의학석사 학위논문

혈액 투석 환자에서 Erythropoiesis-stimulating agents 의 종류에 따른 효능 및 비용 비교

Comparison of the efficacy and cost according to erythropoiesis-stimulating agent types in hemodialysis patients

울산대학교 대학원

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최 유 진

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이 논문을 의학석사 학위 논문으로 제출함

2024 년 2 월

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국문요약

연구 배경: 만성콩팥병 환자의 누적 숫자가 매년 증가함에 따라 의료비 증가가 심각한 상황이다. 만성콩팥병 환자의 빈혈은 심혈관계 합병증 및 사망률 증가와 관련이 있으므로 빈혈의 교정이 중요한데 조혈호르몬의 투여가 주된 치료이며 신이식을 받지 않는 한 지속적으로 요구된다. 이에 본 연구는 혈액투석을 받고 있는 말기콩팥병 환자에서 조혈호르몬의 종류별 효과와 비용에 대해 비교하여 의료비 절감의 가능성을 알아보고자 하였다.

연구 방법: 2018년 1월 1일부터 2019년 7월 2일까지 서울아산병원에서 혈액투석을 받는 말기콩팥병 환자 중 만 18세 이상인 환자들을 후향적으로 분석하였다. 환자들은 epoetin alfa (EPO-α, Epokine®), darbepoetin-alfa (DA-α, Nesp®), methoxypolyethyleneglycor-epoetin-beta (continuous erythropoiesis receptor activator, CERA, Mircera®) 중 한 가지 조혈호르몬만을 1년간 투여 받았다. 일차 지표로 12 개월 간 EPO-α, DA-α, CERA 세 군 간의 평균 혈색소 농도를 비교하였고, 이차 지표로 한 달 동안 투약된 조혈호르몬의 평균 양을 2018 년과 2023 년의 조혈호르몬 단위 최저 가격을 곱하여 비용을 계산하였다.

연구 결과: 세 군 모두에서 평균 혈색소 농도는 관찰 시작 시점 및 12개월 동안 매 달 평가하였고, 세 군 간 유의미한 차이를 보이지 않았다(p = 0.159). 조혈 호르몬 저항성 지표도 관찰 시작 시점 및 1달 마다 평가하였는데, EPO-α군에서 유의미하게 높았으나(p = 0.002), 저항성의 기준인 300 IU/kg/week 미만이었기 때문에 임상적으로 유의미하지는 않았다. 2018년 가격을 기준으로 계산하였을 때, EPO-α군에서는 월 평균 90,193.3 ± 34,510.0원, DA-α군에서는 월 평균 71,142.3 ± 33,312.6원, CERA 군에서는 81,846.3 ± 54,852.9원(p = 0.298)이었다. 2023년 가격을 기준으로 계산하였을 때, EPO-α군에서는 월 평균 87,065.4 ± 33,313.2원, DA-α군에서는 월 평균 49,745.3 ± 23,293.4원, CERA군에서는 80,515.9 ± 53,961.2원(p < 0.001)이었다.

연구 결론: 혈액투석을 받는 말기콩팥병 환자에서 EPO-α, DA-α, CERA 군 간에 평균 혈색소는 유의미한 차이를 보이지 않았지만, DA-α 군에서 월 평균 비용이 가장 낮게 확인되었다. 의료비 절감 방안을 확립하기 위해서는 향후 대한민국 건강 보험 심사 평가원의 대규모 자료를 통한 확인이 필요하겠다.

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Introduction

Anemia is prevalent in chronic kidney disease (CKD) patients and is associated with decreased tissue oxygen delivery and utilization, elevated cardiac output, ventricular hypertrophy, and increased cardiac complications and mortality risks (1). The main cause of CKD-related anemia is erythropoietin deficiency. Consequently, the standard treatment involves the administration of erythropoiesis-stimulating agents (ESAs). The use of ESAs in renal anemia management has been demonstrated to improve survival, reduce cardiovascular morbidity, and enhance the quality of life (2).

Several ESAs are available in Korea, including epoetin alfa (EPO-α, Epokine®), darbepoetin-alfa (DA-α, Nesp®), and methoxypolyethyleneglycol-epoetin-beta (continuous erythropoiesis receptor activator, CERA, Mircera®). EPO-α is usually injected 2–3 times/week and its elimination half-life is approximately 24 hours when injected subcutaneously. DA-α is usually injected 1–2 times/week , and its elimination half-life is approximately 48.8 hours when injected subcutaneously. CERA has a longer elimination half-life of approximately 130 hours; therefore, it is usually injected once every two to four weeks (3). While long-acting ESAs may offer advantage over short-acting ESAs in terms of patient' compliance considering the half-life of ESAs in non-dialysis CKD patients, there is no evidence supporting the superiority of any one ESA over another in end-stage renal disease (ESRD) patients on maintenance hemodialysis (4). Therefore, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in CKD recommends choosing an ESA based on various factors, including the balance of pharmacodynamics, safety information, clinical outcome data, cost, and availability (5).

The number and medical costs of CKD patients in Korea are escalating annually. In 2011, the CKD patient count was 113,442. By 2021, this figure surged to 277,000, representing a more than two-fold increase over the past decade. Concurrently, the medical cost incurred by

CKD patients was 1.1 trillion won in 2011 and increased to, 2.2 trillion won in 2021, reflecting an increase of more than 1 trillion won over the past decade (6). Given the aging demographic and the rise in causative diseases such as hypertension and diabetes mellitus, the prevalence of ESRD is expected to rise (7). Unfortunately, the number of people who can afford health insurance is decreasing. Therefore, reducing the medical costs incurred by ESRD patients is imperative.

This study compared the cost and efficacy of three popular ESAs to determine which is most effective in maintaining the target hemoglobin range and/or reducing the medical costs in ESRD patients on maintenance hemodialysis based on one-year ESA administration data.

Methods

Patients

The study cohort comprised patients aged over 18 years, undergoing hemodialysis at Asan Medical Center from January 1, 2018, to July 2, 2019, and receiving ESA for anemia treatment. Patients with hematologic disease, active malignant disease, significant acute or chronic bleeding, liver disease, transfusion, ESA refusal, and a follow-up period of less than 12 months were excluded from this study. Patients who switched from one ESA to another or discontinued ESA administration during the observation period were also excluded.

