

Comparison of Pain and Efficacy of Darbepoetin Alfa and Epoetin Beta Pegol Treatment in Patients Receiving Peritoneal Dialysis

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Background: Sustained erythropoiesis-stimulating agents (ESAs) have recently been identified as the standard therapeutic agent for anemia in patients undergoing peritoneal dialysis (PD). However, few reports have compared pain between various types of sustained ESAs or between administration routes. Furthermore, the change ratio of the dose of sustained ESAs reportedly ranges from 0.8 to 1.3. In the present study, to compare darbepoetin alfa and epoetin beta pegol (a continuous erythropoietin receptor activator [CERA]), we examined the dolorific differences between administration routes and the effect on anemia by using a change ratio of 0.8 with darbepoetin alfa in patients with renal anemia undergoing PD.

Subjects and Method: We randomly assigned 20 patients with stable hemoglobin levels undergoing PD to either a darbepoetin alfa therapy group or a CERA therapy group. Based on a previous report, the change ratio of the CERA group from CERA to darbepoetin alfa therapy was assumed to be 0.8, and therapy was crossed-over to darbepoetin alfa again 2 months later. The dolorific evaluation (pain measurement) used both a face scale and a visual analogue scale. We compared the agents as well as administration routes with respect to pain. We also measured variables related to anemia and iron metabolism.

Results: The change ratio of the CERA group at the start of the study was 0.821. On resumption of darbepoetin alfa therapy 2 months later, the doses of darbepoetin alfa increased. The darbepoetin alfa group showed a stronger tendency for pain, although the difference was not significant. In contrast, subcutaneous administration in the CERA group showed significant pain just after injection. The CERA group, however, showed a significant decrease in hemoglobin levels after 2 months of treatment ($p=0.0489$). No significant change was found in the hematocrit or the reticulocyte count. There were no significant differences in iron metabolism, as shown by serum iron levels and total iron-binding capacity, in either group. However, serum ferritin levels showed a tendency to decrease in the darbepoetin alfa group.

Conclusion: No significant difference in pain was found between darbepoetin alfa and CERA therapies, but a significant difference in pain was noted between administration routes, just after injection, in the CERA group. The results also suggest that a change ratio of 0.8 from darbepoetin alfa to CERA is low for managing anemia. (J Nippon Med Sch 2015; 82: 21–26)

Key words: darbepoetin alfa, epoetin beta pegol, peritoneal dialysis, pain comparison, change ratio

Introduction

Erythropoiesis-stimulating agents (ESAs), such as recom-

binant human erythropoietin (rHuEPO), are widely used to treat anemia in patients with chronic kidney disease^{1,2}.

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Treatment of anemia in patients with renal disease became easier after rHuEPO was introduced in 1990, but pathosis remains a problem³. Achieving target hemoglobin values also remains difficult, because patients' responses to treatment with EPO are often poor⁴. Furthermore, the need for patients to frequently visit a hospital for rHuEPO administration is a major burden.

Because of the limitations of rHuEPO, sustained ESAs, such as darbepoetin alfa and epoetin-beta pegol (a continuous erythropoietin receptor activator [CERA]), were developed⁵. An advantage of sustained ESAs over conventional rHuEPO is that they have equivalent effects, via either subcutaneous or intravenous administration⁶. Although rHuEPO is commonly administered via the subcutaneous route in patients undergoing peritoneal dialysis (PD), this route of administration can be painful^{7,8}. Few studies have compared darbepoetin alfa and CERA^{9,10} or the pain caused by intravenous and subcutaneous administration.

Furthermore, reported change ratios of sustained ESAs vary widely, ranging from 0.8 to 1.3¹¹⁻¹⁵. The greatest limitation is that few studies involve patients undergoing PD. Generally, the change ratio in Japan is about 0.8.

To compare darbepoetin alfa and CERA, we performed a study to measure the dolorific differences between the routes of administration and anemia management effects by using a change ratio of 0.8 with darbepoetin alfa in patients with renal anemia undergoing PD.

