Comparison of Usage and Effectiveness between Methoxy Polyethylene Glycol Epoetin Beta and Darbepoetin Alfa with Hemodialysis Patients

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Abstract: Methoxy polyethylene glycol epoetin beta which has a long half-life is developed to provide stable control of hemoglobin levels at extended administration intervals compared to darbepoetin alfa. The purpose of this study was to compare the patterns of use, efficiency of therapy and cost with undergoing hemodialysis patients. Electronic medical record system was used to examine administration frequency, hemoglobin response rate, achievement of target hemoglobin, drug costs. Administration frequency was once in 4 weeks with methoxy polyethylene glycol epoetin beta group and 3 times in 4 weeks with darbepoetin alfa group. Hemoglobin response rate was 61.5% in methoxy polyethylene glycol epoetin beta at the time of 16 weeks. It was not significantly different from 66.7% in darbepoetin alfa ($P = 1.000$). The drug cost for methoxy polyethylene glycol epoetin beta group was little higher than darbepoetin alfa group. However, there was no statistically significant difference ($P = 0.164$). Use of methoxy polyethylene glycol epoetin beta is as effective and safe as darbepoetin alfa managing renal anemia in hemodialysis patients. Methoxy polyethylene glycol epoetin beta's extended administration interval improve patient's compliance and enable effective anemia treatment.

Key words: Methoxy polyethylene glycol epoetin beta, erythropoiesis stimulating agent, renal anemia, hemoglobin.

1. Introduction

Anemia is a common complication of chronic renal failure. Anemia decreases the oxygen supply to the use of tissue, the cardiac output increases as the compensation mechanism, and thereby expansion of the heart, left ventricular hypertrophy is displayed. In severe cases, It may cause cardiac complications such as angina pectoris, congestive heart failure [1, 2]. Common symptoms of anemia are tiredness, shortness of breath, dizziness, headache, difficulty concentrating, sleep disorders, and symptoms include bleeding disorders, immune and cognitive dysfunction, distal blood circulation disorders appear.

Cause of anemia in chronic renal failure patients will

gradually decrease as height of EPO (erythropoietin) production decreased renal function. Therefore ESA (erythropoiesis-stimulating agent) is the standard treatment for patients with chronic renal anemia [3]. ESA has developed what can be intravenous or subcutaneous injection has been prescribed to patients themselves abdomen, arms, thigh and injected subcutaneously. EPO, is endogenous growth factor secreted by the kidneys about 90%, stimulates the proliferation and differentiation of red blood cell precursors and induces the production of red blood cells. In addition, they cause stimulated emission of red blood cells from the bone marrow.

ESA first introduced to the market is a recombinant human EPO in EA (epoetin alfa) with a glycoprotein of 165 amino acids and peptide bond. EA is constantly used. However, the major limitation is that it is usually administered by injection two or three times per week [4]. DA (darbepoetin alfa) formulations have been

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developed by replacing the 5-amino acid to create new two N-linked glycosylation [5-7]. DA has three times the longer half-life (25.3 hours during intravenous, 48.8 hours during subcutaneous injections) than EA. However, conventional ESA (erythropoiesis stimulating agent) with EA or DA to manage anemia in CKD (chronic kidney disease) patients requires frequent administration, dose changes, and close monitoring of hemoglobin concentration to maintain target hemoglobin levels [6, 7].

MPG-EPO (methoxy polyethylene glycol epoetin beta) is a new agent that has a different interaction with the receptor [8, 9] unlike the prior formulations with a longer half-life (approximately 130 hours) [10]. MPG-EPO is integrated through amide bonds of the N-terminal amino group or ϵ -amino group. Therefore, slow association and quick dissociation enables the stimulation of continued erythropoiesis [11]. Due to these different pharmacological characteristics, MPG-EPO was administered to enable a long interval. MPG-EPO is approved for once-monthly maintenance therapy for anemia in patients with chronic kidney disease. Korea has been introduced in 2009, usage is on the rise [12-18].

There is Phase III study about the efficacy and safety of treatment of anemia using the MPG-EPO through comparison with the reaction rate of hemoglobin compared EA. However, study is not compared with DA having a longer half-life and has been developed since the EA.

