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Relationship Between Erythropoiesis-Stimulating Agent Usage and Hemoglobin Variability in Hemodialysis Patients

Hemodiyaliz Hastalarında Eritropoezi Uyarıcı Ajan Kullanım ile Hemoglobin Değişkenliği Arasındaki İlişki

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ABSTRACT

OBJECTIVE: Anemia is a common problem in chronic renal failure. Recent studies have shown that there is a close relationship between fluctuations in hemoglobin values and increased mortality. Therefore, treatment of anemia and providing stable hemoglobin (Hb) levels with erythropoiesis-stimulating agent (ESA) is important in the management of chronic renal failure. Hence, ESA usage and relationship between ESA type and Hb variability were investigated in hemodialysis patients.

MATERIAL and METHODS: 130 patients treated at a hemodialysis center were monitored monthly for one year. The mean age was 60±7 years, mean weight was 72±13 kg, and mean dialysis duration was 5 ±2 years (F/M: 64/66). Hb stability was defined as continuous ESA usage at maintenance dosage and Hb levels being at the target level (Hb≥11g/dl) for last 12 months. Hb variability and ESA dose change was accepted as decrease of Hb levels under 11 g/dl during maintenance dosage use and increasing ESA to starting dosage.

In our study, annual mean values of monthly prescribed ESA rates, types of ESA and weekly dosages, and changes in ESA dosages due to monthly changes in hemoglobin (Hb) levels were examined. The relation between ESA type and Hb variability was investigated.

RESULTS: During a one-year period, the number of patients who did not use ESA (Hb levels always >12 g/dl) was 5 (%3.8) and the number of patients who used ESA for different periods was 125 (%96.2). The mean number of patients using ESA monthly was 71 (57%). 32 (45%) patients used short acting, 31 (44%) used medium acting (darbepoetin) and 8 (11%) used long acting ESA (methoxy polyethylene glycol-epoetin beta). 26 patients (21%) used ESA at the starting dose and 45 (36%) at the maintenance dose. One third of the 71 patients (36.6%) were using ESA at the starting dose and two thirds (63.4%) were on the maintenance dose. Mean weekly short acting ESA dose was 9666±2376 IU in the starting dose group and 5400±1142 IU in the maintenance group. Mean weekly darbepoetin dose was 46.6±10,3 mcg in the starting dose group and 26.4±4,9 mcg in the maintenance group. There were no Hb changes in 33 patients (26.4%) but 92 (73.6%) had Hb variability during one year. During one year, the Hb level dropped under 11 g/dl once in 32 patients (35%), twice in 39 patients (42%), three times in 16 patients (17%) and four times in 5 (6%) patients and the ESA dose was increased to the starting dose. Number of monthly Hb changes was higher in the short acting ESA than the medium and long acting ESA groups.

CONCLUSION: Our results revealed that monthly ESA usage rate and weekly ESA dosage were lower than in western countries. During the one year period, there was Hb variability in three in four of the patients and ESA dosages were changed. The number of monthly Hb variability cases was found to be lower in the medium and long acting ESA groups. The most important reason of Hb variability was monthly dose change or discontinuation of ESA, due to the limits in the application of ESA.

KEY WORDS: Hemodialysis, ESA usage, Hb variability

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ÖZ

AMAÇ: Anemi, kronik böbrek yetmezliğinde yaygın bir sorundur. Yakın zamanda yapılan çalışmalar, hemoglobin değişimleri ile artmış mortalite arasında yakın bir ilişki olduğunu göstermiştir. Bu nedenle, anemi tedavisi ve eritropoezi uyarıcı ajanlar (ESA) ile dengeli hemoglobin (Hb) seviyeleri sağlamak, kronik böbrek yetmezliği tedavisinde önemlidir. Bundan dolayı; hemodiyaliz hastalarında ESA kullanımı ve ESA tipi ile Hb değişkenliği arasındaki ilişki araştırıldı.

GEREÇ ve YÖNTEMLER: Bir hemodiyaliz merkezinde tedavi edilen 130 hasta aylık olarak bir yıl boyunca izlendi. Ortalama yaş 60 ± 7, ağırlık 72 ± 13 kg ve diyaliz süresi 5 ± 2 yıl (F/ M:64/66) idi. Hb stabilitesi, idame dozunda sürekli ESA kullanımı ve son 12 ay boyunca Hb seviyeleri hedef seviyede (Hb ≥11g/dl) olarak tanımlandı. Hb değişkenliği ve ESA doz değişikliği ise, idame doz kullanımı esnasında Hb düzeylerinin 11 g / dl'nin altına düşmesi ve başlangıç dozuna ESA'nın arttırılması olarak kabul edildi.