Subjects and Methods

Subjects

The study procedures were performed in accordance with the Declaration of Helsinki, and all patients provided written, informed consent for participation in this study. From outpatients with stable hemoglobin levels undergoing PD, we chose 20 patients aged 20 years or older who were being treated with darbepoetin alfa. Exclusion criteria included peripheral neuropathy, severe dermatitis, severe pruritus, uncontrollable hypertension, congestive heart failure (NYHA New York Heart Association class 3 or greater), malignant tumors, and blood disorders.

Methods

The patients were prospectively and randomly assigned to either a darbepoetin alfa treatment group or a CERA treatment group. The darbepoetin alfa group continued to receive darbepoetin alfa at a consistent dosage, whereas the CERA group received CERA for 2 months, at an initial dose based on a change ratio of 0.8, and then

received darbepoetin alfa again at a dose determined on the basis of the hemoglobin value after treatment with CERA.

Both darbepoetin alfa and CERA products were left at room temperature for at least 30 minutes before administration. A 23-G needle was used for intravenous administration, and a 26-G needle was used for subcutaneous administration. The initial dose was administered intravenously, followed by subcutaneous administration. The same nurse administered both doses. The site for subcutaneous administration was the lateral aspect of the proximal part of an upper limb. The site of intravenous administration of the ESA was a median cubital vein.

We evaluated differences in pain experienced by patients by means of a face scale (FS)¹⁶ and a visual analogue scale (VAS)¹⁷. Pain was assessed at needle insertion, at drug injection, and at 1 and 5 minutes after drug injection. Variables related to anemia and iron metabolism were measured every month, and their values were compared.

Endpoints

The primary outcomes were the dolorific differences between the administration routes of darbepoetin alfa and CERA and between these agents, as assessed using the FS and the VAS.

The secondary endpoints were variables of anemia and iron metabolism. To determine iron metabolism, we screened serum iron levels, total iron-binding capacity (TIBC), and serum ferritin levels. To quantify anemia management, we examined changes in the hemoglobin concentration, hematocrit, reticulocyte count, and ferrokinetics. We also evaluated the change in the darbepoetin alfa dose before and after CERA administration in the CERA group.

Statistical Analysis

The value of each measured variable at the start of the study is expressed as mean±SD. The results of testing with the FS and VAS were analyzed with the Mann-Whitney U-test. Changes in anemia- and iron-related variables over time were analyzed with one-way analysis of variance (ANOVA). Lastly, Dunnett's multiple comparison test was used for posthoc analysis. Statistical analyses were performed with the GraphPad PRISM™ V 6.0 software package (GraphPad Software, San Diego, CA, USA). A *p* value of <0.05 were considered statistically significant. We used a regression line to compare changes in data during the study period.

Table 1 Patients' baseline characteristics

	Darbepoetin-alpha (N=10)	CERA (N=10)	
<i>Variable</i>			
Age (years)	66.0±11.5	66.9±19.7	ns
Male, <i>n</i> (%)	7 (70)	5 (50)	ns
Body-mass index (kg/m ²)	22.76±2.929	24.16±6.778	ns
Peritoneal dialysis duration (month)	38.6±30.2	27.9±15.5	ns
Residual renal function (mL/day)	1,192±602.5	1,282±755.3	ns
Diabetes mellitus, <i>n</i> (%)	3 (30)	5 (50)	ns
Darbepoetin-alpha (µg/M)	214.5±151.5	207.0±123.7	ns
Ferrous citrate, <i>n</i> (%)	3 (30)	2 (20)	ns
Blood pressure (mm Hg)			
Systolic	151.0±13.80	137.0±15.70	<i>p</i> =0.0483
Diastolic	80.5±16.75	79.4±15.84	ns
Hemoglobin (g/dL)	10.09±0.68	9.96±0.96	ns
Hematocrit (%)	30.49±2.08	30.61±3.04	ns
Reticulocytes (%)	0.84±0.42	0.76±0.55	ns
Albumin (g/dL)	3.23±0.42	2.90±0.46	ns
Fe (µg/dL)	80.50±17.96	69.10±39.64	ns
Total iron binding capacity (µg/dL)	276.9±37.09	263.3±66.44	ns
Ferritin (ng/mL)	101.5±134.5	89.1±108.5	ns

Table 2 Pain comparison between erythropoiesis-stimulating agents (ESAs)