Study design and clinical data collection

We conducted a retrospective cohort study using clinical data from electronic medical records. This study was approved by the Institutional Review Board of Asan Medical Center (IRB approval number: 2023-0648). Informed consent was waived because of the retrospective study design.

The following baseline data were collected: age, gender, weight (kg), height (cm), duration of hemodialysis, and primary disease which caused ESRD. Furthermore, the following

monthly data were collected: body weight (kg), white blood cell (WBC) count, hemoglobin (Hb), intact parathyroid hormone (iPTH), iron and ferritin contents, transferrin saturation (TSAT), total iron binding capacity (TIBC), ESA type and dose per week, and iron supplementation.

ESA dose and erythropoietin resistance index (ERI)

The total ESA dose injected in a month was averaged over a week, and the resulting mean IU/week was used as the ESA dose of the month. We converted CERA doses to DA-α and DA-α doses to EPO-α using ratios of 1.2:1 and 250:1 respectively (8). ERI was calculated by dividing the mean weekly ESA dose (IU/week) by the product of with dry weight (kg) and Hb concentration (g/dL) and expressed in IU·dL/week·kg·g Hb.

Outcomes

The primary endpoint was a comparison of the mean Hb concentrations over a year in the EPO-α, DA-α, and CERA groups and the secondary endpoint was a comparison of the cost incurred by each group, calculated as the mean ESA dose (units/month) × price/unit. ESA prices from 2018 and 2023 were used for the cost analysis.

Statistical analysis

To analyze patient characteristics, we employed chi-square tests or Fisher's exact test for categorical variables, analysis of variance (ANOVA) for normally distributed variables, and Kruskal–Wallis tests for non-normally distributed variables. We used general linear model to confirm the group-by-time interaction effect. The repeated measurement was modeled using a covariance pattern model within a linear mixed model to account for the correlation between observations within the same patients.

A p-value < 0.05 was considered statistically significant. The data from this study were analyzed using Statistical Package for Social Science (SPSS) version 23, under the guidance of the Department of Clinical Epidemiology and Biostatistics at Asan Medical Center.

Results

Patients

Patient characteristics are presented in Table 1. A total of 71 patients met the study inclusion criteria. Among them, 10, 48, and 13 patients received EPO-α, DA-α, and CERA, respectively.

The mean age of enrolled patients in the EPO-α, DA-α, and CERA groups was 66.9 ± 10.2 years, 64.6 ± 13.7 years, and 66.8 ± 16.1 years, respectively. The proportion of men in the EPO-α, DA-α, and CERA groups was 40%, 52.1%, and 46.2%, respectively. The mean body weight of patients in the EPO-α, DA-α, and CERA groups was 50.13 ± 8.11 kg, 60.89 ± 10.57 kg, and 64.49 ± 11.29 kg, respectively. A significant difference in baseline body weight was observed among the three groups ($p = 0.005$). The median duration for which patients in the EPO-α, DA-α, and CERA groups underwent hemodialysis was 15.6 years, 7.3 years, and 6.2 years, respectively.

The causes of ESRD are classified into four major categories: diabetes mellitus, hypertension, glomerulonephritis, and others. In the EPO-α group, five patients (50%) had diabetes nephropathy, four (40%) had hypertensive nephropathy, and one (10%) had glomerulonephritis. In the DA-α group, 19 patients (39.58%) had diabetes nephropathy, nine (18.75%) had hypertensive nephropathy, 10 (20.83%) had glomerulonephritis, and another 10 (20.83%) had other causes for ESRD. In the CERA group, six patients (46.15%) had diabetes nephropathy, four (30.77%) had hypertensive nephropathy, and three (23.08%) had glomerulonephritis.

At the beginning of the observation period (month 0), the mean Hb level in the EPO-α, DA-α, and CERA groups was 10.4 g/dL, 10.4 g/dL, and 10.3 g/dL, respectively. The mean TSAT level in the EPO-α, DA-α, and CERA groups at month 0 was 30.1%, 39.4%, and 32.8%, respectively. No significant differences were observed in parameters such as clinical

characteristics, demographics, Hb levels, and TSAT levels among the three groups, except for baseline body weight.

Primary endpoint

The mean Hb concentrations measured every month are depicted in Figure 1. For 12 months, the mean Hb levels in all three groups were within the range of 10.5–12.5 mg/dL, aligning with the guidelines of the Korean Society of Nephrology for managing anemia in CKD patients. No significant difference concerning the mean Hb concentration was observed among the three groups ($p = 0.159$).

The ESA resistance index is influenced by several factors, including infection or inflammation, increased parathyroid hormone levels, and TSAT. First, the mean WBC count at baseline in the EPO-α, DA-α, and CERA groups was 5,440/μL, 5094/μL, and 5,692/μL, respectively. For 12 months, the mean WBC count in the three groups remained within the normal range, as shown in Figure 3. No significant difference concerning the mean WBC counts was observed among the three groups ($p = 0.183$). Second, the mean iPTH level at baseline in the EPO-α, DA-α, and CERA groups was 426.0 pg/mL, 275.7 pg/mL, and 272.3 pg/mL, respectively. No significant difference concerning the mean iPTH level was observed among the three groups ($p = 0.747$; Figure 4). The iPTH levels in all three groups adhered to the KDIGO guidelines, maintaining a range of two to nine times the upper normal limit, corresponding to 130–600 pg/mL. Third, the mean TSAT level at baseline in the EPO-α, DA-α, and CERA groups was 30.1%, 39.4%, and 32.8%, respectively. No difference concerning the mean TSAT level was observed among the three groups ($p = 0.093$). Furthermore, TSAT level in all three groups was over 20%, aligning with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NFK-KDOQI) guideline (Figure 2).

We also compared the ESA resistance index (ERI, IU/kg/week/g/dL) of the three groups. ERI is an indicator of hyporesponsiveness to ESA treatment. Resistance to ESA is defined as

the target Hb levels with doses exceeding 20,000 IU/week of EPO (300 IU/kg/week) or 100 mg/week of DA (1.5 mg/kg/week)(9). The mean ERI values during the 12-month observation period are depicted in Figure 5. A significant difference in ERI was observed among the three groups ($p = 0.002$). Nevertheless, ERI in all three groups remained below 300 IU/kg/week.