Çalışmamızda, aylık reçete edilen ESA dozlarının yıllık ortalama değerleri, ESA tipi ve haftalık dozlar ve aylık olarak hemoglobin (Hb) düzeylerindeki değişiklikler nedeniyle ESA dozlarındaki değişiklikler incelendi. ESA tipi ve Hb değişkenliği arasındaki ilişki araştırıldı.

BULGULAR: Bir yıllık dönemde, ESA kullanmayan (Hb düzeyi> 12 g / dl) hasta sayısı 5 (%3,8) ve farklı dönemlerde ESA kullanan hasta sayısı 125 (%96,2) olarak saptandı. Aylık ESA kullanan ortalama hasta sayısı 71 (%57) iken, 32 (%45) hastada kısa etkili, 31 (%44) hastada orta etkili (darbepoetin) ve 8 hastada (%11) uzun etkili ESA (metoksi polietilen glikol-epoetin beta) kullanıldı. 26 (%21) hastada başlangıç dozunda ESA kullanırken 45 (%36) hastada idame dozda kullanıldı. Aylık ESA kullanan 71 hastanın yaklaşık üçte biri (%36,6) başlangıç dozunda üçte ikisi (%63,4) ise idame dozunda ESA kullanıyordu. Ortalama haftalık kısa etkili ESA dozu; başlangıç dozu grubunda 9666 ± 2376 IU, idame grubunda ise 5400 ± 1142 IU bulundu. Ortalama haftalık darbepoetin dozu ise başlangıç dozu grubunda 46.6 ± 10.3 mcg iken idame grubunda 26,4 ± 4,9 mcg bulundu. 33 hastada (%26,4) Hb değişikliği gözlenmezken 92 hastada (%73,6) bir yıl boyunca Hb değişkenliği saptandı. Bir yıl boyunca 32 hastada (%35) Hb 11 g/dl'nin altına düşerken, 39 hastada (%42) iki kez, 16 hastada (%17) üç kez ve 5 hastada (%6) dört kez düşüş gözlendi ve ESA dozu tekrar başlangıç dozuna yükseltildi. Kısa etkili ESA kullanan grupta aylık Hb değişikliklerinin sayısı, orta ve uzun etkili ESA gruplarına göre daha yüksekti.

SONUÇ: Bulgularımız aylık ESA kullanım oranımızın ve haftalık kullanılan ESA dozunun batı ülkelerinden daha düşük olduğunu ortaya koymuştur. Bir yıllık dönemde, dört hastanın üçünde Hb değişkenliği gözlendi ve ESA dozları değiştirildi. Orta ve uzun etkili ESA kullanılan gruplarda aylık Hb değişkenlik olgularının sayısı daha düşük olduğu saptandı. Hb değişkenliğinin en önemli nedeni ise; ESA uygulamasında ki sınırlamalar nedeniyle aylık doz değişikliği veya ESA kullanımının bırakılmasıdır.

ANAHTAR SÖZCÜKLER: Hemodiyaliz, ESA kullanımı, Hb değişkenliği

INTRODUCTION

Anemia, which is associated with the grade of renal dysfunction, is a common complication in chronic renal failure. Bone marrow suppression (erythropoietin failure, inflammatory cytokines), iron deficiency, and hemodilution play a role in the etiology (1). According to clinical trials, when anemia is corrected, physiological features and quality of life will improve. At the same time, higher hematocrit and hemoglobin levels are associated with lower mortality and higher quality of care (2). Therefore, correcting the anemia and providing stabilized hemoglobin levels with the erythropoiesis-stimulating agent (ESA) is important in the management of the chronic renal failure (3).

Target hemoglobin values were determined to be 10-11.5 g/dl in the guidelines of Kıdney Disease Improving Global Outcomes (KDIGO) (4). The European Renal Best Practice guideline recommends the use of ESA therapy in chronic renal patients with an Hb value of 10-12 g/dl while avoidance of values above 13 g/dl is recommended because of poor clinical outcome (5).

ESA is a drug that increases the availability of plasma erythropoietin in the plasma shortly and temporarily. A steady increase in hemoglobin values is seen with the use of ESA (6). In our country, ESA is used for anemia treatment in approximately 60% of chronic hemodialysis patients according to the Turkish Society of Nephrology (TSN) 2012 records. ESA's utilization rate and dose may vary among centers. Hemoglobin variability is defined as hemoglobin fluctuation above or below the target (7).

In 2003, Lacson et al found that only approximately 38% had hemoglobin levels within the range of 11 to 12 g/dl in >65,000 dialysis patients. In addition; despite a mean hemoglobin level of 11.5 g/dl, the patients had a ±1.4 g/dl fluctuation in hemoglobin during the course of 1 year on the basis of 3-month rolling average values (8). Recent studies have shown that monthly fluctuations in hemoglobin levels are associated with increased mortality (9-11).

In our study, annual mean values of monthly prescribed ESA rates, types of ESA and weekly dosages, and changes in ESA dosages due to monthly changes in hemoglobin (Hb) levels were examined. The relation between the ESA type and Hb variability was investigated.

