The Korean Journal of Internal Medicine
Vol. 7, No. 2 July 1992

Effect of Periodic Transfusion on Erythropoietin Concentration in End Stage Renal Disease

Sae Yong Hong M.D. and Dong Ho Yang M.D.

Department of Internal Medicine, Soonchunhyang University Chunan Hospital, Chungnam, Korea

Background: *It has been reported that a feedback circuit exists between erythropoietin (EPO) concentration and the degree of anemia even in end stage renal disease (ESRD), and growing experience with subcutaneous EPO administration confirms that only slight increases in EPO levels are required to correct renal anemia. Keeping in mind these findings, if a small portion of reserved EPO production could be reactivated in ESRD, it might be biologically significant and vice-versa. From this viewpoint, it is conceivable that periodic long term transfusion might suppress EPO production in ESRD.*

Methods: *In order to see whether periodic transfusion influences the EPO concentration in ESRD, a cross-sectional retrospective study was undertaken by reviewing medical records of 28 non-transfusion patients and 22 transfusion patients with ESRD undergoing hemodialysis.*

Results: *The EPO concentration of the ESRD group (29.1±8.0 mU/ml) but only about one twentieth of the control group (578.8±69.1 mU/ml). In ESRD group, It was 27.9±8.0 mU/ml in transfusion group and 30.6±7.9 mU/ml in non-transfusion group. EPO concentration at varying hematocrit (Hct) levels did not differ between the non-transfusion group and transfusion group. There was an inverse relationship seen in the non-transfusion group ($p<0.05$) but no relationship was seen between the EPO concentrations and varying Hct levels in the transfusion group. The EPO concentration at equal levels of Hct did not differ between the non-transfusion group and transfusion graup. The relationship between EPO concentration and the changes in Hct during the observation period did not differ between the non-transfusion group and transfusion group. Both the total amount of transfusion and the frequency of transfusions did not influence EPO concentration.*

Conclusion: *periodic long term transfusion does not seem to decrease the sensitivity of the EPO producing cell to the degree of anemia in ESRD.*

Key Words: *Erythropoietin concentration, Endstage renal disease, Periodic transfusion*

INTRODUCTION

The most important factor limiting optimal rehabilitation in ESRD is anemia[1,2] which is an inevitable and serious complication in these patients. The severity of anemia and/or the requiremint of blood transfusion varies among ESRD patients[3]. The primary cause of anemia in ESRD is a deficiency of EPO, a glycoprotein which is nomally produced in the kidney in response to anoxia[4]. In dialysis patients, EPO concentrations are frequently above "normal" but are still very low when compared to control group with the same degree of anemia[4]. Despite their inability to respond to chronic anemia with a sustained increase in serum EPO, between the EPO concentration and the degree of anemia, there is feedback circuit[5], and uremic patients have been reported to produce substantial amounts of EPO upon acute reductions in oxygen saturation[6,7]. These findings suggest that the diseased kidney, seen in patients with

Address reprint requests to: Sae Yong Hong M.D., Department of Internal Medicine, Soonchunhyang Hospital, 23-20 Bongmyangdong Chungnam, 330-100, Korea

ESRD, retain the ability to produce substantial amounts of EPO in certain clinical situations and that transfusion should suppress the EPO production. Recently, growing exprience with subcutaneous EPO administration confirms that, in many ESRD patients, only slight increases in EPO levels are required to correct anemia [8~10]. These reports suggest that even a minimal change in EPO concentration has biological significance in ESRD. These reports prompted us to assess the effect of periodic, long term transfusion on EPO concentration in ESRD.