Secondary endpoint

The secondary endpoint involved comparing the cost incurred by each group, calculated as the mean ESA dose (units/month) × price/unit. At the maximum dose of each ESA, the prices for EPO-α, DA-α, and CERA in 2018 were 21,799 won/10,000 IU, 67,840 won/120 mcg, and 242,751 won/360 mcg, respectively. The mean ESA dose (units/month) for the EPO-α, DA-α, and CERA groups was 41,375.0 IU/month, 125.8 mcg/month, and 121.4 mcg/month, respectively. Thus, the mean cost incurred by the EPO-α, DA-α, and CERA groups in 2018 was 90,193.3 ± 34,510.0 won, 71,142.3 ± 33,312.6 won, and 81,846.3 ± 54,852.9 won, respectively ($p = 0.298$; Figure 6).

At the maximum dose of each ESA, the prices for EPO-α, DA-α, and CERA in 2023 were 21,043 won/10,000 IU, 47,436 won/120 mcg, and 238,805 won/360 mcg, respectively. When calculated using the 2023 prices, the mean cost for the EPO-α, DA-α, and CERA groups was 87,065.3 ± 3,3313.1 won, 49,745.5 ± 23,293.4 won, and 80,515.9 ± 53,961.2 won, respectively ($p < 0.001$; Figure 7).

Table 1. Baseline characteristics of the study population

Characteristics	Type of ESAs			
	EPO-α (n = 10)	DA-α (n = 48)	CERA (n = 13)	p-value
Age (yrs) , SD	66.9 (10.2)	64.6 (13.7)	66.8 (16.1)	0.813
Sex, n (%)				0.761
Male	4 (40%)	25 (52.1%)	6 (46.2%)	
Female	6 (60%)	23 (47.9%)	7 (53.9%)	
Dry body weight (kg), SD	50.1 (8.1)	60.9 (10.6)	64.5 (11.3)	0.005
Duration of hemodialysis (yrs), Median, IQR	15.6 (10.7, 21.0)	7.3 (3.9, 12.8)	6.2 (3.5, 13.0)	0.068
Cause				0.312
Diabetes mellitus	5 (50%)	19 (39.6%)	6 (46.2%)	
Hypertension	4 (40%)	9 (18.8%)	4 (30.8%)	
Glomerulonephritis	1 (10%)	10 (20.8%)	3 (23.1%)	
Others	0 (0%)	10 (20.8%)	0 (0%)	

Abbreviations: ESAs, erythropoiesis-stimulating agents; SD, standard deviation; IQR, inter Quartile Range; TSAT, transferrin saturation

Table 2. Comparisons of hemoglobin levels and the factors contributing to erythropoiesis

	Months of follow-up					p-value for interaction	p-value for group
	0	**2**	**5**	**8**	**11**		
Hb (g/dL)						0.524	0.159
EPO-α	10.4 (9.9, 11.0)	10.8 (10.2, 11.4)	10.7 (10.1, 11.2)	10.8 (10.2, 11.4)	10.5 (9.8, 11.2)		
DA-α	10.4 (10.2, 10.7)	10.8 (10.5, 11.0)	11.2 (10.9, 11.4)	10.9 (10.6, 11.2)	10.6 (10.3, 10.9)		
CERA	10.3 (9.8, 10.7)	11.0 (10.5, 11.6)	10.9 (10.4, 11.3)	11.0 (10.4, 11.5)	10.5 (9.9, 11.1)		
TSAT (%)						0.077	0.093
EPO-α	30.1 (21.6, 38.5)	30.5 (21.2, 39.7)	31.9 (25.1, 38.8)	34.9 (27.7, 42.1)	30.0 (21.6, 38.4)		
DA-α	39.4 (35.6, 43.3)	43.8 (39.6, 48.0)	40.1 (37.0, 43.2)	35.1 (31.8, 38.4)	37.7 (33.8, 41.6)		
CERA	32.8 (25.4, 40.2)	32.6 (24.5, 40.7)	32.7 (26.7, 38.7)	35.7 (29.3, 42.0)	32.1 (24.7, 39.5)		
WBC (count/uL)						0.799	0.183
EPO-α	5,440 (4,444, 6,436)	5,530 (4,472, 6,588)	5,660 (4,579, 6,741)	6,210 (4,937, 7,483)	6,020 (4,865, 7,175)		
DA-α	5,094 (4,639, 5,548)	5,156 (4,673, 5,639)	5,263 (4,769, 5,756)	5,221 (4,640, 5,802)	5,004 (4,477, 5,531)		
CERA	5,692 (4,819, 6,566)	5,700 (4,722, 6,628)	5,685 (4,737, 6,633)	6,269 (5,153, 7,386)	6,308 (5,295, 7,321)		
iPTH (pg/mL)						0.611	0.747
EPO-α	369.7 (146.5,593.0)	197.5 (-26.05,421.0)	202.5 (-16.56,421.5)	267.6 (93.7,441.4)	260.2 (95.0,425.3)		

DA-α	273.4 (184.1,362.7)	388.3 (298.6,478.0)	255.1 (170.6,339.6)	285.9 (207.3,364.5)	257.9 (179.6,336.3)			
CERA	268 (94.9,441.0)	289.7 (130.0,449.5)	400.1 (251.3,548.8)	269.7 (133.7,405.6)	272.2 (85.0.459.4)			
ERI (IU/kg/wk/g/dL)						0.564	0.002	
EPO-α	21.3 (14.4,28.1)	20.7 (13.8,27.5)	19.7 (12.9,26.6)	20.4 (13.5,27.2)	18.4 (11.6,25.3)			Ref.
DA-α	15.8 (12.7,19.0)	11.3 (8.1,14.4)	9.6 (6.4,12.7)	13.2 (10.1,16.4)	14.1 (11.0,17.3)			0.003
CERA	14.3 (8.3,20.3)	8.8 (2.8,14.8)	10.0 (4.0,16.0)	8.2 (2.2,14.2)	10.0 (4.0,16.0)			0.001

Abbreviations: Hb, hemoglobin; TSAT, transferrin saturation; WBC, white blood cell; iPTH, intact parathyroid hormone; ERI, erythropoietin resistance index; EPO-α, epoetin alfa; DA-α, darbepoetin-alfa; CERA, continuous erythropoiesis receptor activator; Ref, reference