METHODS

This observational study was performed in 130 patients who were treated at a hemodialysis center. Hb, albumin, urea, creatinine and Kt/V values were analyzed monthly. In addition, CRP, PTH and ferritin levels were measured every three months and a yearly average of these values was taken. Blood samples were taken before the first dialysis of the week.

Patients with a cancer diagnosis, blood transfusion and major bleeding episodes were excluded. Iron therapy was administered according to the patient's serum transferrin saturation and serum ferritin level.

Hb stability was defined as ESA continuous usage at maintenance dosage (Erythropoietin alpha-beta-zeta 75 U/kg/week, darbepoetin 0.75 mcg/kg/week, methoxypolyethylene glycol epoetin beta 0.94 mcg/kg) and Hb levels being at the target level (Hb≥11 g/dl) for the last 12 months. Hb variability and ESA dose change was accepted as decrease of Hb levels under 11 g/dl during maintenance dosage use and increasing ESA to the starting dosage (Erythropoietin alpha-beta-zeta 150 U/kg/week, darbepoetin 0.35 mcg/kg/week, methoxypolyethylene glycol epoetin beta 1.88 mcg/kg). ESA treatment was prescribed according to criteria (150 U/kg/week if less than 11 g/dl and 75 U/kg/week if 11 to 12 g/dl) in the government refund criteria.

Statistical Analysis

The statistical analysis was carried out using the Statistical Package for Social Sciences for Windows ver. 17.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as the mean±SD, with a significance level of $P<0.05$. For dichotomous variables, the frequency of positive occurrences were given along with their corresponding percentages. Statistical comparisons of individual groups were based on Student's t-test for continuous variables whereas the correlations between groups were evaluated by chi-square test.

Table I: Mean laboratory values of patients.

Hemoglobin (g/dl)	11.8±1.2 (8.8-16)
Albumin (g/dl)	3.8±0.3 (3.1-4.7)
Kt/V	1.54±0.25 (0.87-2.32)
CRP (mg/dl)	2.21±7.1 (0-34)
PTH (pg/ml)	179±192 (3-1124)

RESULTS

The mean age was 60±7 years, mean weight was 72±13 kg, and mean dialysis duration was 5 ±2 years for the 130 (F/M: 64/66) patients. 59 patients (45%) were diabetic. The average laboratory values of the patients who participated in the study are shown in Table I.

The number of patients who did not use ESA for 1 year (Hb values> 12 g/dl) was 5 (3.8%) and the number of patients who used ESA for various periods was 125 (96.2%). In a month, the average number of patients using ESA was 71 (57%). In addition, 26 patients (%21) used an initial dose of ESA and 45 patients (%36) used a maintenance dose of ESA (Table II).

On average, short-acting ESA was used in 32 patients (45%), moderate-acting ESA (darbepoetin) was used in 31 patients (44%) and long-acting ESA (methoxy polyethylene glycol-epoetin beta) was used in 8 patients (11%) monthly. The mean weekly ESA doses are shown in Table III.

There was no significant difference between, male and female and diabetic and nondiabetic patients according to the weekly ESA dose ($p> 0.05$). There was no difference in albumin or Kt/V between all three groups when patients who used initial or maintenance dose of ESA and patients who did not use ESA were compared in terms of laboratory tests. Although the mean PTH values were higher in the initial dose of ESA group than the other two groups, no statistically significant difference was found. However, the mean CRP level was significantly higher in the two groups using ESA than in the non-treated group ($p<0.05$), (Table II).

Hb variability was observed in 92 patients (73.6%) during the year. The ratio of patients who had Hb variability and the number of monthly variability episodes were higher in patients

Table II: ESA usage rate (average of 12 months) and laboratory results of patients who using initial or maintanance dose of ESA and not using ESA.

	Initial dose (n=26)	**Maintanance dose (n=45)**	**Not using (n=54)**
Hb (g/dl)	10.4±0.7	11.5±0.3	12.8±0.9
Albumin (g/dl)	3.82±0.2	3.85±0.3	3.88±0.3
Kt/V	1.55±0.23	1.6±0.34	1.50±0.22
CRP (mg/dl)	2.82±6.0	2.25±4.2	1.02±1.1
PTH (pg/ml)	190±180	182±227	150±139

Table III: ESA doses in patients who using initial or maintanance doses of ESA.

	Short-acting ESA	Darbepoetin	mPEG-Epoetin beta
ESA Dose	**Weekly total dose**	**Weekly total dose**	**Monthly total dose**
Initial	9666±2376	46.6±10.3	150±0
Maintanance	5400±1142	26.4±4.9	124±25
ESA Dose	**U/kg/week**	**mcg/kg/week**	**mcg/kg/month**
Initial	139±24	0.70±0.09	0.90±0.22
Maintanance	75.7±12	0.34±0.05	1.80±0.16

Table IV: The number of variability in 92 patients with Hb variability and the effect of ESA type.

