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Original

Hemoglobin Variability in Patients on Hemodialysis: Comparison Between Epoetin Beta and Darbepoetin Alfa Therapy

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Background: Treatment with erythropoietic-stimulating agents (ESA) exerts effects quite different from biologic erythropoietic processes; treatment involves short, intermittent, non-physiologic bursts of plasma erythropoietin availability. A recent study revealed that repeated, cyclical, up-and-down movements of hemoglobin levels are a common occurrence during ESA treatment in patients on hemodialysis. We attempted to determine whether the variations in hemoglobin levels differed between patients treated with epoetin Beta (EPO) and those treated with darbepoetin Alfa (DPO). **Methods:** Twenty-five patients on hemodialysis who were switched from EPO to DPO in July 2007 were enrolled in this study. We investigated 24 sets of data from July 2006 to June 2007 obtained while the patients were treated with EPO and 24 sets of data from October 2007 to September 2008 when they were treated with DPO. We excluded the first 3 months after the ESA switch from the observation period, because hemoglobin values could change with switch of the type of ESA itself. The change in the hemoglobin values were compared between the EPO treatment period and DPO treatment period. **Results:** There was no difference in the mean hemoglobin value (10.0 ± 0.4 g/dl, 10.0 ± 0.4 g/dl, respectively) and hemoglobin variability (6.4 ± 2.1, 7.1 ± 1.6, respectively) between the period of treatment with EPO and that of treatment with DPO. **Conclusion:** There were no significant differences in the hemoglobin variability induced between EPO and DPO. The same hemoglobin variability may be obtained regardless of the type of ESA used, if the ESA is used in adequate doses.

Key words: anemia, darbepoetin Alfa, epoetin Beta, hemoglobin cycling, hemoglobin variability

Introduction

Treatment with erythropoietic-stimulating agents (ESA) has been a major advance in improving the lives of hemodialysis patients. However, treatment with ESA exerts effects quite different from biologic erythropoietic processes; treatment involves short, intermittent, non-physiologic bursts of plasma erythropoietin availability, which do not directly coincide, either temporally or in magnitude, with that under physiologic circumstances. A recent study revealed that repeated, cyclical, up-and-down movements of hemoglobin levels are a common occurrence during ESA treatment in patients on hemodialysis[1]. There is only one report on the difference in the hemoglobin variability with change of ESA from epoetin Beta (EPO) to darbepoetin Alfa (DPO)[2]. We attempted to determine whether the variations in hemoglobin levels differed between patients treated with EPO and those treated with DPO.

Materials and Methods

Twenty-five outpatients who were switched from EPO to DPO in July 2007 and were not admitted with gastrointestinal bleeding were retrospectively

enrolled in this study. The background data of the study participants (age, gender, duration of hemodialysis, cause of primary end-stage kidney disease) were recorded. All the blood samples were obtained before the first dialysis session of the week. Hemoglobin was measured every two weeks and c-reactive protein (CRP), iron (Fe) and the total iron binding capacity (TIBC) were measured once a month. Routine chemistry profiles were determined by standard methods. Fe saturation was calculated as Fe divided by TIBC. As the index of body fluid volume, we investigated body eight at the time of blood sampling. We obtained 24 sets of data from July 2006 to June 2007 obtained while the patients were treated with EPO and 24 sets of data from October 2007 to September 2008 when they were treated with DPO.

The conversion ratio from EPO to DPO was 225:1. We excluded the first 3 months after the ESA switch from the observation period, because hemoglobin values could change with switch of the type of ESA itself.

Not only the value of hemoglobin, but also the change in the hemoglobin value is considered to be important to determine the dosage of ESA. The same doctor determined the dosage of EPO and DPO. We aimed for a hemoglobin level of over 10-11 g/dl, which is the recommended value in Japan[3]. Hemoglobin variability was calculated as the standard deviation from the individual patients' hemoglobin divided by the patients' mean hemoglobin ×100[4]. The variability of body fluid volume was also calculated as the standard deviation from the individual patients' body weight divided by the patients' mean body weight. The change in the hemoglobin values were compared between the EPO treatment period and DPO treatment period. This study was conducted in accordance with the principle of the Declaration of Helsinki.

The paired t-test was used to compare the variables. Data values are presented as means ± SD. A probability value of less than 0.05 was considered to represent significance. All statistical calculations were performed with Stat View SE.

Results

The clinical characteristics of the subjects are summarized in Table 1. Out of 25 patients, 14 patients were male. The mean age of the patients was 69.0 ± 8.2 years. The mean duration of hemodialysis was 21.1 ± 11.4 years. Primary cause of end-stage kidney disease was chronic glomerular nephritis in 17 patients, diabetic nephropathy in 5, nephrosclerosis in 2 and unknown in 1. The comparison of iron and inflammation markers and hemoglobin variability is shown in Table 2. Fe saturation was higher during the EPO treatment period (29.4 ± 7.1%) than during the DPO treatment period (25.1 ± 7.7%, $p < 0.01$). There were no difference in the serum CRP level (0.42 ± 0.41 mg/dl, 0.41 ± 0.49 mg/dl, respec-

Table 1 Background characteristics of the study participants

Characteristic	
Number (Male/Female)	25 (14/11)
Age (years)	69.0 ± 8.2
Duration of hemodialysis (years)	21.1 ± 11.4
Primary cause of ESKD	
Chronic glomerulonephritis	17 (68.0%)
Diabetic nephropathy	5 (20.0%)
Nephrosclerosis	2 (8.0%)
Unknown	1 (4.0%)

ESKD: end-stage kidney disease.

