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# SERUM ERYTHROPOIETIN IN CHILDREN WITH IRON DEFICIENCY ANEMIA*

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**SUMMARY: Çetin M, Gürgey A, Gümrük F, Altay Ç. (Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Serum erythropoietin in children with iron deficiency anemia. Turk J Pediatr 1997; 39: 459-464.**

**Serum erythropoietin (EPO) levels were determined in 30 children with iron deficiency anemia. The mean age of the children, hemoglobin (Hb) levels, serum EPO levels and log EPO values were 4.7 ± 5 years, 6.7 ± 1.7 g/dl, 2284 ± 3177 mU/ml and 2.81 ± 0.82, respectively. In 83 percent of the patients poor diet was the determined cause of iron deficiency and in the remaining 17 percent, chronic blood loss. A significant negative correlation was found between the log EPO values and Hb values ($r = 0.62$, $p < 0.01$). There was no significant correlation between log EPO values and the other parameters [sex, age, mean corpuscular volume (MCV) red blood cell (RBC) red cell distribution width (RDW), serum iron, iron binding capacity]. There was a significant difference in the age of the patients with an Hb value < 5.5 g/dl and those with a value ≥ 5.5 Significant differences were also observed in log EPO levels among these patients ($p < 0.004$). The mean Hb value of patients with log EPO values ≥ 3 was lower than that in patients with log EPO values < 3 ($p < 0.003$). In 20 percent of the patients, serum EPO levels were much lower than the values expected from their Hb level. Serum EPO levels were high in all five patients with a history of chronic blood loss.**
*Key words: erythropoietin, iron deficiency anemia.*

The serum erythropoietin (EPO) level increases in anemia of various etiologies except for those which result from inefficient endogenous production of EPO, such as that seen in patients with renal failure, anemia in premature infants and anemia associated with chronic infection[1-3]. Although an inverse correlation between EPO and hemoglobin (Hb) levels is observed in general, EPO levels in iron deficiency anemia give heterogeneous results. In some studies the EPO level was not found to be as high as expected from the Hb value[4]. The age of the patients, duration (chronicity) of anemia, and underlying pathology leading to anemia might contribute a great deal of influence on the heterogeneous distribution of EPO levels in iron deficiency anemia. In order to assess possible

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effects of these factors on serum EPO levels, we studied quite a high number of patients belonging to various age groups and with various underlying pathologies leading to iron deficiency anemia.

## Material and Methods

A total of 30 patients with iron deficiency anemia were the subjects of this study. Twelve healthy children with a mean age of 8.1 ± 8.5 years (0.8-23) were used as controls. All patients were questioned regarding their dietary history and history of bleeding. Diagnosis of iron deficiency anemia was based on the presence of an Hb value ≤ 10 g/dl associated with microcytosis, hypochromia, low serum iron and increased iron-binding capacity. Stools were examined for occult blood. routine hematological evaluations were made by standard procedures. EPO level was measured by radioimmune assay.

## Results

The mean age and mean hematological parameters at diagnosis are given in Table I. Twelve of the 30 patients were older than three years of age. The mean Hb, EPO and log EPO values were 6.7 ± 1.7 g/dl, 2284 ± 3177 mU/ml, and 2.81 ± 0.82, respectively. The mean EPO and log EPO values in the control group were 17.8 ± 5.9 mU/ml and 1.24 ± 0.12, respectively. A correlation study indicated the presence of a significant negative correlation between log EPO and Hb values ($r = 0.62$, $p < 0.01$) (Fig. 1). There was a significant difference between the age of the patients with an Hb value < 5.5 g/dl and those with a value ≥ 5.5. A significant difference was also observed in the log EPO levels among these patients ($p < 0.004$) (Table II). There was no significant correlation between the other parameters given in Table I. In three patients (patients 1-3) with a Hb value less than 3.6 g/dl or a hematocrit (Htc) less than 16.2 percent, EPO levels were higher than in the rest of the patients (Table I) (Fig. 1). When the patients were divided according to their log EPO values being ≥ 3 (12 patients) and (18 patients), a significant difference in the mean Hb values ($p < 0.003$) was noted (Table III). In five of the 12 (40%) patients with a value ≥ 3, disorder was present (patients 1, 7, 14, 15, 17) (Table I). In three of them, chronic idiopathic thrombocytopenic purpura (ITP) was the underlying disorder (patients 1, 15, 17). In patient seven, occult blood was positive in the stool examination (Table I) without any bleeding disorder or gastrointestinal pathology. In the remaining 25 patients, anemia was chronic and resulted from an iron-poor diet. In 6 (20%) of the 30 patients, the serum EPO level was much lower than the value expected from their hemoglobin levels (patients 7, 8, 9, 20, 21 and 28) (Table I). Two of these six patients were infants.

