. This study was conducted to evaluate the frequency and causes of EPO resistant anemia in CKD children.

Methods: This observational retrospective study was performed in Ali Asghar Children's Hospital in 2008. Children who were treated by EPO and still had hemoglobin concentrations (Hb) below 10 g/dl or required very high erythropoietin doses (more than 150 IU/kg/week) were considered as EPO resistant anemic cases. Therefore, their data including demographic data, EPO dosage, medications, underlying diseases, mode of dialysis, and lab test results were collected from their medical records.

Results: The Hb concentration was below 8 g/dl in eight cases (40%). The male to female ratio was 1.66 and the median age was 7.9 years old. The median hemoglobin concentration was 6.25 g/dL. Three patients (37.5%) were true cases of resistance in EPO (two patients had bone marrow fibrosis due to hyperparathyroidism and one had EPO Ab) while five cases (62.5%) received inadequate doses of EPO (anemia improved upon an acceptable EPO dosage).

Conclusion: True resistance to erythropoisis stimulatin agent is not frequent and because of there are heterogeneous causes for Lack of appropriate response to EPO, so full investigation is needed especially complete history to find the underlying reason.

Keywords: Anemia; Chronic Kidney Disease; Erythropoietin.

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Introduction

Anemia is common in patients with chronic kidney disease (CKD). The main cause of this type of anemia is reduced erythropoietin production due to kidney damage (1).

Erythropoiesis-stimulating agents (ESAs) are the preferred initial therapy for anemia of CKD. However, there is variation in response to ESAs and some CKD patients have partial or no response to ESAs (2). Patients who do not reach target hemoglobin concentrations regardless of high doses of ESAs are ESA resistant. The criteria of ESA resistance are not well defined.

We use the Kidney Disease Outcomes Quality Initiative (KDOQI) criteria of inability to achieve a desired Hb concentration using a maximum dose of 150 units/Kg/week subcutaneous erythropoietin (2). Resistance to ESAs can be a risk factor for increased mortality in CKD patients; on the other hand, long-term consumption of high doses of ESAs can cause complications, including hypertension, thromboembolism, cardiac attack, and cardiac failure; therefore, early diagnosis and treatment of resistance to erythropoietin (EPO) are essential (3,4). Several mechanisms could explain resistance to EPO.

The most frequent cause of EPO resistance is iron deficiency. Other etiologies include inflammation, infection, malnutrition, insufficient EPO dosage, inadequate dialysis, and hyperparathyroidism.
Since EPO resistance depends on demographic variables such as age and gender distribution and modality of dialysis, this study was conducted to determine the prevalence and causes of ESAs resistance in an Iranian pediatric nephrology center.

Methods

This study observational retrospective study was conducted in the Nephrology Research Center of Ali Asghar Children's Hospital, Iran University of Medical Sciences, Tehran, Iran between June 2008 and December 2018. The study was approved by the Human Research Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC 1396.9511359001) and informed consent was obtained from the patients' parents/guardians prior to the study.
Of 30 admitted cases with CKD and anemia between 2008 to 2017, 20 cases were recruited (children between 1 to 17 years suffering from CKD and drug resistant anemia).
At first dosage and method of EPO usage were reformed and after 3-month follow-up anemia was corrected in 12 patients.
EPO resistance was defined as a persistent anemia (hemoglobin <10 g/dL) or the necessity of very high erythropoietin doses (more than 150 IU/kg/week subcutaneously)
All cases with an adequate response to EPO treatment were excluded from the study. The study variable included age, gender, weight, height, hemoglobin concentration, underlying diseases, duration and mode of dialysis, EPO dosage, duration of EPO treatment, serum calcium level, serum phosphate level, and parathyroid hormone (PTH) and C – reactive protein (CRP) levels.

Results

Of 20 enrolled patients, eight had resistant anemia (three female and five male patients). The patients' data are presented in Table 1. The mean age, weight, and height of the subjects was 7.93 years, 32.12 kg, and 109 cm, respectively.