Number of variability (12 months)	Short-acting ESA (n=56)	Medium-long-acting ESA ESA (n=36)	Total (%)
1 time	14	18	32 (35%)
2 times	25	14	39 (42%)
3 times	12	4	16 (17%)
4 times	5	0	5 (6%)
Total	56 (61%)	36 (39%)	p<0.05

who were using short-acting ESA. During the year, while using medium-long-acting ESA, the ratio of patients with only one time Hb variability was higher. In addition, the ratio of patients with 2 or more monthly Hb/ESA dose variability events was higher when using short-acting ESA (Table IV).

DISCUSSION

The main findings of this study were as follows: ESA usage was lower in our country than western countries in hemodialysis patients and the number of monthly Hb variability was higher with short acting ESA.

Treatment of anemia and providing stable hemoglobin (Hb) levels with erythropoiesis-stimulating agent (ESA) is important in the management of chronic renal failure. When compared with western countries, the ratio of ESA usage and dose was very low in our country. In the DOPPS study, the rate of patients using ESA was 89%, however the rate in our country was 60.4% according to TSN-2012 records. In our study, similar to the TSN records, the monthly mean ESA usage was 57% (Table II). Approximately two-thirds of the patients used ESA in maintenance dose. In addition, in our study, ESA doses were approximately half of the doses used in the DOPPS study (12).

Hemoglobin variability is the fluctuation of hemoglobin above or below the target range over time and there has been a close relationship between fluctuations in hemoglobin values and increased mortality (9-11).

In a study by Fishbane and Berns, the variation of hemoglobin levels in 281 hemodialysis patients who were treated with epoetin was investigated. Hemoglobin cycling, repeated up-and-down undulations of hemoglobin levels, was found in >90% of the patients. More than three ESA dose changes were made in 85% of patients and ESA dose change was responsible for 80% of Hb variability (13).

In another analysis by Ebben et al., 90% of the patients showed fluctuation in the Hb level. The hemoglobin level is stable in only 10% of the patients and only 6.5% of patients were found to meet the target continuously (11-12.5 g/dl). A wide fluctuation pattern (above and below of target) was observed in approximately 40% of the patients during a 6-month period (9).

Although there are studies showing that Hb variability in hemodialysis patients is not an independent risk factor for mortality increase (14), in a six-month observational study conducted by Gilbert and Eben, the mortality rate was found to be approximately 2-fold higher in patients who were below the target level of Hb than in the group meeting the target (10). In addition; Yang and Ismani's study showed that hemoglobin variability was associated with increased mortality (11). In our study, Hb variability was observed in 92 patients (73.6%) during the year and two or more variabilities were detected in 65% of our patients with Hb variability.

Hb variability can depend on many factors. Factors such as iron therapy, heparinization and bleeding, the time the blood

was drawn, infection, malignancy, heart failure, age, sex, fluid status, reimbursement and frequency or dosing of ESA are responsible for hemoglobin variability (7). In addition, the dose of ESA is also affected by conditions such as dialysis adequacy, nutritional status, hyperparathyroidism and inflammation (15).

In a study by Fishbane et al., it was shown that problems such as pneumonia, catheter obstruction, gastrointestinal bleeding, etc., made it difficult to keep hemoglobin at target values and that treatment costs were increased (13). In our study, there was no difference in Kt/V or albumin in the groups using initial and maintenance dose of ESA. PTH values were higher in the high dose ESA using group compared to the other two groups, but no statistically significant difference was found. In addition, the mean CRP level was significantly higher in both groups using ESA than in the group not using ESA ($p<0.05$), (Table II).

ESA dose changes are the most important cause of Hb variability and are dependent on the monthly dose change or ESA discontinuation due to the limitations of ESA administration. Long dosing intervals cause less peaks or falls in hemoglobin levels at a certain time. Fewer dose adjustments in this way can provide a more stable trend of hemoglobin (7). In our study; Hb variability and the number of variability events were less with mid-long-term ESA and this finding can be explained with this hypothesis.

Our study has several limitations. First, the sample size was relatively small in our study. Second, all of the patients enrolled in the study were Turkish. One should consider that our results cannot therefore be applied to all patients because of the differences between nationalities. Finally, therapeutic interventions and medical treatments were not evaluated in the present study.

In conclusion, monthly ESA usage rate and weekly ESA doses in our country were observed to be lower than in western countries. In addition, the number of patients with Hb variability and the number of monthly variability in Hb were found to be lower with medium and long-acting ESA. However, the most important reason of Hb variability was the monthly dose change or discontinuation of ESA, due to the limits in the application of ESA.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest

The authors declare no conflict of interest.

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