MATERIALS AND METHODS

A cross-sectional retrospective study was undertaken by reviewing medical records of fifty patients with ESRD who were maintained on chronic hemodialysis at Soonchunhyang University Chunan Hospital, Korea. The control group consisted of seven non-renal origin chronic anemia patients with same degree of anemia (control group Hct : 23.1±3.4%, vs ESRD : 21.5±4.1%). The clinical profiles and the underlying disease of the control group is presented in table 1. Blood transfusion was recommended for the ESRD patients whose Hct fell below 18% on routine monthly CBC check. Some patients who refused blood transfusion, due to financial problems or fear of contracting an infectious disease, were assigned to the non-transfusion group. The transfusion group was given two pints of packed RBC's. The interval between transfusions was every 2 months in 14 cases, every 3 months in 6 cases and every 4 months in 4 cases. Blood samples for EPO and hematocrit were obtained in the pre-dialysis state (two or three days after postdialysis). The average weight gain between dialysis sessions was 3-4 Kg. The time interval between blood sampling for EPO and the transfusion was more than one month in all cases. The underlying diseases, Hct, distribution of age and sex and hemodialysis duration of the ESRD patients, divided into the transfusion group and nontransfusion group, are presented in tables 2, 3, 4. Normal pooled serum was collected from 10 healthy adults (male:5, female:5), ages between 30-50 years. Underlying diseases of the ESRD patients were chronic glomerulonephritis in 29 cases (male:11, female: 18), diabetes mellitus in 6 cases (male:4, female:2), poiycystic kidney disease in 2 cases (male:1, female:1) and hypertension or unknown (ill defined or overlap) in 13 cases (male:7, female : 6). Twenty-three cases were hypertensive and antihypertensive medication included a combination of atenolone, captopril, minoxidil and lasix. Duration of hemodialysis was ; 6-24 months in 9 cases of the transfusion group and 13 cases of the non-transfusion group,; 49-72 months in 3 cases of the transfusion group, 7 cases of the non-transfusion group,; 73-92 months in 2 cases of the transfusion group, 1 case of the non-transfusion group. All of the ESRD patients were dialyzed with a cellulose hollow-fiber dialyzer two or three times per week. Folate and vitamin B and C were routinely prescribed for the hemodialysis patients. Iron was given to the patients on the basis of serum iron (80-100 μg/dl) and total iron binding capacity (250-300 μg/ml).

Erythropoietin antigen: Commercially available enzyme-linked immunosorbent assay kit (AMGEN Diagnostics. CLINIGEN erythropoietin EIA Kit, Thousand Oaks, CA) was used to determine EPO. This ELISA is based on the double antibody principle, using one monoclnal and one polyclonal antibodies.

STATISTICS

A comparison of EPO, depending on the duration of hemodialysis and hematocrit level, between the transfusion group and non-transfusion group was tested by using the Mann-whitney U test, and the relation between EPO and variables was tested by regression. Statistical significance was considered to be present if $p<0.05$.

RESULTS

Fig. 1 A, B show the frequency of distribution for Hct at the beginning and at the end of the observation period in ESRD. The EPO concentration was 12 mU/ml in the normal pooled serum, 578.8±69.1 mU/ml (range; 497.4 -718.8 mU/ml) in the control group and 29.1±8.0 mU/ml (n=50. range 10.9-46.5 mU/ml) for ESRD patients. It was 27.9±8.0 mU/ml in transfusion group and 30.6±7.9 mU/ml in non-transfusion group (Fig. 2,3, Table 2). The EPO concentration for Hct levels between 15.0-20.0% was 30.4±8.2 mU/ml (n=16) in the transfusion group, 32.5±4.0 mU/ml (n=10) in the non-transfusion group; Hct levels between 20.1-25.0 was 31.3±7.7 mU/ml in the transfusion group, 25.7±9.1 mU/ml (n=12) in the non-