Table 1. Patients' data

Cases / Data	Case1(true resistance)	Case2(true resistance)	Case3	Case4(true resistance)	Case5	Case6	Case7	Case8
Age (year)	10	17	10	1	14	1.5	8	2
Gender	Male	Male	Female	Female	Female	Male	Male	Male
Weight (kg)	51	56	40	8	32	9	52	9
Height (cm)	120	157	120	60	150	60	125	80
Underlying disease	VUR	VUR	NS	HUS	VUR	HO	NS	NS
Type of dialysis	H+P	H	P	H	H	P	H	H
Duration of dialysis (years)	7	10	3	¼	2	1/6	5	1
EPO dosage (IU)	4000	10000	2000	2000	4000	2000	2000	2000
Duration of EPO use (weekly)	2	3	1	1	1	1	3	1
Hemoglobin (g/dL)	5.1	5	5.3	5.9	7.9	9.5	5.3	6
Serum Ca	8.7	7.7	9.4	8	8.1	8.7	7.7	7.2
Serum P	6.2	2.3	4.3	8.4	5.5	3.8	7.5	5.6
PTH	478	1857	456	289	270	1172	61	486
CRP	Negative	Negative	negative	Negative	negative	negative	negative	negative

H: hemodialysis; P: peritoneal dialysis; EPO: erythropoietin; PTH: Parathyroid hormone; CRP: C - reactive protein; VUR: vesicoureteral reflux; NS: nephrotic syndrome; HUS: hemolytic uremic syndrome; Ho: hyperoxaluria.

The underlying causes of CKD were vesicoureteral reflux (four patients), nephrotic syndrome (two patients), hyperoxaluria (one patient), and hemolytic uremic syndrome (one patient). Two cases were on peritoneal dialysis and the rest of them were on hemodialysis. The average duration of dialysis was 4 years. The mean EPO dose was 150 IU/Kg/week. The mean Hemoglobin, Ca, P and PTH levels were 6.25 g/dL, 7.22 mg/dL, 5.45 mg/dL, and 633.62 pg/mL, respectively. The

hemoglobin concentration was below 8 g/dl in eight patients (40%); two of them had hyperparathyroidism and all of them had negative CRP.

Three patients (37.5%) were true cases of resistance to EPO (two patients had bone marrow fibrosis due to hyperparathyroidism and one had EPO Ab) and five cases (62.5%) had a poor compliance for medication use.

Discussion

This study demonstrated that resistance to EPO was a less frequent cause of persistent anemia in children with CKD compared to inadequate dosage and poor compliance. In this study incorrect dosage and poor compliance were the most common reasons for resistant anemia. Mehmet et al. conducted a study in Romania and found that true resistance to EPO was rare (5). Infections, malnutrition, iron deficiency, malignancies, and hemoglobinopathies were reported as the most prevalent conditions (5).

Several studies found that the main risk factors of resistant anemia in CKD patients were infection; inflammation; malnutrition; Iron, vitamin D, vitamin C, vitamin B12, folic acid, and L-carnitine deficiency, aluminum intoxication, chronic hemolysis, and hemoglobinopathies (6, 7).

Vesicoureteral reflux and nephrotic syndrome were the prevalent underlying disease. Karlijn et al. conducted a retrospective study in children with chronic kidney disease and anemia in 19 countries and reported that congenital anomalies of the urinary tract were the most common underlying diseases (8).

Conclusion

Management of anemia is very challenging in CKD children. Lack of response to erythropoietin (EPO) in these children is frequent and. It is very important to identify the etiological factors of resistant anemia and their treatments due to its morbidity, mortality and extra costs. A lack of or inadequate response to EPO may be secondary to some factors such as poor compliance, hyperparathyroidism, malnutrition, and inadequate dosage/duration of treatment, and true resistance to EPO is less frequent.

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Conflict of Interest

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