Figure legends

Figure 1. The mean hemoglobin level of each group during the 12-month observation period

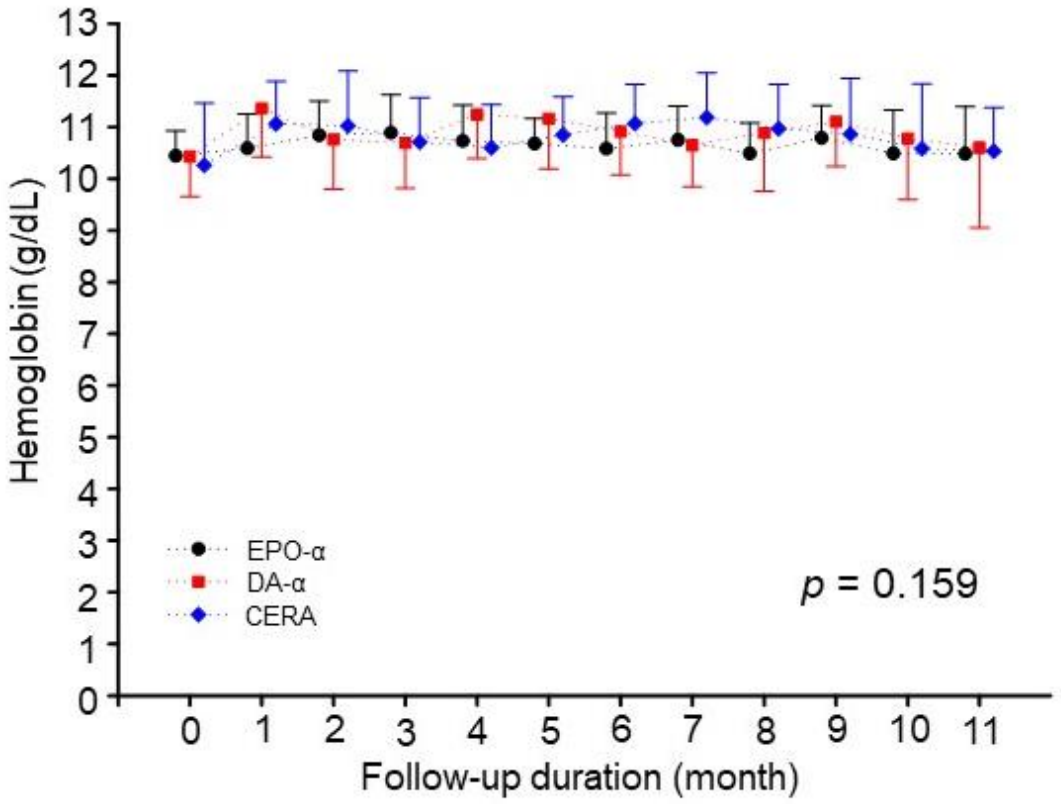


Figure 2. The mean transferrin saturation (TSAT) level of each group during the 12-month of observation period

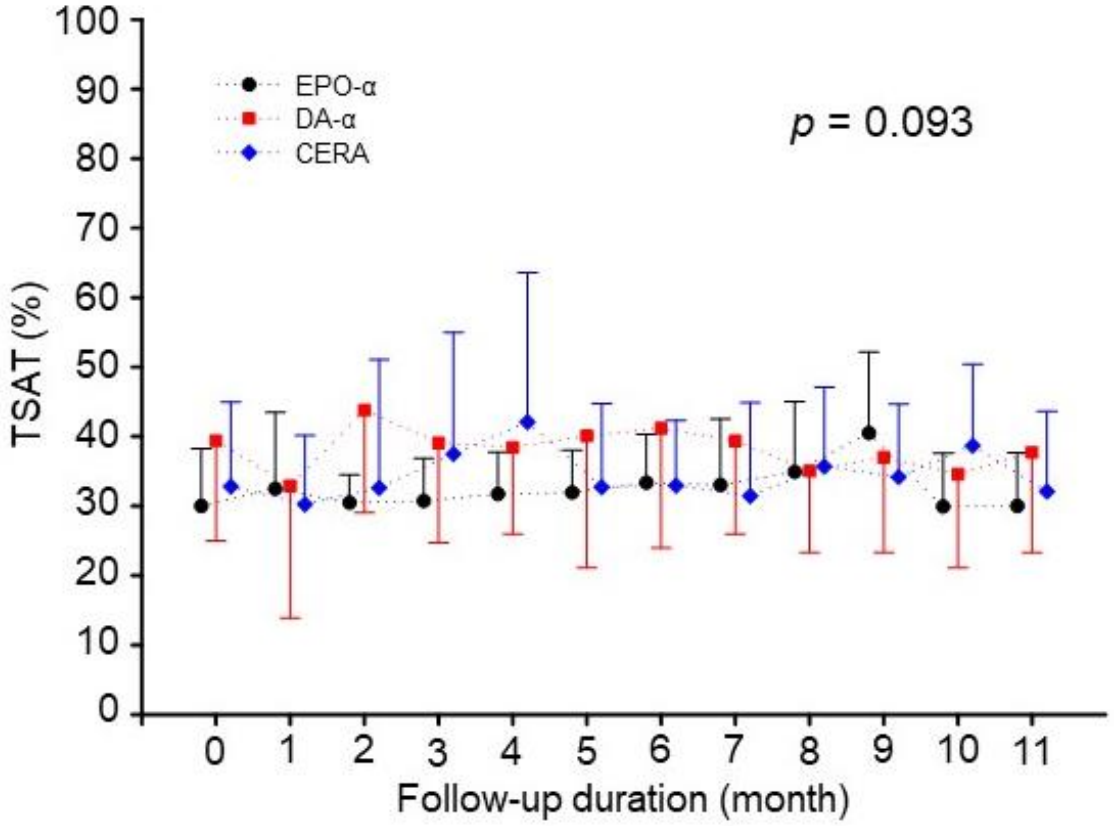


Figure 3. The mean white blood cell (WBC) count of each group during the 12-month of observation period

