SERUM ERYTHROPOIETIN LEVELS IN THALASSEMIA MAJOR AND INTERMEDIA

Watana Chaisiripoomkere[1], Saengsuree Jootar[2], Suporn Chanjarunee[2], Artit Ungkanont[2]

Division of Hematology, [1]Department of Research Center, [2]Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand

Abstract. Serum erythropoietin (EPO) levels were determined by enzyme linked immunosorbent assay (ELISA) in 61 thalassemic patients, consisting of 23 thalassemia major (TM) patients with multiple transfusion, 38 patients with thalassemia intermedia (TI). Thirty-two normal controls were also studied. The mean serum EPO levels were significantly higher in both groups with TM (165.96 ± 17.31 mIU/ml) and TI (126.43 ± 50.56 mIU/ml) compared with the control group (8.33 ± 3.91 mIU/ml). The mean value of hematocrit (Hct) in the patients with TM (18.70 ± 3.51%) was lower than those with TI (25.24 ± 4.19 %) whereas the mean serum EPO level were significantly higher in TM than TI patients. An inverse correlation between the serum values of EPO and Hct was observed in both TI and TM patients, however this correlation was significant only in TI ($r = -0.61$, $p<0.001$). These data showed that serum EPO levels increased in all thalassemia patients despite repeated transfusion. Multiple transfusion may modulate the response of serum EPO to the degree of anemia, resulting in increased EPO levels and independent anemia in the TM patients.

INTRODUCTION

Erythropoietin (EPO) is a glycoprotein produced primarily by the kidney in response to hypoxia and anemia (Penington, 1961), it is the principal factor initiating and regulating red cell production (Graber and Krantz, 1989). Serum EPO levels increase exponentially as hemoglobin (Hb) or hematocrit (Hct) decrease (Klerk *et al*, 1981; Garcia *et al*, 1982). The level of serum EPO have been studied in anemias and in thalassemia syndromes, which are a group of disorders, each of which are results from an inherited abnormality of globin chain production (Weatherall and Clegg, 1981). The different types of thalassemia exhibit a wide range of variation in the degree of anemia.

The aim of this study was to evaluate the serum level of EPO in thalassemia major (TM) and thalassemia intermedia (TI) patients and to analyse the relationship between the EPO concentration and Hct.

SUBJECTS AND METHODS

Sixty-one thalassemic patients and 32 normal healthy controls were studied. The thalassemia phenotypes were 23 TM, consisting of β-thalassemia homozygous and β-thalassemia/Hb E (15 males and 8 females), aged between 2 and 34 years, and 38 TI, consisting of β-thalassemia/Hb E and Hb H disease (19 males and 19 females), aged between 2 and 35 years. The diagnosis of TM and TI were made according to the clinical criteria proposed by Weatherall and Clegg (1981). All of the TM patients had transfusion therapy every 1 to 3 months and 5 patients were splenectomized. For the TI group, 22 patients had never received transfusion therapy while the remaining 16 patients had been sporadically transfused and 13 patients were splenectomized.

The blood samples were drawn before transfusion. Hct was determined by using micro-hematocrit centrifuge (IEC, USA). Serum EPO concentration were determined by Elisa (R and D systems, Inc. Minneapolis, MN 55413, USA). The sensitivity was 0.6 mIU/ml.

Results were evaluated by Student's unpaired *t*-test and by correlation analysis between percents of Hct and the logarithm of the EPO levels.

RESULTS

Mean EPO levels and Hct in TM and TI patients and normal controls are shown in Table 1. The mean serum levels of EPO were significantly higher in the TM patients than in the TI patients, whereas the degree of anemia was observed to be greater in TM patients.

When the values of serum EPO were plotted in

Correspondence: Watana Chaisiripoomkere, Division of Hematology, Research Center, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand.

Table 1
Mean serum EPO levels and Hct in thalassemic patients and controls.

Group	Serum EPO (mIU/ml)		Hct (%)	
Thalassemia major	165.96 ± 17.31	p<0.001	18.70 ± 3.51	p<0.001
Thalassemia intermedia	126.43 ± 50.56		25.24 ± 4.19	
Controls	8.33 ± 3.91		40.67 ± 3.14	

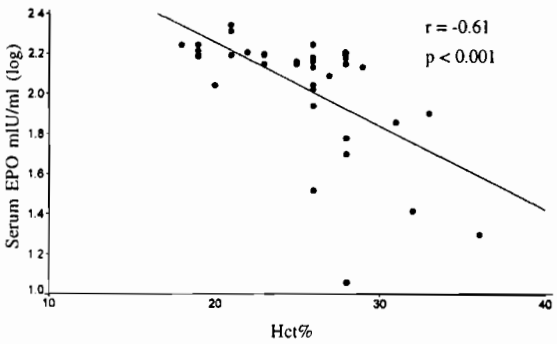

Fig 1–Correlation between Hct and logarithm of EPO levels in patients with thalassemia intermedia.