The purpose of this study was to compare the patterns of administration frequency, hemoglobin response rate, achievement of target hemoglobin and cost during 16 weeks with CKD patients between DA and MPG-EPO group undergoing hemodialysis in Korea.

2. Materials and Methods

2.1 Study Participants

Patients were screened at Samsung medical center in Korea from April 2011 to October 2012, undergoing hemodialysis more than 16 weeks and were all over 18

years old. To be included in the study, patients must have had hemoglobin concentration less than 11 g/dL before starting drug administration. Patients have been prescribed MPG-EPO or DA during study period. Patients were excluded from this study if they had no records about administration. A total of 48 patients were screened at Samsung medical center undergoing hemodialysis more than 16 weeks and were all over 18 years old. 26 patients have been prescribed MPG-EPO or DA during study period. 4 patients with no test results were excluded. Therefore MPG-EPO group was 13 patients, DA group was 9 patients.

The retrospective study was approved by Samsung medical center institutional review board (IRB No.201305055001). This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

2.2 Procedures

Electronic medical record system was used to examine patient characteristics; age, gender, weight, height, diagnosis, underlying disease, lab data; Scr (serum creatinine), Hct (hematocrit), serum ferritin, TIBC (total iron binding capacity), TSAT (transferin saturation), serum iron, i-PTH, whether taking oral iron therapy. In addition, administration frequency, hemoglobin response rate, and achievement of target hemoglobin for each time point (4, 8, 12, 16 weeks) were investigated; if the clinical test results do not hold true in the exact interval used as a final measure of the nearest day. High frequency of adverse events; hypertension, diarrhea, nose throat, headache, upper respiratory tract infection whether expressed and drug costs were irradiated [16].

Response rate was defined as the proportion of patients who were examined elevated concentrations above 1.0 g/dL from baseline [19].

Achievement of hemoglobin was based on NKF-K/DOQI (national kidney foundation kidney disease outcome quality initiative) guideline in 2007; target hemoglobin concentration equals from 11.0 to

12.0 g/dL and Korea national HIRA (health insurance and assessment services) criteria; applicable insurance hemoglobin concentration equals from 10.0 to 11.0 g/dL. This study analyzed the degree of achievement of the treatment on the basis of the above two targets.

ERI (erythropoietin responsiveness index) was defined as ESA dose per body weight per week for hemoglobin. The total amount of the ESA was defined as the total amount used of administration to a patient during 16 weeks. Hemoglobin was used as the average concentration during 16 weeks. Drug costs were based on drug insurance.

2.3 Analysis Methods

A statistical analysis of the study in the case of categorical data uses Fisher's exact test. The number of continuous data which cannot be assumed normality was analyzed by Mann-Whitney test. If normality of the data cannot be assumed, results are expressed as

median (range). Analysis of the data was used as the SPSS® version 12.0 (SPSS Inc., Chicago, USA). P values less than 0.05 were deemed statistically significant.

3. Results

3.1 Study Population

Table 1 shows baseline characteristics for all patients. The median age in each group was 70 years old, 58 years old. Although patients with a diagnosis of diabetes were more in MPG-EPO group, it was not significantly different. Baseline hemoglobin levels before drug administration, approximately 9.4 g/dL in both, did not differ between groups. Hematocrit also did not show a significant difference. Although there is a significant difference for the Serum ferritin ($P = 0.009$), TIBC, TSAT, serum iron, i-PTH were no significant differences.

Table 1 Baseline characteristics of patients.