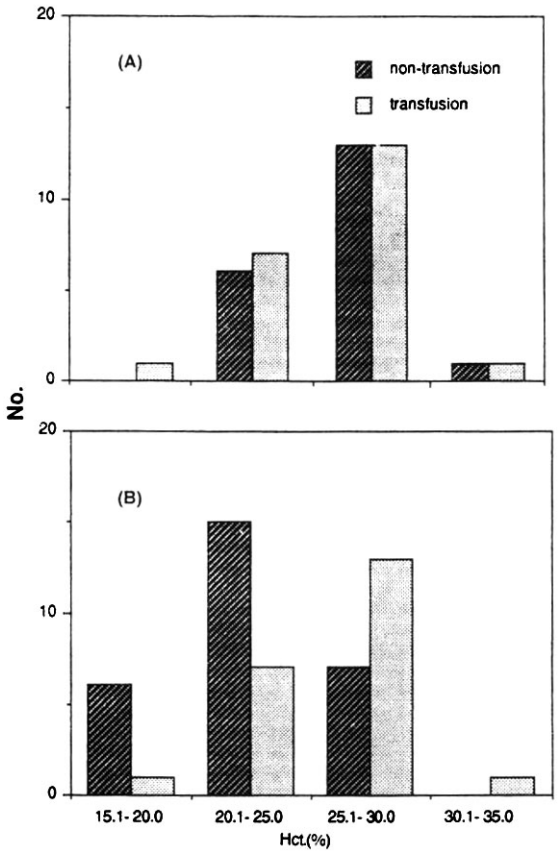

Fig. 1. Frequency distribution of Hct at the beginning (A) and at the end (B) of the observation period in ESRD patients. At the beginning, Hct was commonly between 25.0~35.0% in both transfusion group and non-transfusion group but, at the end of the observation period, it was commonly between 20.1~25.0% in non-transfusion group and between 25.1~35.0% in transfusion group.

transfusion group; and Hct level between 25.1-35 was 24.5±8.0 mU/ml (n=7) in the non-transfusion group (Fig. 4). The EPO concentration, depending on the duration of hemodialysis, is

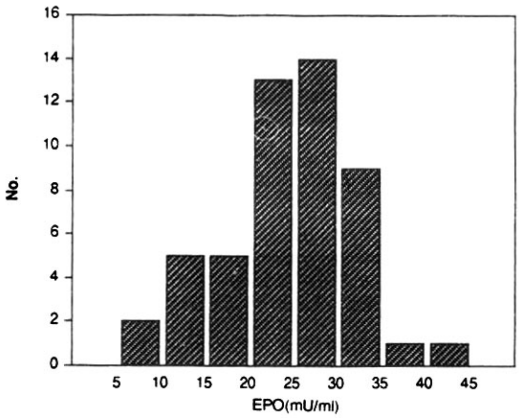

Fig. 2. Frequency distribution of the EPO concentrations in ESRD patients.

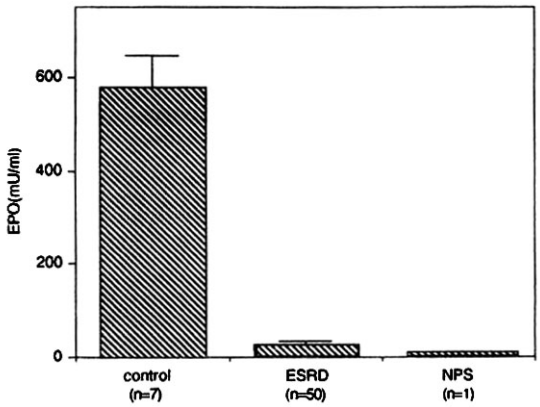

Fig. 3. EPO concentration in the control group, ESRD patients and nomal pooled serum (NPS).

Table 1. Clinical Profiles of the Control Group (non-renal origin anemia patients)

Case	Sex/Age (yrs)	Hb/Hct (gm%/%)	S. Iron/TIBC (ug%/ug%)	Underlying disease	EPO (mU/ml)
1.	F/34	8.3/28	25/500	vaginal bleeding	497.4
2.	M/58	5.8/20.2	50/400	UGI bleeding	588.6
3.	F/80	5.2/19.3	27/530	pernicious anemia	540.6
4.	M/48	6.1/20.4	120/480	L.C., varix rupture	718.8
5.	F/49	6.4/26.1	62/550	vaginal bleeding	576.0
6.	M/60	7.7/22.1	60/580	UGI bleeding	550.2
7.	F/62	8.0/25.0	70/450	UGI bleeding	580.0

TIBC: total iron binding capacity

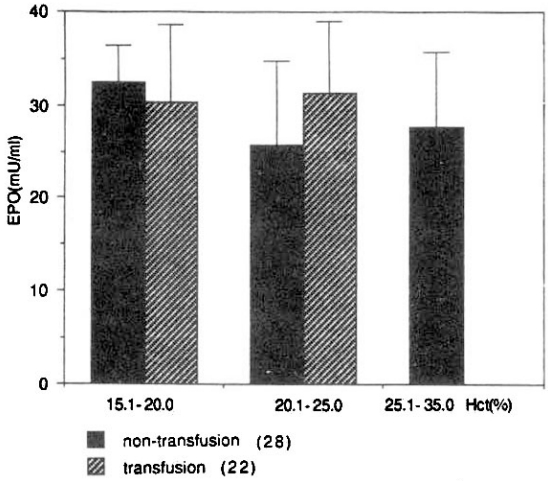

Fig. 4. The changes in EPO concentration according to the Hct levels in the transfusion group and non-transfusion group. There was no difference between the transfusion group and the non-transfusion group in each of Hct.