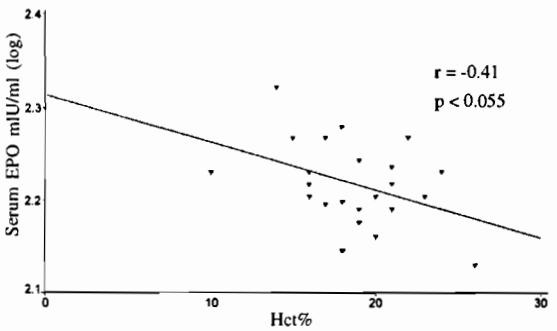

Fig 2–Correlation between Hct and logarithm of EPO levels in patients with thalassemia major.

correlation with Hct, there was a significant inverse linear relationship (r = -0.61, p<0.001) in TI (Fig 1). In the TM group a correlation between EPO and hematocrit was also observed but was not statistically significant (r = -0.41, p = 0.055) (Fig 2).

DISCUSSION

In this study, we demonstrated the increased EPO levels in both transfused and non-transfused TM and TI patients. Our finding agrees with the observations reported by many previous investigators (Alessi *et al*, 1990; Andre *et al*, 1991; Buemi *et al*, 1987; Chen *et al*, 1998; Dore *et al*, 1993; Kalmanti *et al*, 1991; Nisli *et al*, 1997) but not with that of Manor *et al* (1986). Our findings also showed that the TM patients with more anemia had higher serum EPO levels than less anemic TI patients. However, the inverse correlation between EPO level and Hct was statistically significant only in TI patients who had only a few transfusions. In TM patients who were often transfused this inverse correlation although seems to be observed but was not statistically significant. Our observation in this regard agrees with those reported by Dore *et al* (1993) and Nisli *et al* (1997), but not with Chen *et al* (1998) who found a significant inverse correlation between serum EPO levels and Hct in polytransfused β-thalassemia major patients. The conflicting data on the studies of EPO level in thalassemic patients may be due to the method of serum EPO evaluation and the time of drawing the sample at pre or post transfusion. An increase in circulating hematopoietic progenitor cells along with an elevated serum EPO level was observed by Chen *et al* (1992). This observation suggested that physiologic regulation of erythropoiesis still operated in patients with thalassemia major who were oftenly transfused. From our study, we conclude that the serum EPO levels increased in both transfused and non-transfused thalassemic patients. This finding indicated that polytransfusion cannot prevent hypoxia and anemia leading to the erythropoietin response. However, the polytransfusion may modulate the response of EPO to the degree of anemia resulting in the increased EPO levels and independent anemia.

ACKNOWLEDGEMENTS

We thank the nurses in outpatients Division of Pediatric Hematology for providing the specimens, Mrs Umaporn Udomsubpayakul for advice in statistics and Mrs Hataya Suparp for typing the manuscript. We are grateful to Professor Tanomsri Srichaikul for kindly reviewing the manuscript.

REFERENCES

Alessi M, Longo G, Di Martino G, Cacciola E, Sortino B. Erythropoietin serum levels in beta thalassemia. *Ann NY Acad Sci* 1990; 6: 534-6.

Andre M, Bergmann P, Ferster A, Toppet M, Fondu P. Serum immunoreactive erythropoietin level: a new parameter for monitoring transfusion management of thalassemia. *Nouv Rev Fr Hematol* 1991; 33: 299-302.

Buemi M, Sardo A, Musolino C, *et al.* Pattern of plasma erythropoietin in Cooley's disease. In: Sirchia G, Zanella A, eds. Thalassemia today. Milan: Centro transfusionale, 1987; 627-31.

Chen JS, Lin KH, Tsao CJ. Peripheral blood hematopoietic progenitor cells in beta thalassemia major. *Int J Cell Cloning* 1992; 10: 338-43.

Chen JS, Lin KH, Wang ST, Tsao CJ, Yeh TF. Blunted serum erythropoietin response to anemia in patients polytransfused for beta-thalassemia major. *J Pediatr Hematol Oncol* 1998; 20: 140-4.

Dore F, Bonfigli S, Gaviano E, *et al.* Serum erythropoietin levels in thalassemia intermedia. *Ann Hematol* 1993; 67: 183-6.

Garcia JF, Ebbe SN, Hellander L, Cutting HO, Miller MO, Cronkite EP. Radioimmunoassay of erythropoietin: Circulating levels in normal and polycythemic human beings. *J Lab Clin Med* 1982; 99: 624-35.

Graber SE, Krantz SB. Erythropoietin: biology and clinical use. *Hematol/Oncol Clin North Am* 1989; 3: 369-400.

Kalmanti M, Kalmantis T, Liacopoulou T, Tsoumakas K, Ladis V, Kattamis C. Serum erythropoietin in regularly transfused thalassemic patients. *Haematologia Budap* 1991; 24: 129-34.

Klerk G-de, Rosengarten PCJ, Vet RJWM, Goudsmit R. Serum erythropoietin (ESF) titers in anemia. *Blood* 1981; 58: 1164-70.

Manor D, Fibach E, Goldfarb A, Rachmilewitz EA. Erythropoietin activity in the serum of beta thalassemia patients. *Scand J Haematol* 1986; 37: 221-8.

Nisli G, Kavakli K, Aydinok Y, Oztop S, Cetingul N. Serum erythropoietin levels in patients with beta thalassemia major and intermedia. *Pediatr Hematol Oncol* 1997; 14: 161-7.

Penington DG. The role of erythropoietin hormone in anemia. *Lancet* 1961; 1: 301-6.

Weatherall DJ, Clegg JB. The thalassemia syndromes. Oxford: Blackwell Scientific Publication, 1981.