	Total ($n = 22$)	Treatment Group		P-value
		MPG-EPO ($n = 13$)	DA ($n = 9$)	
Gender, n (%)				
Male	15 (100.0)	9 (60.0)	6 (40.0)	1.000
Female	7 (100.0)	4 (57.1)	3 (42.9)	
Age (year)	64.5 (66.0)	70.0 (39.0)	58.0 (65.0)	0.122
Body Weight (kg)	60.3 (40.0)	60.0 (29.0)	64.0 (28.1)	0.857
Height (m)	1.62 (0.29)	1.62 (0.28)	1.67 (0.25)	0.806
Serum Cr (mg/dL)	6.69 (9.98)	6.51 (7.97)	7.04 (9.51)	0.601
eGFR-MDRD	8.5 (12.2)	8.5 (11.3)	8.6 (9.3)	0.744
Hemoglobin (g/dL)	9.5 (2.6)	9.4 (1.9)	9.5 (2.3)	0.987
Hct (%)	29.7 (8.6)	30.3 (8.0)	29.5 (5.7)	0.215
Serum Ferritin ¹ (ng/mL)	306.9 (5705.6)	197.2 (388.0)	796.4 (5575.6)	0.009*
TIBC ² (μg/dL)	191.0 (128.0)	198.0 (113.0)	177.0 (118.0)	0.236
TSAT ² (%)	35.6 (88.5)	30.1 (22.0)	43.3 (88.5)	0.465
Serum Iron ² (μg/dL)	76.0 (161.0)	68.0 (46.0)	87.0 (161.0)	0.409
i-PTH ³ (pg/mL)	204.3 (360.4)	211.2 (360.4)	172.2 (203.0)	0.589
Clinical condition n (%)				
DM				
Yes	14 (100.0)	10 (71.4)	4 (28.6)	0.187
No	8 (100.0)	3 (37.5)	5 (62.5)	
Hypertention				
Yes	22 (100.0)	13 (59.1)	9 (40.9)	-
Iron supplements				
Yes	16 (100.0)	8 (50.0)	8 (50.0)	0.333
No	6 (100.0)	5 (83.3)	1 (16.7)	

TIBC, total iron binding capacity; i-PTH, parathyroid hormone.

¹4 cases with missing values are excluded; ²5 cases with missing values are excluded; ³10 cases with missing values are excluded.

* indicates P -value < 0.05.

3.2 Usage

3.2.1 Administration Frequency

The frequency of administration of MPG-EPO group was 4 times per 16 weeks, DA group was 12 times per 16 weeks. In the MPG-EPO groups, it showed a less frequency of administration (Table 2).

3.2.2 Administration Dosage

Total doses of MPG-EPO group were 485.0 µg, range was 120 µg to 730 µg and DA group were 300.0 µg, ranging from 140 µg to 570 µg. There was no significant difference (Table 2).

ERI represents the requirements of the ESA was in the MPG-EPO group and DA group each 7.8 U per gram per deciliter per kg per week and 5.3 U per gram per deciliter per kg per week. There was no significant difference between the two groups (Fig. 1).

3.3 Efficacy

3.3.1 Hemoglobin Variation

Hemoglobin variations in the evaluation period of administration of MPG-EPO group and DA group were both significantly higher than before administration.

Table 2 Description of prescribed medications.

	MPG-EPO	DA
Total Dosage/16 weeks, (µg)		
Min	120.0	140.0
Max	730.0	570.0
Mean (SD)	411.5 (174.9)	345.6 (170.9)
Median (range)	485.0 (610.0)	300.0 (430.0)
Number of Dosing/16 weeks, times		
Min	3	7
Max	7	20
Mean (SD)	4.5 (1.2)	12.1 (4.7)
Median (range)	4.0 (4)	12.0 (13)

Min—minimum; Max—maximum; SD—standard deviation.

P-value 0.523 from Mann-Whitney test.

Fig. 1 Comparison of ERI between MPG-EPO and DA therapy group.

MPG-EPO group: 7.8 (14.3), DA group: 5.3 (7.9), *P*-value 0.481 from Mann-Whitney test.

Hematocrit levels were similar increased rather than prior to administration in both groups (Table 3). The concentration of hemoglobin was increased by 4, 8 weeks and 12, 16 weeks showed a tendency to be somewhat declined (Fig. 2). Variation of hemoglobin and hematocrit during of the DA group was showed a significant increase after 8, 16 weeks (Tables 3 and 4). The concentration of hemoglobin was showed a tendency to increase until after 4, 8, 12 weeks and was reduced after 16 weeks (Fig. 3).