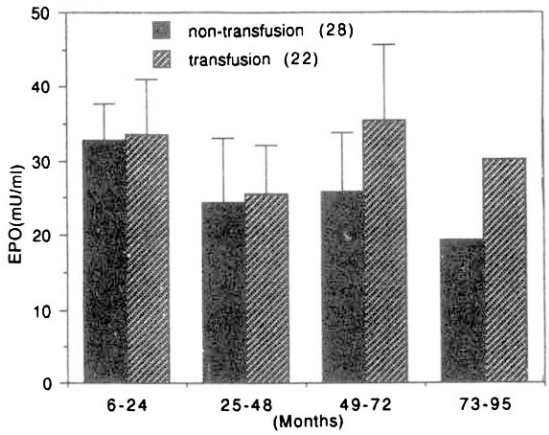

Fig. 5. EPO concentration according to the duration of hemodialysis in the transfusion group and non-transfusion group. The duration of hemodialysis (months) is pressented in absicssa. There was no difference between the transfusion group and the non-transfusion group in the duration of hemodialysis.

Table 2. Age and Sex Distribution of the Transfusion and Non-transfusion Group

Group	Age (years)	Sex M/F	Total number	EPO (mU/ml)
transfusion	46.7±13.0	10/12	22	27.9±8.0
non-transfusion	46.7±12.7	13/15	28	30.6±7.9

Table 3. Underlying Diseases of the Transfusion and Non-transfusion Group

disease	EPO (mU/ml), Mena±SD(number of cases) transfusion group	non-transfusion group
CGN	28.5±6.0 (12)	26.7±9.0 (17)
DM	27.7±9.3 (3)	29.6±2.2(3)
cystic DZ	0	33.5±1.7(2)
other	35.4±9.1 (7)	28.5±8.5 (6)

CGN: Chronic Glomerulonephritis
DM: Diabetes Mellitus

Table 4. Distribution of Hematocrit Values in the Transfusion and Non-transfusion Group

Hematocrit (%)	EPO(mU/ml), mean±SD (number of cases) transfusion group	non-transfusion group
15.0-20.0	30.4±8.1 (16)	32.5±4.0 (10)
20.1-25.0	31.3±7.7 (6)	25.7±9.0 (12)
25.1-35.0	(0)	24.5±8.3(6)

presented in Fig. 5. EPO concentrations according to the Hct levels did not differ between the non-transfusion group and transfusion group. The EPO concentration and Hct showed no relationship in the transfusion group ($p=0.37$) (Fig. 6-A) but showed a reverse correlation in the non-transfusion group ($p<0.05$) (Fig. 6-B). During the observation period, Hct increased in 7 cases and decreased in 15 cases of transfusion group. In 13 cases during the observation period. There was no difference of EPO concentration between increased group and decreased group in both transfusion group and non-transfusion group (Fig. 7-A, B). Both the total amount of transfusion and the frequency of transfusions did not influence EPO concentration (Fig. 8-A, B).

DISCUSSION

Since damage to the kidney in ESRD is usually associated with a dramatic decrease in renal cell mass, it is generally assumed that the destruction of renal EPO producing cells leads to inappropriately low EPO production[9]. It is not clear whether the degree of EPO production cell loss is uniform in ESRD. But the renal function, measured by creatinine clearance, fell under the 10% range of