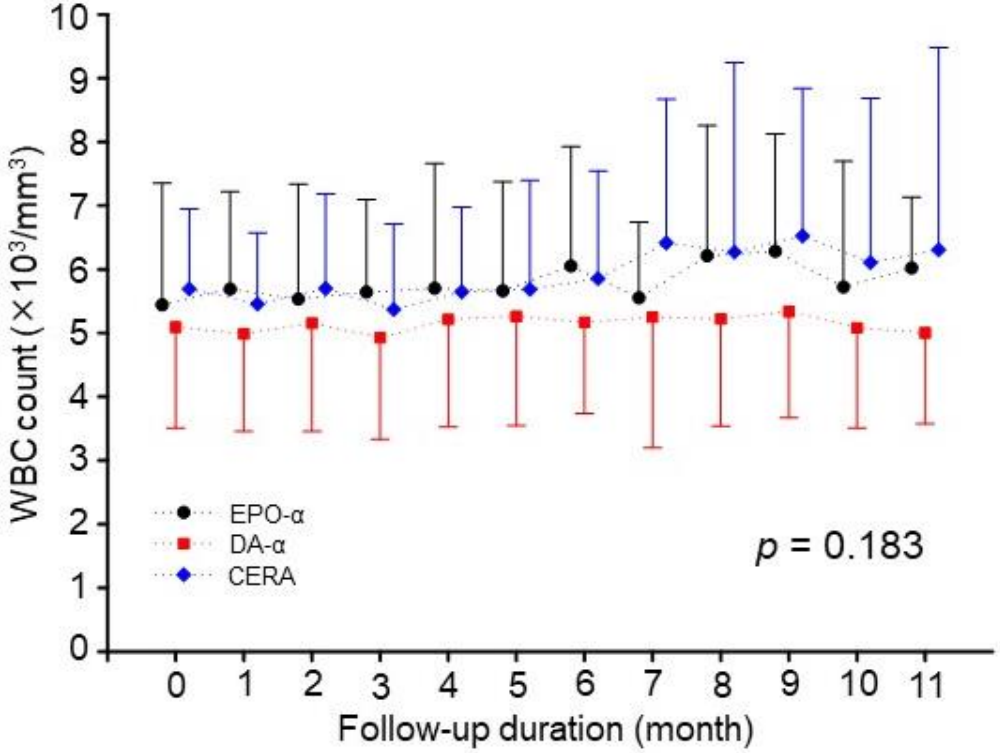


Figure 4. The mean intact parathyroid hormone (iPTH) level of each group during the 12-month of observation period

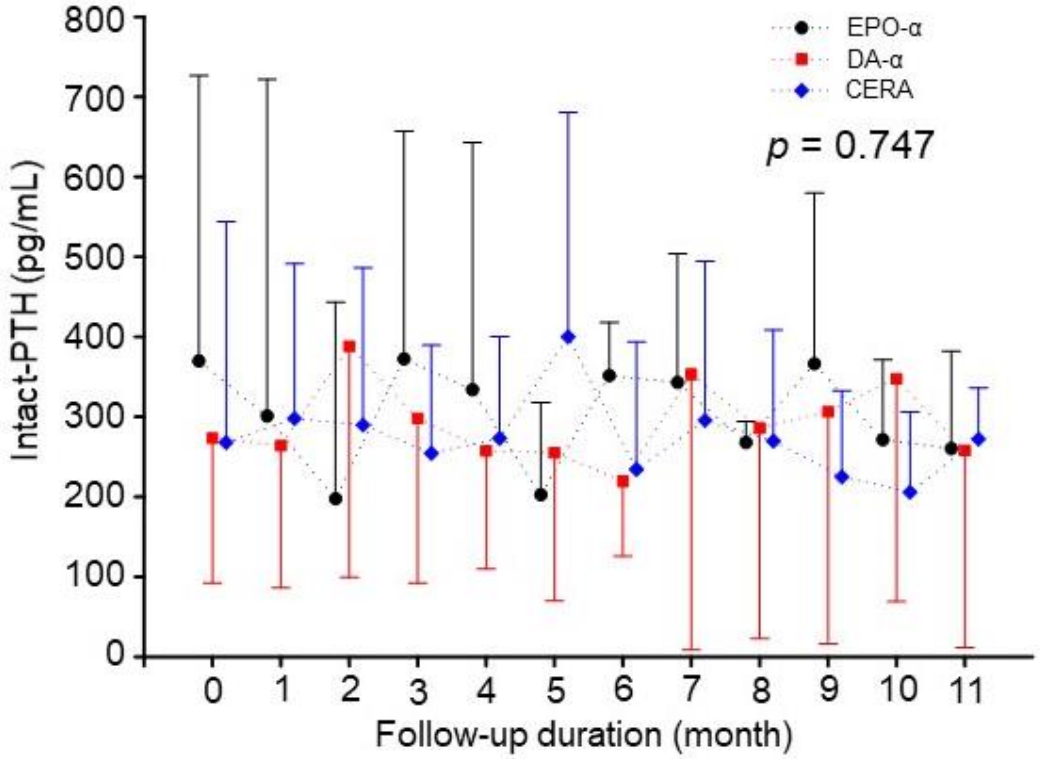


Figure 5. The mean erythropoietin resistance index (ERI) value of each group during the 12-month observation period