Table I: Some of the Clinical and Laboratory Findings

| No. | Age (yr) | Sex | Hb g/dl | Hct % | MCV fl | SI µg/dl | SIBC µg/dl | Log EPO | Etiology |
|---|---|---|---|---|---|---|---|---|---|
| 1. | 12 | F | 2.6 | 9.7 | 59 | 10 | 479 | 4.01 | Chronic ITP-rectal bleeding |
| 2 | 3 | F | 3.4 | 11 | 49.9 | 10 | 400 | 4.01 | PD |
| 3 | 1 | M | 3.5 | 16 | 68.6 | 10 | 396 | 3.94 | PD |
| 4 | 1.5 | M | 5.2 | 18 | 53 | 30 | 342 | 3.89 | PD |
| 5 | 4 | M | 5.5 | 19 | 52 | 12 | 317 | 3.98 | PD |
| 6 | 5 | M | 5.2 | 18 | 68 | 13 | 408 | 3.55 | PD |
| 7 | 11 | M | 4.7 | 16.3 | 50.3 | 27 | 396 | 2.28 | occult blood in stool |
| 8. | 15 | F | 4.8 | 15 | 64 | 32 | 371 | 2.42 | PD |
| 9 | 12 | M | 5.2 | 16 | 58.8 | 24 | 279 | 2.46 | PD |
| 10 | 2 | F | 6.3 | 22 | 55.4 | 10 | 283 | 2.86 | PD |
| 11 | 5 | F | 7.5 | 24 | 60.6 | 10 | 330 | 2.86 | PD |
| 12 | 1 | M | 7.3 | 27 | 47.6 | 55 | 400 | 2.85 | PD |
| 13 | 15/12 | M | 7.3 | 26 | 48.3 | 10 | 321 | 2.87 | PD |
| 14 | 1.5 | M | 6.5 | 28 | 46.6 | 25 | 427 | 3.25 | epistaxis |
| 15 | 13 | F | 7 | 25 | 58 | 12 | 386 | 3.24 | Chronic ITP |
| 16 | 1.5 | F | 7.5 | 25 | 52.6 | 18 | 304 | 3.22 | PD |
| 17 | 13 | F | 7.2 | 24 | 58 | 10 | 383 | 3.36 | Chronic ITP |
| 18 | 7/12 | M | 6.9 | 21 | 50.1 | 12 | 479 | 3.52 | PD |
| 19 | 2 | M | 7.2 | 23 | 46.9 | 32 | 400 | 3.59 | PD |
| 20 | 1 | M | 6.3 | 22 | 50.2 | 15 | 408 | 1.81 | PD |
| 21 | 10/12 | M | 6.7 | 24 | 51.5 | 13 | 429 | 1.92 | PD |
| 22 | 15/12 | F | 7.6 | 25 | 50.9 | 12 | 333 | 2.17 | PD |
| 23 | 10/12 | M | 8.3 | 27 | 45.8 | 13 | 383 | 2.75 | PD |
| 24 | 8/12 | M | 8.6 | 28 | 60.9 | 10 | 300 | 2.51 | PD |
| 25 | 10 | F | 8.2 | 27 | 63.6 | 10 | 342 | 2.49 | PD |
| 26 | 1.5 | M | 8.3 | 29 | 56.8 | 33 | 292 | 2.16 | PD |
| 27 | 1.5 | M | 8.8 | 23 | 53.2 | 23 | 346 | 1.90 | PD |
| 28 | 14 | F | 7.8 | 26 | 52.8 | 10 | 396 | 1.10 | PD |
| 29 | 1.5 | F | 9.9 | 30 | 57.1 | 12 | 354 | 1.20 | PD |
| 30 | 1.5 | M | 8.5 | 28 | 65 | 20 | 350 | 2.16 | PD |
| | 4.7 ± 5 | | 6.7 ± 1.7 | 22.4 ± 5.4 | 55.2 ± 6.4 | 17 8 ± 10.5 | 368 ± 53 | 2.81 ± 0.82 | |

PD : poor diet.
ITP : Idiopathic thrombocytopenic purpura.