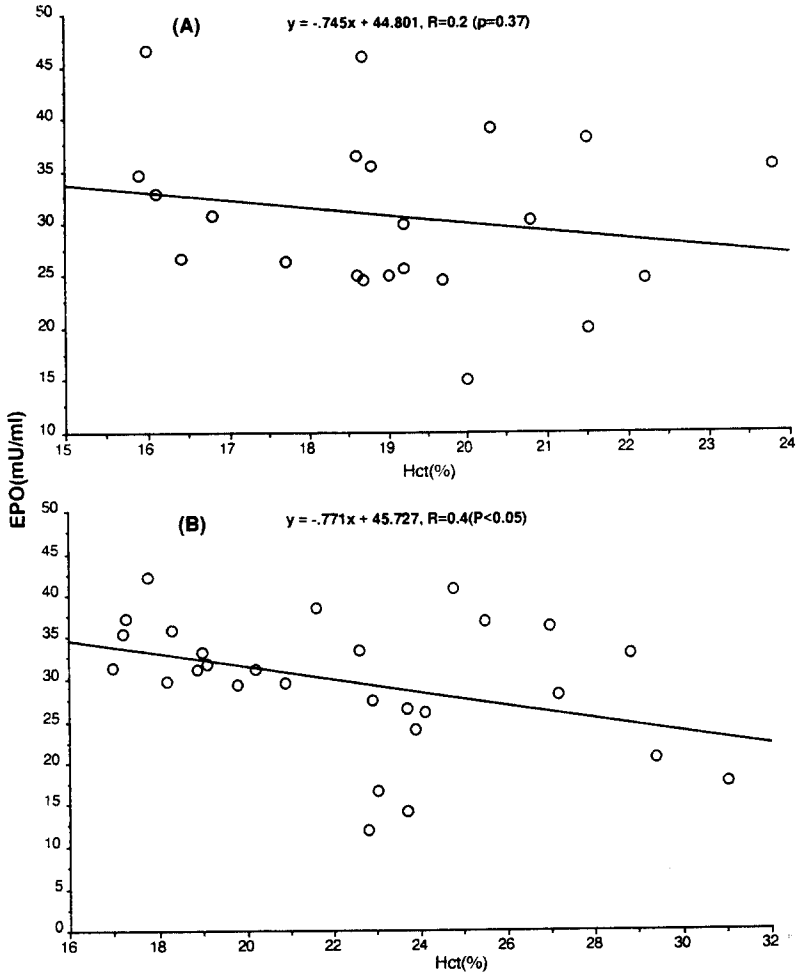

Fig. 6. Relationship between EPO concentration and Hct in the transfusion group (6-A) and the non-transfusion group (6-B). There is no correlation between Hct and EPO concentration in the transfusion group but there is reverse correlation in the non-transfusion group ($p<0.05$).

healthy persons and the kidney size decreased markedly in all the patients, and our study was performed on the assumption that individual variance of remnant renal function was negligible. The EPO concetration of the ESRD group was only about one twentieth of the control group but twice that of normal pooled serum. Recently, growing experience with subcutaneous EPO administration in ESRD patients confirms that in many patients only slight increases in EPO levels are required to correct renal anemia[8~10]. Keeping in mind this experience, if a small portion of reserved EPO production could be reactivated, it might be biologically significant. It has been reported that a feedback circuit exists between EPO concentration and the degree of anemia in ESRD and the EPO concentration increases or decreases within several hours after blood loss or transfusion[5]. In addition, uremic patients have been reported to produce substantial amonunts of EPO when exposed to acute reductions in oxygen saturation or acute hypoxic stress, such as pulmonary edema, acute hemolysis, heart failure and hypotension from sepsis[11~13]. From this viewpoint, it is