	Facial scale			Visual analogue scale		
	Darbepoetin-alpha	CERA	<i>p</i> value	Darbepoetin-alpha	CERA	<i>p</i> value
Intravenous						
Needle insertion	1.4±1.17	0.8±0.42	0.2468	0.83±0.888	0.83±0.946	0.8964
Start of injection	1.7±1.6	0.4±0.69	0.0501	2.64±2.85	0.77±1.11	0.1680
1 minute after injection	0.5±0.97	0	0.2105	0.56±1.22	0.47±0.835	0.8585
5 minutes after injection	0.3±0.67	0	0.4737	0.33±0.775	0.13±0.258	0.7028
Subcutaneous						
Pre	0.7±0.67	0.8±0.79	0.9782	0.68±0.733	0.73±0.506	0.5901
0	2.9±1.10	2.1±0.74	0.1133	5.16±2.79	2.92±2.12	0.0749
1	0.4±0.69	0.3±0.48	0.9999	0.67±1.101	0.62±1.051	0.6123
2	0.3±0.67	0	0.4737	0.45±1.18	0.11±0.167	0.8200

Results

Comparison of Baseline Variables

The patients' backgrounds are shown in **Table 1**. Systolic blood pressure was significantly higher in the darbepoetin alfa group ($p=0.0483$) than in the CERA group, but other variables did not differ significantly between the groups.

Pain Comparison between ESAs

As measured with the FS and VAS, pain was slightly, but not significantly, more intense in the darbepoetin alfa group than in the CERA group (**Table 2**).

Comparison of Pain between Different Routes of Administration

As assessed with FS and VAS, the darbepoetin alfa group showed a tendency for more painful just after subcutaneous administration of darbepoetin. However, significant differences in pain were not noted between administration routes. In the CERA group, subcutaneous administration was significantly more painful just after the injection, as observed with both FS ($p=0.0004$) and VAS ($p=0.0172$).

Change in the ESA Dose

The mean initial darbepoetin alfa dose for the CERA group was 207.0±127.7 µg/month. The mean dose of

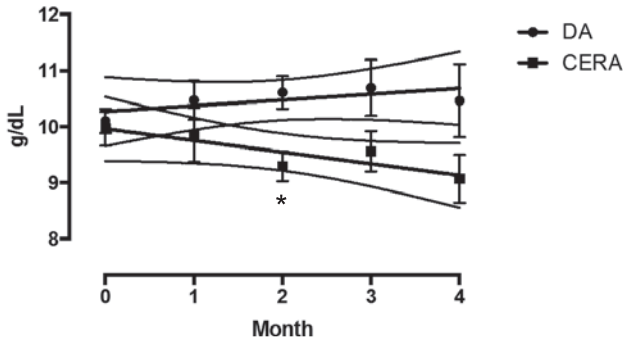


Fig. 1 Changes in hemoglobin levels in the darbepoetin alfa group and the CERA group
 Darbepoetin alfa: $Y=0.1033X+10.27$, CERA: $Y=-0.2070X+9.960$. CERA, epoetin beta pegol, a continuous erythropoietin receptor activator.
 Note: * $p<0.05$, One-way ANOVA

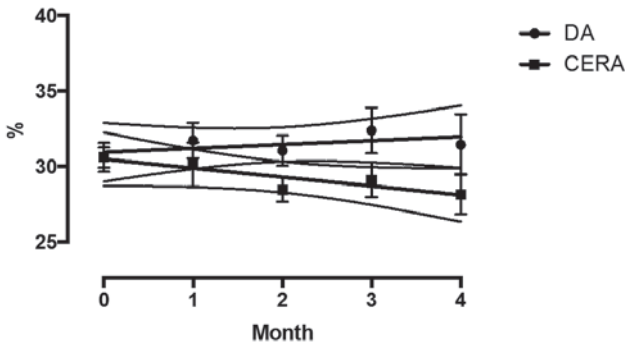


Fig. 2 Changes in hematocrit levels in the darbepoetin alfa and CERA groups
 There was no significant difference before and after treatment ($p=0.0891$). A negative gradient is shown in the CERA group. Darbepoetin alfa: $Y=0.2578X+30.94$; CERA: $Y=-0.5920X+30.48$. CERA, epoetin beta pegol, a continuous erythropoietin receptor activator.