Table 2 Comparison of iron, inflammation and body fluid markers and hemoglobin variability

	Epoetin Beta	Darbepoetin Alfa	p value
Fe Saturation (%)	29.4 ± 7.1	25.1 ± 7.7	0.01 >
CRP (mg/dl)	0.42 ± 0.41	0.41 ± 0.49	n.s.
Hemoglobin (g/dl)	10.0 ± 0.4	10.0 ± 0.4	n.s.
Hemoglobin variability	6.4 ± 2.1	7.1 ± 1.6	n.s.
Body fluid volume variability	1.3 ± 0.8	1.7 ± 0.7	n.s.
ESA dosage (u/week, μg/week)	3,730 ± 1,760	22 ± 11	

CRP: c-reactive protein, ESA: erythropoietic-stimulating agents.

tively), the mean hemoglobin value (10.0 ± 0.4 g/dl, 10.0 ± 0.4 g/dl, respectively), body fluid volume variability (1.3 ± 0.8, 1.7 ± 0.7, respectively) and hemoglobin variability (6.4 ± 2.1, 7.1 ± 1.6, respectively) between the period of treatment with EPO and that of treatment with DPO.

Discussion

Hemoglobin variability results in fluctuation in oxygen delivery to vital organs. Repeated episodes of relative ischemia in organs, such as the heart, may result in disordered pathologic organ function, and suboptimal patient outcomes. Ebben et al found that both the risk of mortality and hospitalization were associated with high-amplitude hemoglobin swings[5]. Yang et al also reported greater hemoglobin variability was independently associated with a higher mortality[6]. On the other hand, Gilbertson et al reported number of months for which the hemoglobin values remain below the target range rather than hemoglobin variability itself may be the primary predictor of the increased risk of death[7]. Since hemoglobin variability is determined by many factors, its validity as a surrogate outcome predictor of a poor prognosis remains to be determined, and will require RCTs[8].

Hemoglobin levels tend to rise and fall in a cyclic pattern, one that varies from patient to patient[1]. So in our study, the same patients were examined as both cases and controls. The longer circulating half-life of DPO (25.3 hr) than of EPO (8.5 hr)[9] may affect hemoglobin variability. In Australia, Walker R et al reported that the mean variance in hemoglobin levels was greater in patients receiving DPO than in those receiving EPO[2]. But in our study, there were no significant differences in the hemoglobin variability between EPO and DPO in hemodialysis patients with switch of the ESA from EPO to DPO. Response to ESA is affected by functional iron deficiency and inflammatory conditions. As the marker of iron repletion, Fe saturation was higher during the EPO treatment period than during the DPO treatment period. As the marker of inflammation, serum CRP level was not different between the period of treatment with EPO and that of treatment with DPO. Body fluid affects hemoglobin value. So we estimated body weight at the time of blood sampling as the index of body fluid and found there was no significant difference in body fluid volume variability between the period of treatment with EPO and DPO. We considered not only the value of hemoglobin, but also the change of the hemoglobin value to control the dosage of ESA. The same hemoglobin variability may be obtained regardless of the type of ESA used, if the ESA is used in adequate doses.

There are some limitations in this study. First, the study design was retrospective and there were no clear protocol for the dosage of ESA and Fe supplement. The difference of Fe saturation between the period of treatment with EPO and that of treatment with DPO meant more Fe supplements were used in EPO treatment period than DPO treatment period. That might be due to the difference in cost between EPO and DPO. Second, the sample size was very small. Further investigation with larger samples under a rigid protocol is necessary to estimate the differences arising from the type of ESA used.

Conclusion

There were no significant differences in the hemoglobin variability between EPO and DPO in hemodialysis patients with switch of the ESA from EPO to DPO.

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血液透析患者におけるヘモグロビン変動：Epoetin Beta と Darbepoetin Alfa の比較

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目的　慢性腎臓病患者の重大な合併症として腎性貧血があり，その治療として erythropoiesis stimulating agents（ESA）が使用されている．近年，ESA による加療中の多くの患者に，繰り返されるヘモグロビン値の上下の変動があり，また，ヘモグロビンの変動が入院，死亡に関連すると報告されている．今回，半減期の異なる epoetin Beta（EPO）と darbepoetin Alfa（DPO）でヘモグロビンの変動に差があるか検討した．方法　三軒茶屋病院において，2007 年 7 月に EPO から DPO に変更した 25 名の外来維持透析患者を対象とした．変更前の 12 ヵ月と変更後の 4～16 ヵ月目の 12 ヵ月間のヘモグロビン値を月 2 回，合計それぞれ 24 回測定した．ヘモグロビン変動は（標準偏差/平均ヘモグロビン）×100 で評価し，EPO で治療した期間と DPO で治療した期間を比較した．結果　EPO の治療期間でのヘモグロビンの平均値は 10.0±0.4 g/dl で，ヘモグロビン変動は 6.4±2.1 であった．一方，DPO の治療期間ではヘモグロビンの平均値は 10.0±0.4 g/dl，ヘモグロビン変動は 7.1±1.6 であった．両者においてヘモグロビンの平均値，ヘモグロビン変動に有意差は認めなかった．結論　EPO と DPO のどちらの ESA でも同様なヘモグロビン変動を得られる可能性があった．