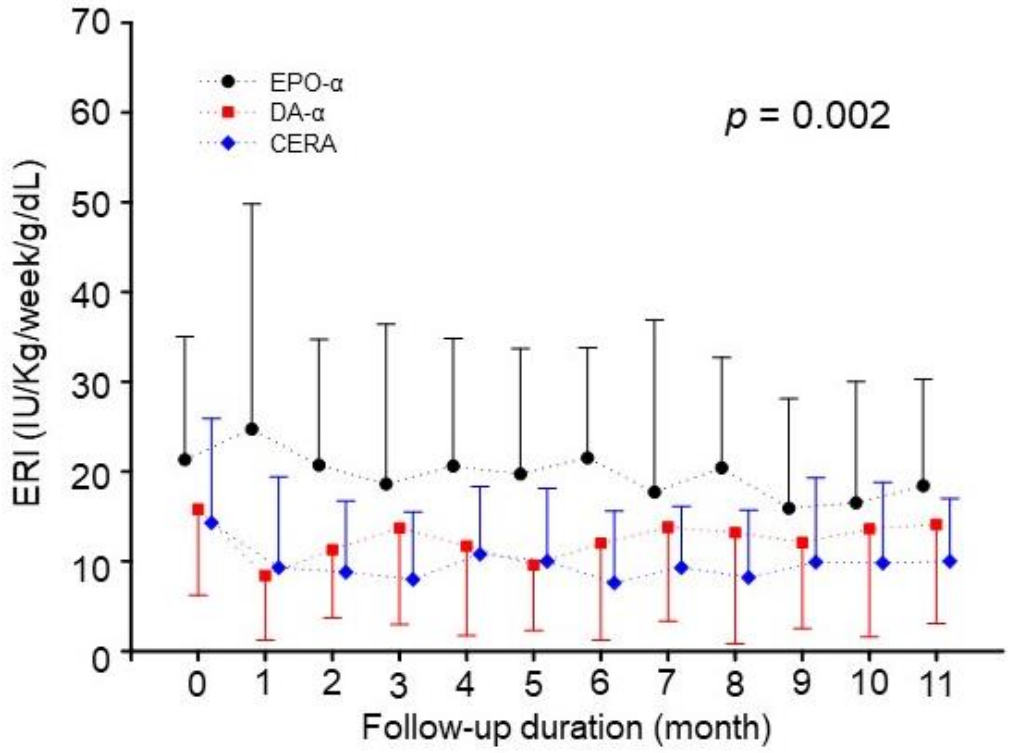


Figure 6. The cost of erythropoiesis-stimulating agent (ESA) calculated as the mean ESA dose (units/month) × price/unit for each group based on the 2018 prices.

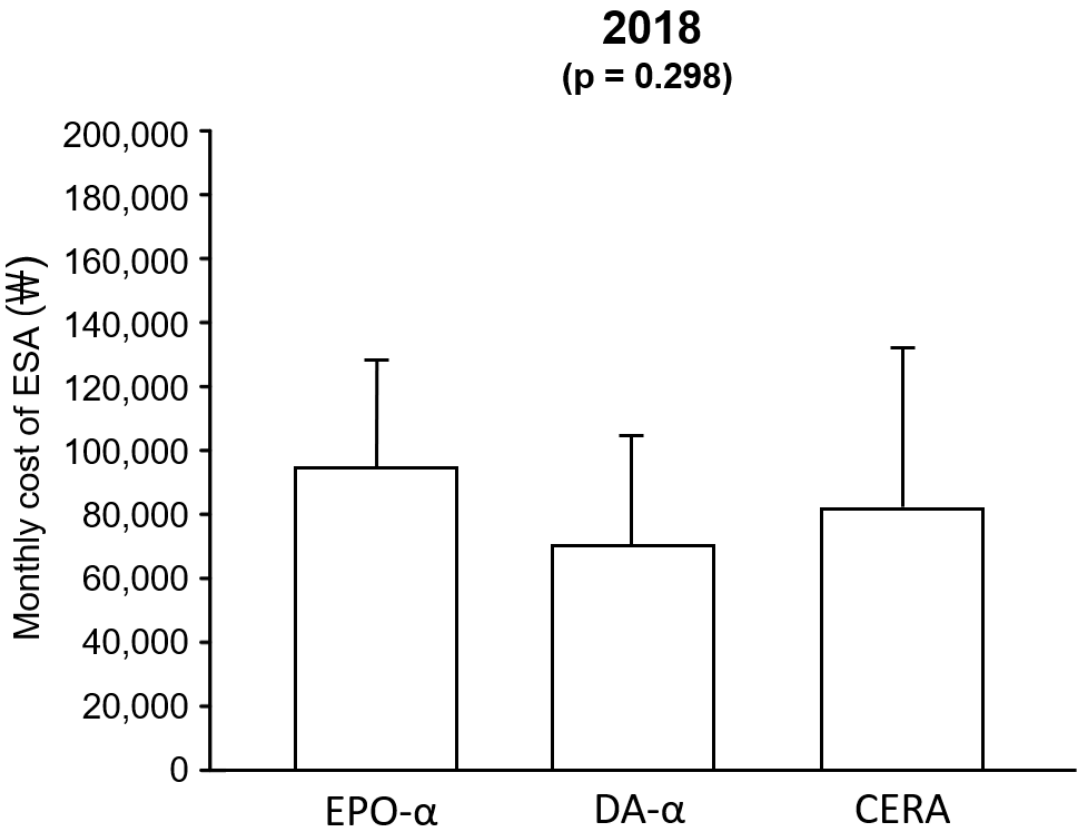
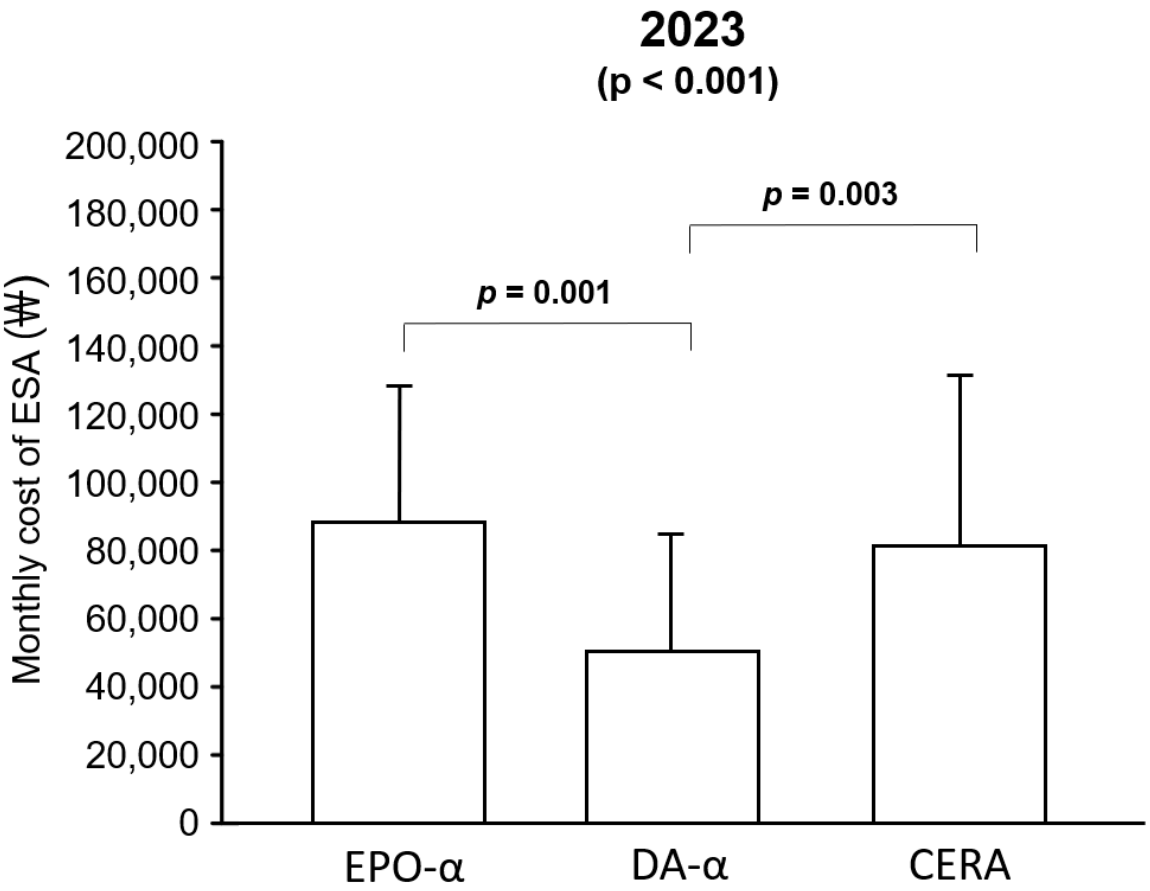