CERA was $170.0\pm 103.3 \mu\text{g}/\text{month}$, and the change ratio was 0.821. After the ESA was changed back to darbepoetin alfa in the CERA group, the mean darbepoetin alfa dosage increased to $225.0\pm 116.0 \mu\text{g}/\text{month}$ ($p=0.0811$).

Comparison between ESAs of Variables Related to Anemia and Iron Metabolism

The CERA group showed a significant decrease in hemoglobin levels after 2 months of treatment with CERA ($p=0.0489$; Fig. 1). No significant difference was observed using the regression line ($p=0.0766$), but a negative gradient, nevertheless, showed an adverse effect in the CERA group, unlike the darbepoetin alfa group ($y=-0.2070x+9.960$). The hematocrit tended to decrease, similar to the tendency shown by hemoglobin levels, but there was no significant difference before or after treatment ($p=0.0891$)

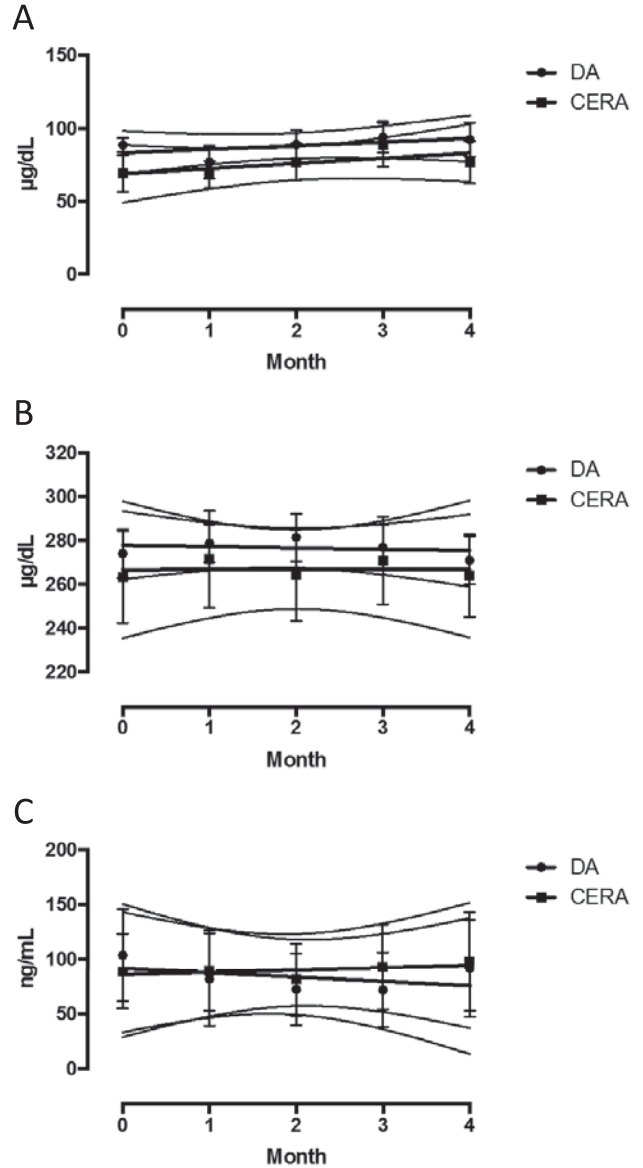


Fig. 3 Changes in iron metabolism-related variables (A) Fe, (B) TIBC, and (C) ferritin. There were no significant differences in iron metabolism in either group. CERA, epoetin beta pegol, a continuous erythropoietin receptor activator; TIBC, total iron-binding capacity.
 (A) Fe, $Y=2.450X+83.20$ (darbepoetin alfa), $Y=3.560X+68.86$ (CERA); (B) TIBC, $Y=-0.6282X+277.8$ (darbepoetin alfa), $Y=0.0800X+266.6$ (CERA); and (C) ferritin, $Y=-4.062X+91.70$ (darbepoetin alfa), $Y=2.070X+85.98$ (CERA).

(Fig. 2). There was no significant change in reticulocyte count (data not shown).