3.3.2 Hemoglobin Response Rate

Hemoglobin response rate defined as the proportion of patients with hemoglobin concentration is increased

more than 1.0 g/dL after administration of the drug. The response rate of the MPG-EPO group administered after 4, 8, 12, 16 weeks was 30.8%, 46.2%, 61.5%, 61.5%, showed a tendency to gradually increase. While DA group was 22.2%, 77.8%, 66.7% and 66.7%, after 8 weeks period showed the highest response rate. The mean response rate analyzed by comparing hemoglobin concentrations before drug administration was MPG-EPO group at 46.2%, DA group at 77.8%. DA group was higher but there was no significant difference (Table 5).

3.3.3 Achievement of Hemoglobin

Based on NKF-K/DOQI (national kidney foundation

Table 3 Change of hematocrit levels during study period.

MPG-EPO			DA	
	Hct, (%)	<i>P</i> -value ^b	Hct, (%)	<i>P</i> -value ^b
Baseline	30.3 (8.0)	-	29.5(5.7)	-
Week 4	31.6 (9.0)	0.104	30.4 (7.7)	0.156
Week 8	31.6 (10.8)	0.414	34.8 (9.3)	0.020*
Week 12	31.8 (16.4)	0.273	34.9 (17.2)	0.055
Week 16	31.7 (10.5)	0.077	33.1 (10.8)	0.039*

Values are expressed as median (range). Value of each time point is compared with baseline data and *P*-values are from Wilcoxon's signed rank test.

* indicates *P*-value<0.05.

Fig. 2 Change of hemoglobin levels during study period in MPG-EPO therapy group (*n* = 13).

Table 4 Comparison of Hb (hemoglobin) and Hct (hematocrit) levels between MPG-EPO and DA therapy group.

Time (Week)		MPG-EPO group (n = 13)	DA group (n = 9)	P-value
4	Hb (g/dL)	10.3 (3.4)	9.9 (2.4)	0.682
	Hct (%)	31.6 (9.0)	30.4 (7.7)	0.568
8	Hb (g/dL)	10.7 (3.7)	11.0 (2.9)	0.502
	Hct (%)	31.6 (10.8)	34.8 (9.3)	0.284
12	Hb (g/dL)	10.3 (5.0)	11.1 (5.2)	0.420
	Hct (%)	31.8 (16.4)	34.9 (17.2)	0.659
16	Hb (g/dL)	10.5 (2.1)	10.9 (3.1)	0.706
	Hct (%)	31.7 (10.5)	33.1 (10.8)	0.695

Values are expressed as median (range).

P-values are from Mann-Whitney test.

Fig. 3 Change of hemoglobin levels during study period in DA therapy group (n = 9).

Table 5 Comparison of hemoglobin responder rate between MPG-EPO and DA therapy group.

Group	Time (Week)	4	8	12	16	Mean ¹
MPG-EPO (%)		30.8	46.2	61.5	61.5	46.2
DA (%)		22.2	77.8	66.7	66.7	77.8
P-value		1.000	0.203	1.000	1.000	0.203

¹Evaluated from mean hemoglobin level of 4, 8, 12 and 16 weeks.

P-values are from Fisher's exact test

kidney disease outcome quality initiative) guideline, achievement was 23.1%, 15.4%, 7.7%, 30.8% administered after 4, 8, 12, and 16 weeks in MPG-EPO group. 22.2%, 44.4%, 33.3%, 33.3% in DA group. A higher rate in the DA group showed. Achievement by the average hemoglobin concentration was 38.5% in

MPG-EPO group, 22.2% in DA group based on NKF-K/DOQI guideline. MPG-EPO group was slightly higher but no significant difference (Table 6).

Based on Korea national health insurance criteria, achievement was 38.5%, 30.8%, 46.2%, 61.5% administered after 4, 8, 12, and 16 weeks in MPG-EPO

group. 22.2%, 33.3%, 22.2%, 22.2% in DA group. Achievement by the average hemoglobin concentration was 30.8% in MPG-EPO group, 66.7% in DA group. There was no significant difference (Table 7).

3.4 Adverse Events

A patient (7.7%) had diarrhea and 2 patients (15.4%) had upper respiratory tract infection in MPG-EPO group in evaluation period. And no patient had an adverse event in DA group.

3.5 Drug Cost

The median of drug insurance cost was KRW495,274 in MPG-EPO group, KRW367,335 in DA group. MPG-EPO beta group was higher KRW127,939 but significant difference.