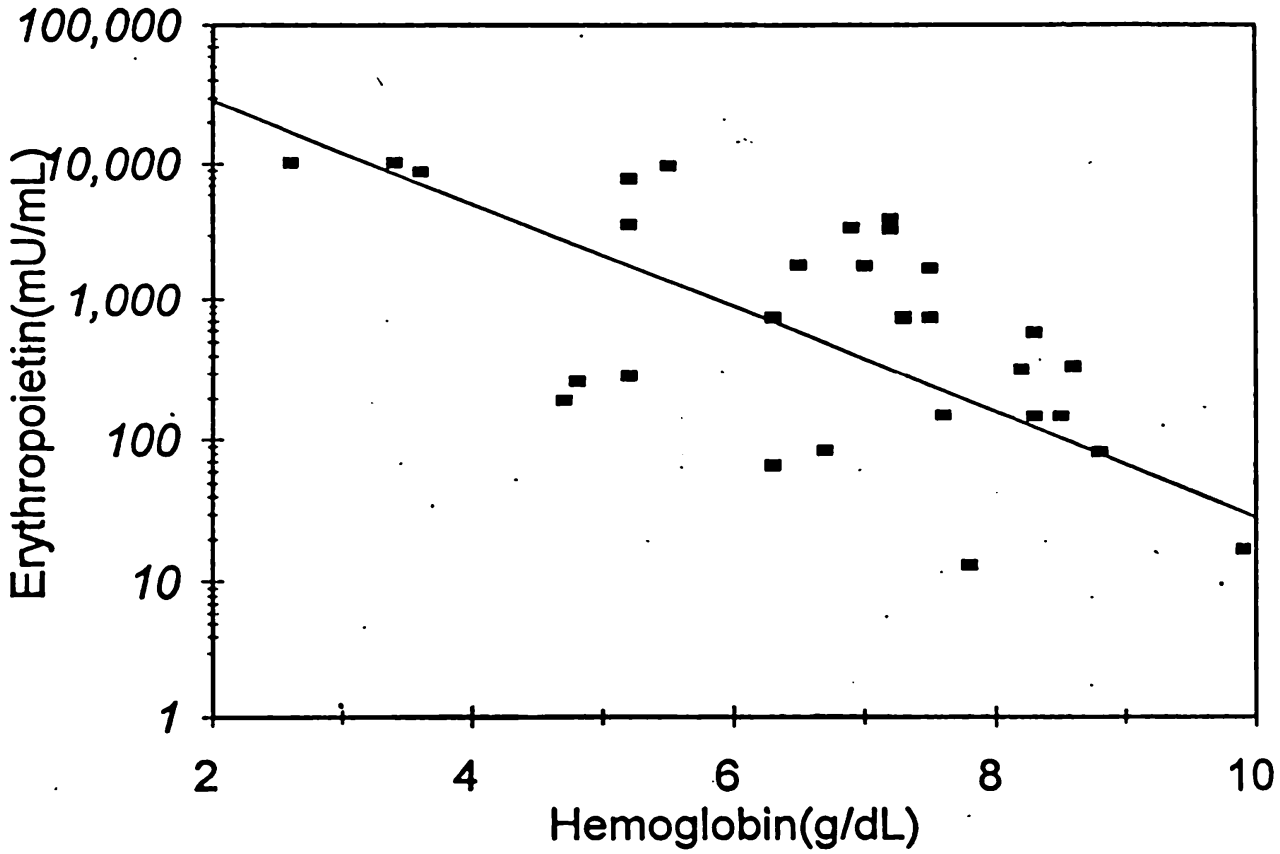


Fig. 1: Relationship between the hemoglobin concentration and the logarithm of the serum EPO level in patients with iron deficiency anemia.