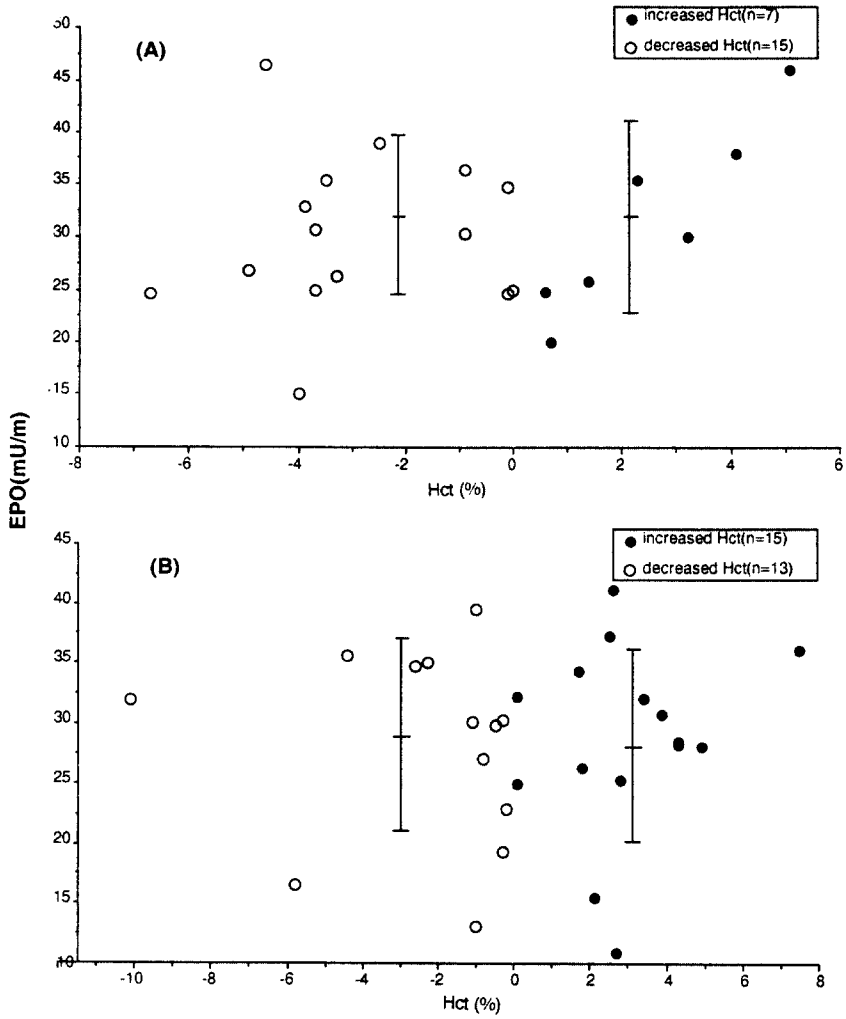

Fig. 7. The relationship of EPO concentration to the changes in Hct during the observation period in the transfusion group (A) and the non-transfusion group (B). In transfusion group, Hct increased in 7 cases and decreased in 15 cases. In non-transfusion group, Hct increased in 15 cases and decreased in 13 cases. There was no difference of EPO concentration between increased group and decreased group in both transfusion group and non-transfusion group.

conceivable periodic long term transfusion might suppress EPO production in ESRD. Because the EPO concentrations were measured more than one month after the preceding transfusion, in our study, the effect of the transfusion may have ceased to exist at the time of EPO measurement. But considering that the adaptation of EPO producing cell to chronic hypoxia is a very important factor for decreased EPO production in ESRD[8], we can still question whether or not periodic long term transfusion changes renal oxygen sensor function. Our results showed that there is no difference in EPO concentration between the transfusion group and non-transfusion group. And, in the transfusion group, the EPO concentration was not related to either the total amonunt of