4. Discussion

This study showed that administration frequency was once a month in MPG-EPO group, three times a month in DA group. However, the total dosage of the two drugs was no significant difference. In the Fernando study, MPG-EPO and DA were administered once a month in the same interval, MPG-EPO therapy

showed a higher efficacy [14]. In this study, patients were not administered with the same dosing interval. Therefore, efficacy when administered in the same dosing intervals could not be derived.

Hemoglobin concentration after administration of the drug was compared before administration was significantly increased in MPG-EPO and DA group administered after 4, 8, 12, 16 weeks. Variation of hemoglobin was increased up to 4, 8 weeks but showed a tendency to decrease slightly 12, 16 weeks in MPG-EPO group. DA group showed a tendency to increase up to 12 weeks and to decrease after 16 weeks. This can be determined because the drug due to control of the dose or dose interval depending on the target range of hemoglobin according to the medication instructions. In Lee ji young study, patient seems to be a difference in reactivity for ESA [20]. The degree of absorption of the drug when injected subcutaneously every patient is different, and due to individual differences in reactivity to the administration frequency. The exact cause is difficult to cover in this study.

Achievement of treatment goals has a low tendency based on the NKF-K/DOQI therapeutic guidelines; 11.0 to 12.0 g/dL. This is a study conducted by

Table 6 Achievement of target hemoglobin based on NKF-K/DOQI guideline (11.0-12.0 g/dL).

Achievement	Time (Week)	4	8	12	16	Mean ¹
MPG-EPO therapy						
Yes, n (%)		3 (23.1)	2 (15.4)	1 (7.7)	4 (30.8)	5(38.5)
DA therapy						
Yes, n (%)		2 (22.2)	4 (44.4)	3 (33.3)	3 (33.3)	2(22.2)
P-value		1.000	0.178	0.264	1.000	0.648

¹Evaluated from mean hemoglobin level of 4, 8, 12 and 16 weeks.

P-values are from Fisher's exact test.

Table 7 Achievement of hemoglobin based on the Korean National Health Insurance Criteria (10.0-11.0 g/dL).

Achievement	Time (Week)	4	8	12	16	Mean
MPG-EPO Therapy						
Yes, n (%)		5 (38.5)	4 (30.8)	6 (46.2)	8 (61.5)	4 (30.8)
DA therapy						
Yes, n (%)		2 (22.2)	3 (33.3)	2 (22.2)	2 (22.2)	6 (66.7)
P-value		0.648	1.000	0.380	0.099	0.192

collecting data from patients treated according to national insurance standards. In most cases, in consideration of the economic situation of the patient, dosage of the ESA was reduced based on the hemoglobin concentration 11.0 g/dL, or stopping the administration. Due to the ESA interruption, loss of erythropoietin precursor period is extended. Also the period of maintaining low hemoglobin compared to the reference target can be long and amplify the hemoglobin cycling [19]. In addition, there are reports that concentration of hemoglobin rapidly changing may increase morbidity and mortality in ESRD patients. Analysis for morbidity and survival of the administration of ESA treatment for the anemia of chronic renal failure in hemodialysis patients and for evaluation the quality of life will be a follow-up study conducted.

In the present study, the drug costs were slightly higher in the MPG-EPO group. Drugs can be used by subcutaneous injection [16]. Patients have been prescribed to themselves abdomen, arms, thigh. Cost comparison of the drug was applied only to simple drug costs in this study. Administration fee, drug management storage fee, medical fee, etc. did not take into account costs. Because all drug costs calculated in the insurance price, normal price according to the hemoglobin value will have to be adjusted.

5. Conclusion

Use of MPG-EPO is as effective and safe as DA managing renal anemia in hemodialysis patients. MPG-EPO's extended administration interval improves patient's compliance and enables effective anemia treatment. Therefore, this study can contribute to drug selection for the treatment of anemia of hemodialysis patients. Limitation is that the study was conducted retrospectively recorded by clinical examination performed on medical records. Only clinical examination data in medical records could be reviewed. In spite of this figure shows the difference between the absolute value of the test, patients with

less number is statistically in significant results came out. However clinically, there are parts that can be interpreted as a meaningful result. The clinical significance of this effect must be determined in larger, long term trials.

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