Table II: Comparison of Some of the Parameters in Patients with Hb Values

| Number | Hb < 5.5 g/dl | Hb ≥ 5.5 g/dl | p |
|---|---|---|---|
| | 9 | 21 | |
| Age (yr) | 7.2 ± 5.3* | 3.6 ± 4.6 | 0.03 |
| | 1-15** | 0.7-14 | |
| MCV (ft) | 58.2 ± 7.4 | 53.9 ± 5.7 | 0.047 |
| | 49.9 ± 68.6 | 45.8-65 | |
| Serum iron | 18.7 ± 9.4 | 17.4 ± 11.2 | 0.38 |
| (µg/dl) | 10-32 | 10-55 | |
| Iron-binding | 376 ± 58 | 364 ± 51 | 0.28 |
| capacity (µg/dl) | 279-408 | 283-479 | |
| Log EPO | 3.39 ± 0.77 | 2.56 ± 0.72 | 0.004 |
| | 2.28-4.01 | 1.1-3.59 | |

* mean ± ISD.
** minimum and maximum values.

Table III: Comparison of Some of the Parameters in Patients with log EPO Levels ≥3 and log EPO <3

| | Log EPO <3 | Log EPO ≥3 | p |
|---|---|---|---|
| Number | 18 | 12 | |
| Age (yr) | 4.5 ± 5.2 | 4.8 ± 4.9 | 0.44 |
| Hb (g/dl) | 7.3 ± 1.4 | 5.6 ± 1.7 | 0.003* |
| MCV (fl) | 55.2 ± 6.0 | 55.2 ± 7.3 | 0.48 |
| RBC $(X10)^6$ | 4.2 ± 0.9 | 3.6 ± 1.3 | 0.07 |
| RDW | 22.6 ± 3.0 | 20.7 ± 2.8 | 0.05* |
| SI (µg/dl) | 19 ± 12 | 16 ± 8 | 0.25 |
| SIBC (µg/dl) | 351 ± 47 | 377 ± 57 | 0.09 |

SI : Serum iron.
SIBC: Serum iron-binding capacity.

## Discussion

Presence of a significant negative correlation between the EPO level and Hb value supports previously published studies. However, the EPO values in our patients seemed quite high in comparison to the values in some of the previously published studies[1,3]. This probably resulted from the severity of anemia in our group of patients. It was suggested that in severe anemia oxygen-binding heme protein fails to work, probably due to an abnormality in its heme-containing component[4,5]. Contrary to this prediction, our study, as was reported previously, indicated that the highest EPO value was found in patients with severe anemia as shown Figure 1, and Tables I and II. This indicates that even in severe iron deficiency anemia organisms either conserve the heme component of oxygen-sensing protein or some other mechanism replaces the function of oxygen-sensing protein in control of EPO production. In some studies, the EPO level was not as high as predicted from the severity of iron deficiency anemia[4]. It was shown that the EPO level returns to normal within a few days after administration of iron, long before the rise in Hb value or before restoration of iron depletion[6]. This observation indicates that either the patients or their parents should be questioned regarding and any medication before EPO determination. It is well documented that in infection, EPO levels dietary history fall below normal[7]. Therefore, it is not unlikely that in patients with iron deficiency anemia, the EPO level decreases when the patient acquires an infection. This indicates the importance of establishing a patient's health status during EPO determinations.

Our study indicated that as a whole, the age of the patients is not an important factor in modification in the EPO level in iron deficiency anemia. However, the mean Hb value was lower, and serum EPO value higher, in patients in the older age group. In infancy, the duration of anemia is several months, whereas in

older age groups, its duration is usually several years. Absence of any significant changes in EPO values in infants and older patients may indicate that the duration of anemia is not an important modifying factor in EPO levels. Presence of chronic blood loss in 40 percent of patients with a high EPO level and absence of any bleeding history in the rest of the patients suggested to us that chronic blood loss usually results in a higher serum EPO level.

This study indicated that in iron deficiency anemia in any age group, prior to any iron supplementation either as medication or as a dietary supplement and in the absence of any coexistent infection, serum EPO levels rise to a very high level and a significant correlation between Hb levels and EPO values can be expected.

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