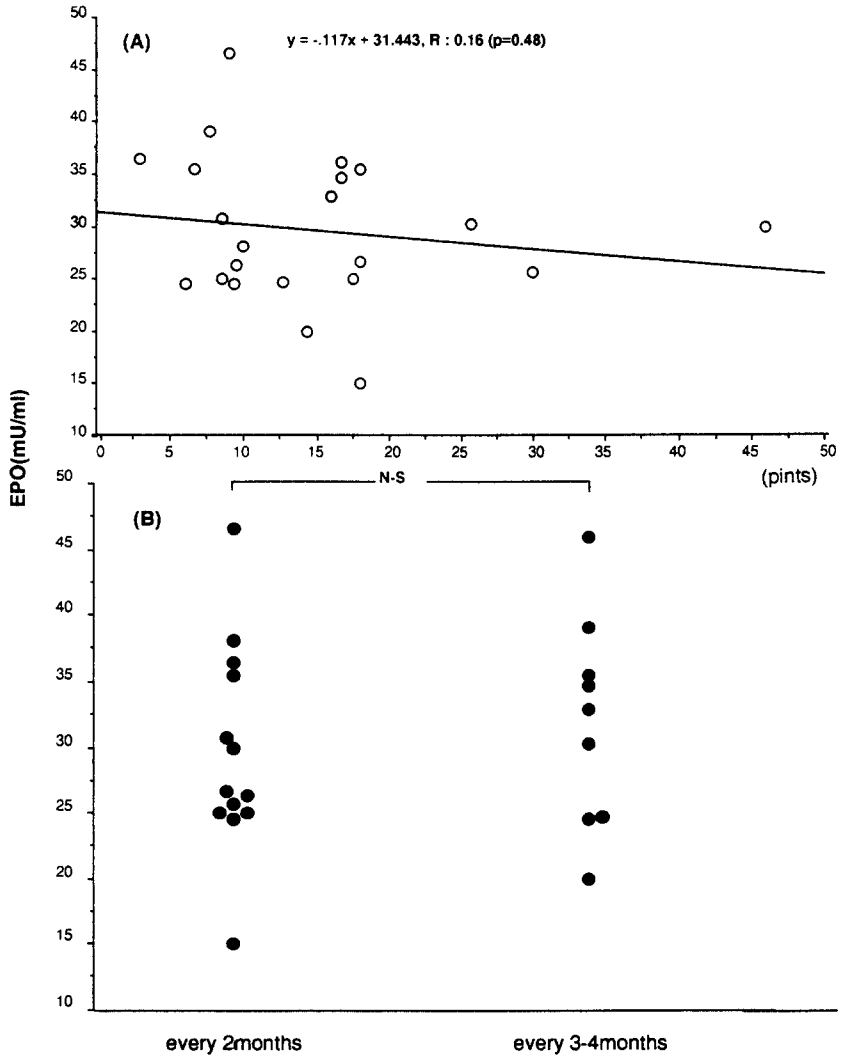

Fig. 8. The effect of the total amount of transfusion (pints) (8-A) and the frequency of transfusion (8-B) on EPO concentration. There is no difference of EPO concentration in both the total amount of transfusion and the frequency of transfusion.

transfusion or the frequency of transfusion. In conclusion, periodic long term transfusion does not seem to decrease the sensitivity of EPO production to the degree of anemia in ESRD.

REFERENCES

1. Eschbach JW, Adamson JW, Cook JD: *Disorders of red cell production in uremia. Arch Intern Med 126:812, 1970*
2. Fried W: *Hematologic abnormalties in chronic renal failure. seminars in nephrology 1:176, 1981*
3. Kokko J: *Chronic renal failure : In Wyngaarden JB, Smith LH (eds) Cecil textbook of medicine, 18 th edition, p563. W.B Saunder Co, Philadelphia, 1988*
4. Blumberg A, Keller H, Marti HR: *Effect of altitude*

on erythropoiesis and oxygen affinity in anemic patients on maintenance hemodialysis. Eur J Clin Invest 3:93, 1973

5. Walle AJ, Wong GY, Clemons GK, Garcia JF, Niedermayer W: *Erythropoietin-hematocrit circuit in the anemia of end-stage renal disease. Kidney Int 31:1205, 1987*
6. Chandra M, Clemons GK, McVicar MI: *Relation of serum erythropoietin levels to renal excretory function: Evidence for lowered set point for erythropoietin production in chronic renal failure. J Pediatr 13:1015, 1988*
7) Eckardt KU, Drueke T, Leski M, Kurtz A: *Unutilized reserves: The production capacity for erthropoietin appears to be conserved in chronic renal disease. In Gurland HJ, Moran J, Samtleben W, Scigalla P, wieczorek L (eds) p18: Erythropoietin in renal and non-renal anemia. Contrib Nephrol. Basel, Karger 1991*
8) Victoria SL, Richard LD, Donald Z, Peter TK, Robert A, Paul P, Jerry F: *Recombinant human erythropoietin treatment in pre-dialysis patients. Ann Internal Med 110:108, 1989*
9) Lui SF, Chung WWM, Leung CB, Chan K, Lai KN: *Pharmacokinetics and ,pharmacodynamics of subctaneous and intraperitoneal administration of recombinant human erythropoietin in patients on continuous ambulatory peritoneal dialysis. Clin Nephrol 33:47, 1990*
10) Besarab A: *Recombinant human erythorpoietin: Physiology, pathophysiology of anemia in renal failure and economic aspects related to dosing. Am J Nephrol 10 (Suppl): 2, 1990*
11) Eckardt KU, Kurtz A, Bauer C: *Regulation of erythropoietin formation is related to proximal tubular function. Am J Physiol 256:942, 1989*
12) Eckardt KU, Kurtz A, Bauer C: *Triggering of erythropoietin production by hypoxia is inhibited by respiratory and metabolic acidosis. Am J Physiol 258:678, 1990*
13) Schuster S, Wilson JH, Erslev AJ, Caro J: *Physiologic regulation and tissue localization of renal erythropoietin messenger RNA. Blood 70: 316, 1988*