Using serum levels of iron and TIBC as surrogate endpoints, no significant difference in iron metabolism was found in either group (Fig. 3). The regression line in the darbepoetin alfa group, unlike that in the CERA group, did show a decrease in the serum ferritin level ($y=-4.062x+91.70$).

Discussion

Darbepoetin alfa has recently been the sustained ESA of choice for patients undergoing PD, but CERA, which became available in 2011, has a longer half-life than darbepoetin alfa^{7,8,18-21}.

Various factors are involved in quantifying pain upon administration of an ESA, including the tolerability of the method of injection, the patient's individual tolerance, and drug properties. To control for these factors in the present study, we sought to inject the agents under equivalent conditions in the clinic. However, to administer equivalent doses of the active ingredients, darbepoetin alfa requires 0.5 mL of the solution, whereas CERA requires 0.3 mL of the solution; this difference in volume may cause a difference in pain between the therapies after subcutaneous administration. Because we found the difference in pain not to be significant, however, we believe that the difference in volume influences pain for only approximately 1 minute after administration. In a previous study, the volume of solution was equalized after pH was regulated and a placebo was added, and pain was compared¹⁰; less pain was observed in the CERA group than in the darbepoetin alfa group, and the difference was considered when it may be the influence of the medicine additive. Another study also compared epoetin beta, and the authors concluded that the volume of the solution does not affect pain⁹. In our study, because patients were randomly assigned to the darbepoetin alfa group or the CERA group, the patient's individual pain tolerance might have influenced the outcome.

When we compared intravenous and subcutaneous routes in the CERA group, we found that the latter caused significant pain just after instillation. The same tendency, albeit insignificant, was observed in the darbepoetin alfa group. The significant difference noted in the CERA group cannot be attributed to any known factor, but is likely an unknown characteristic of the drug. Because of its chemical composition, CERA might cause vascular irritation after intravenous injection that is not felt after subcutaneous injection.

The measurement of anemia-related variables in the present study showed a significant decrease in hemoglobin levels after 2 months of treatment with CERA. The darbepoetin alfa group did not show any significant difference by using the regression line as a comparison, but a negative gradient was seen in the regression line of the CERA group. We saw a similar tendency in the hematocrit levels of the CERA group. These results clearly suggest that the CERA dose was insufficient. The target

change ratio (0.8) used in the present study was selected on the basis of many studies reporting a darbepoetin alfa-to-CERA change ratio of 0.8 to 0.9^{12,13,15,22,23}. The exact change ratio in our study was 0.821. However, higher change ratios have been reported^{11,14}. Furthermore, other Japanese clinical trials have shown that 4 to 8 weeks are necessary to demonstrate the effects of CERA²⁴, and the observation period used in these studies might have been too short to show all the effects of CERA. According to the results of other studies, a higher change ratio is needed with low-dose darbepoetin alfa. Because the average dosage of darbepoetin alfa was quite high (207 µg/month) before the switch to CERA in the present study, a higher change ratio might be necessary.

There were almost no differences in serum iron levels or TIBC in the darbepoetin alfa or CERA groups. However, the darbepoetin alfa group did show a tendency for ferritin levels to decrease. We speculate that patients in the CERA group used less iron than did those in the darbepoetin alfa group, because darbepoetin alfa uses iron more efficiently than does CERA and because anemia became more severe in the CERA group. In contrast, Hiramatsu et al. have suggested that the efficiency of iron utilization is improved upon switching from darbepoetin alfa to CERA²⁵. Oka et al. have reported that, during a 6-month examination period, anemia improved, serum iron level decreased, and ferritin level increased slightly²⁶. Various studies have examined the efficiency of iron utilization by CERA. Because of our limited study period, we suspect that significant differences, if any, require more than 2 months to appear.

Conclusions

We did not observe a significant difference between the dolorific effects of darbepoetin alfa and CERA, but we did observe difference between the administration routes in the pain felt just after injection in the CERA group. Finally, our results suggest that a change ratio from darbepoetin alfa to CERA of 0.8 is low for managing anemia.

Conflict of Interest: The authors have no financial conflicts of interest to declare with regard to the publication of this article.

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