Figure 7. The cost of ESA, calculated as the mean ESA dose (units/month) × price/unit, for each group based on the 2023 prices.



Discussion

Given that erythropoietin deficiency is the primary cause of renal anemia, the administration of ESAs to treat renal anemia in ESRD patients is crucial. This approach offers various benefits, including the avoidance of blood transfusion-associated side effects, improvement of the quality of life, and reduction in mortality (10, 11). In this study, the Hb levels were consistently maintained at normal levels irrespective of whether EPO-α, DA-α, or CERA was used in the treatment of renal anemia. Notably, DA-α was the most cost-effective among the studied ESAs.

Contrary to the short half-life (approximately 5 h) of native EPO produced in the kidneys (12), the currently used ESAs have longer half-lives, suggesting a prolonged hematopoietic effect. However, various studies have indicated that this expectation does not align with reality. Lee et al. reported that, in a randomized crossover study comparing the hematopoietic effects of EPO-α and DA-α in hemodialysis patients, no significant difference was observed between the two groups in the rate change in Hb levels. Furthermore, no significant difference was observed in the time taken for Hb levels to decrease lower than 11.0 g/dL after stopping ESAs when the initial Hb level was higher than 11 .0 g/dL (13). Macdougall et al. revealed that, in their randomized clinical trial comparing CERA administered once every two weeks and DA-α administered once every week in CKD patients who are not on dialysis, no significant difference was observed between the two groups in terms of anemia correction. However, the median response time in the CERA group was slower than that in the DA-α group (14). Another randomized trial comparing CERA administered once every four weeks and DA-α administered once every week, showed that CERA successfully corrects anemia and maintains stable Hb levels in non-dialysis CKD patients. However, the median time for Hb response was 43 days in the CERA group, whereas it was only 29 days in the DA-α group (15).

As previous studies have indicated, a longer half-life of ESA does not necessarily translate

to prolonged hematopoiesis or quicker anemia correction. About this, Egrie et al. proposed an inverse relationship between the half-life of ESA and receptor-binding affinity (16). McGowan et al. demonstrated that the ESA administration interval and dose are more important than the half-life of ESAs used in anemia treatment. In their study, they highlighted similar changes in the mean Hb levels of non-dialysis CKD patients receiving one of the following four EPO-α dosing regimens: 50 IU/kg three times/week, 10,000 IU once every week, 20,000 IU once every two weeks, or 40,000 IU once every four weeks (17). Therefore, even for ESAs with a short half-life, the dosing interval can be extended by increasing the single dose. This approach can reduce the nursing work for ESA injection, eliminating the need to use ESAs with a long half-life in hemodialysis patients who visit the hospital thrice a week. Similarly, an open-labelled, prospective, observational study revealed no significant differences in the efficacy of once-biweekly treatment with EPO-α 10,000 IU or DA-α 50 μg, implying that a higher dose of EPO-α can be administrated at extended dosing intervals without effecting the overall drug efficacy (18).

Unlike previous studies, our study did not evaluate ESA from multiple perspectives. However, despite using three types of ESAs with different half-lives, no significant difference in the Hb level was observed over a year among the three groups ($p = 0.159$; Figure 1). Therefore, the cost-effectiveness of the three types of ESA was compared to confirm the possibility of reducing medical costs.

For ESA to be effective in correcting renal anemia, there must be no ESA hyporesponsiveness. ESA hyporesponsiveness refers to a situation where excessive amounts of ESA are required to maintain the target Hb level, and it is associated with increased mortality. ESA hyporesponsiveness is defined as the inability to increase Hb levels beyond 11g/dL, even with the administration of 450 units/kg/week of ESA intravenously or 300 units/kg/week of recombinant human erythropoietin (rHuEPO) subcutaneously, as per the KDOQI guideline

(19), or1.5 μg/kg/week of DA-α, as per the European Best Practice guideline (20). While ESA hyporesponsiveness for CERA is undefined, using the conversion ratio of CERA doses to DA-α at 1.2:1 could be helpful (8).

The etiology of ESA hyporesponsiveness is commonly attributed to inflammatory conditions or insufficient iron availability for erythropoiesis. However, considering additional contributory factors, including chronic blood loss, hyperparathyroidism, aluminum toxicity, hemoglobinopathy, vitamin B 12 or folate deficiency, multiple myeloma, myelofibrosis, other malignancies, malnutrition, and hemolysis, is imperative (21). In this study, patients with malignant diseases or significant acute or chronic bleeding were excluded. Furthermore, none of the patients exhibited hemoglobinopathy or bone marrow disease. Additionally, there was homogeneity in the dialysis methods employed, and no clinical manifestations of aluminum toxicity were observed.

The most common reason for ESA hyporesponsiveness is iron deficiency. According to NFK-KDOQI guidelines, patients undergoing hemodialysis and receiving ESAs should maintain a TSAT level higher than 20% (19). In this study, the monthly mean TSAT level in all three groups was consistently above 20%. Therefore, the possibility of ESA hyporesponsiveness due to iron deficiency is deemed low ($p = 0.093$; Figure 2).

Inflammatory or infectious conditions are associated with ESA hyporesponsiveness through several mechanisms: 1) an increased hemophagocytosis by macrophages can lead to slightly shortened red blood cell (RBC) survival; 2) inflammatory cytokines, such as interleukin-1-β (IL-1- β), interleukin-6(IL-6), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ) can contribute to impaired erythroid proliferation and differentiation via radical formation or apoptosis induction; 3) an increase in hepcidin synthesis can inhibit iron absorption and recycling, resulting in altered iron metabolism (20),(22). WBC counts and C-reactive protein (CRP) have long been used as infection and inflammation markers. Usually, leukocytosis

occurs earlier than CRP elevation in infection or inflammatory conditions. In our study, we used WBC count as an inflammatory marker. In all three groups, the mean WBC counts were in the normal range, indicating that all patients were not in an infectious or inflammatory condition that could influence ESA hyporesponsiveness (p = 0.183; Figure 3).

Elevated serum iPTH levels lead to a significant decrease in erythropoietin production, inducing an inhibitory effect on erythroid progenitors by downregulating erythropoietin receptors, and increasing the insensitivity of erythroid progenitor cells to erythropoietin. Moreover, increased iPTH levels lead to a hemolytic effect (due to calcium disturbance) and enhance osmotic pressure and the fragility of RBCs (23). According to the KDIGO guidelines, iPTH levels are recommended to be two to nine times the upper normal limit, corresponding a range of 130–600 pg/mL. In our study, the mean iPTH levels in all three groups were in the recommended range (p = 0.747; Figure 4).

The present study employed ESAs with different half-lives, recommended usage, and target patient body weights, necessitating standardization. Therefore, we compared the efficiency of the three ESAs using ERI, standardized by body weight. In our study, a significant difference in baseline body weight was observed among the three groups (p = 0.005), prompting the use of ERI to overcome this variation. During the 12-month observation period, the mean ERI values of EPO-α were significantly higher than those of the other two groups (p = 0.002). However, these values did not exceed the reference value of 300 IU/kg/week, indicating no clinical significance.

In a cohort study based on the dialysis registry in Japan, out of 194,698 hemodialysis patients, users of long-acting ESAs (DA or CERA) exhibited a 13% higher mortality rate compared to users of short-acting ESA (EPO-*α*/*β* or EPO-*κ)*; this difference was statistically significant (p < 0.001). The study also revealed that the use of long-acting ESAs was associated with an increased rate mortality from cardiovascular diseases, infection, and

malignancies (24).

In another systemic review and meta-analysis study comprising nine randomized trials to compare the effects of EPO-α and DA-α, 126 of the 2,024 CKD patients, including those requiring hemodialysis, died during the follow-up period. The follow-up period ranged from 20 to 52 weeks, and no significant difference in mortality was observed between patients administered EPO-α and DA-α (Odds ratio = 1.33, 95% Confidence interval = 0.88–2.01) (25).

While the earlier mentioned cohort study in Japan has the limitation of being an observational study rather than a large-scale randomized controlled trial, it demonstrated that using an ESA with a short half-life is safe. Conversely, another study demonstrated that there is no significant difference in mortality between the EPO-α and DA-α groups. Therefore, considering the cost-effectiveness of DA-α demonstrated in our study, active use of DA-α is advantageous in terms of reducing medical costs.

This study has a few limitations. Firstly, the small number of patients may limit the generalizability of the results. Secondly, the number of patients in the DA-α group was higher than those in the EPO-α and CERA groups. Thirdly, as a retrospective observational study conducted over one year, this study does not provide insights into the long-term side effects of ESAs.

In summary, the EPO-α, DA-α, and CERA groups did not show significant differences in maintaining the target Hb level in ESRD patients undergoing hemodialysis. Furthermore, although the mean ERI values of the EPO-α group were significantly higher than those of the other two groups, they were consistently below 300 IU/kg/week during the 12-month observation period; thus, the values did not align with the definition of ESA hyporesponsiveness. On the other hand, the DA-α group exhibited the lowest mean medical cost to maintain the target Hb range compared to the other two groups, based on both 2018 and 2023 prices. These findings should be further validated through a large-scale study using

data from the Health Insurance Review and Assessment Service of the Republic of Korea.

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Abstract

Background & Aims: Anemia in chronic kidney disease (CKD) patients is associated with increased cardiovascular complications and mortality. Therefore, the administration of erythropoiesis-stimulating agents (ESAs) until renal transplantation is indispensable. This study compared the effects and costs of ESAs in CKD patients undergoing hemodialysis, aiming to reduce medical costs.

Methods: This retrospective cohort study comprised patients aged over 18 years, undergoing hemodialysis at Asan Medical Center from January 1, 2018, to July 2, 2019, and receiving ESA [epoetin alfa (EPO-α, Epokine®), darbepoetin-alfa (DA-α, Nesp®), and methoxypolyethyleneglycol-epoetin-beta (continuous erythropoiesis receptor activator, CERA, Mircera®)] for anemia treatment. The mean hemoglobin concentrations and the costs incurred [mean ESA dose (units/month) × price/unit (during 2018 and 2023)] for the EPO-α, DA-α, and CERA groups over a year were compared.

Results: The mean hemoglobin levels exhibited no significant difference among the three groups ($p = 0.159$). Furthermore, although the mean erythropoietin resistance index (ERI) values were significantly higher in the EPO-α group ($p = 0.002$), they remained below 300 IU/kg/week throughout the 12-month follow-up period, failing to meet the definition of ESA resistance. Meanwhile, based on the 2018 and 2023 prices, the DA-α group incurred the lowest mean cost of 71,142.3 ± 33,312.6 won and 49,745.5 ± 23,293.4 won, respectively. ($p < 0.001$).

Conclusions: While the three groups exhibited no significant differences in hemoglobin levels, the DA-α group achieved the target range at the lowest mean cost. To reinforce these results, a comprehensive study using data from the Health Insurance Review and Assessment Service of the Republic of Korea is warranted.