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Impact of Altitude on Anemia, Erythropoietin-Stimulating Agent, and İntravenous Iron Requirement in Hemodialysis Patients

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ABSTRACT

Anemia is an important cause of morbidity and mortality in chronic kidney disease (CKD). Previous studies have shown the curative effects of altitude on anemia in hemodialysis (HD) and non-hemodialysis CKD. This study examined the effect of altitude on erythropoietin stimulating agent (ESA), İntravenous (IV) iron requirement in HD patients.

This retrospective observational study was conducted between January and June 2023. The study group was divided into two groups according to altitude: HD patients living in Van Province (1,730 meters, 5,765 feet) in the high-altitude group (HAG) and HD patients living in Istanbul Province (sea level) in the low-altitude group (LAG). In addition to hemoglobin (Hgb) and ferritin levels, ESA and IV iron doses were recorded at monthly visits for six months. These values of the HAG and LAG were compared.

A total of 184 patients were included in the study (HAG: 108 patients and LAG: 79 patients). HD patients living at high altitudes had statistically significantly higher Hgb and ferritin values compared to low altitudes (HAG: 11.5 g/dL, 749 pg/L vs. LAG: 11.3 g/dL; 543 pg/L; p=0.04, p< 0.001, respectively). In addition, ESA (HAG: 53 IU/kg/week, 12000 IU/month vs. LAG: 100.6 IU/kg/week, 24000 IU/month; p<0.001) and IV iron (HAG: 208.3±151 mg/month vs. LAG:364.9±300.8 mg/month; p=0.002) dose was significantly lower.

HD patients living at high altitude needed lower doses of ESA and IV iron to reach higher Hgb values than patients living at lower altitude.

Keywords: Altitude, anemia, hemodialysis, erythropoietin stimulating agent, iv iron

Introduction

Anemia is an important problem associated with increased mortality and morbidity in chronic kidney disease (CKD). As renal functions deteriorate, the frequency and severity of anemia intensify (1-5). The etiology of anemia in CKD is multifactorial, with the most prominent cause attributed to relative erythropoietin (EPO) deficiency due to decreased kidney volume. Anemia is mainly treated with intravenous (IV) iron supplementation and erythropoiesis-stimulating agents (ESAs) in hemodialysis (HD) patients (1, 5).

Erythropoietin is produced in the cortical peritubular fibroblasts of the kidney under the

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control of oxygen-dependent genes. The most important stimulus in this process is generated by hypoxia-inducible factors (6). When oxygen and iron are sufficiently available, hypoxia-inducible factor prolyl hydroxylase (HIF-PH) facilitates the degradation of HIF. Conversely, under hypoxemic conditions, HIF-PH is inactivated, resulting in the accumulation and activation of HIF molecules within the cytoplasm. This activation subsequently triggers the essential cascade leading to EPO production (7-9).

The partial oxygen pressure decreases when ascending to higher altitudes above sea level, resulting in an increase in EPO production and stimulation of erythropoiesis through the HIF pathway. In previous studies examining the effects of high altitude in HD patients, it has been reported that the prevalence of anemia is lower in patients living at high altitudes, and these patients require lower doses of ESA and IV iron (10-12). Additionally, decreased mortality has been reported in HD patients living at high altitudes compared to patients living at low altitudes (12-15).

In this study, we primarily aimed to examine the effect of altitude on the prevalence of anemia. Our second goal was to investigate the differences in ESA and IV iron requirements in HD patients.

Material and Methods

The study was approved by the local ethics committee (number 2022/11-03) and conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

This retrospective observational study was conducted between January and June 2023, encompassing HD patients under regular follow-up across two distinct HD facilities situated in Istanbul and Van provinces. Eligibility criteria included patients who had undergone HD at the same location for at least six months.

Van Province, elevated at 1,730 meters (5,675 feet) above sea level, constituted the high-altitude group (HAG), comprising patients receiving HD in this region. In contrast, Istanbul Province, situated at sea level, constituted the low-altitude group (LAG), encompassing patients from this region.

Exclusion criteria involved patients younger than 18 years old and those with a history of kidney transplantation, peritoneal dialysis, solid organ or hematological malignancies, rheumatic disease, active infection, hypoxemic conditions, and hemoglobinopathy.

Data were collected from patient files and the electronic databases of the centers. Demographic data (age, gender, height, weight, body mass index), CKD etiologies (diabetes mellitus, hypertension, chronic glomerulonephritis, polycystic kidney disease, urologic problems), HD access type, mean arterial pressure, HD duration, dialysis efficacy (Kt/V), and residual urine volume were recorded.

Laboratory data, including white blood cell (WBC) count, hemoglobin (Hgb) level, platelet count (PLT), transferrin saturation, ferritin, albumin, parathyroid hormone (PTH), and C-reactive protein (CRP), were recorded by taking the averages of monthly visits from the past six months. Information concerning IV ESA and iron treatments administered during dialysis sessions was also documented.

Procedures: During the six-month period, patients were assessed through monthly visits. The type of ESA used (darbepoetin alfa, epoetin zeta, and epoetin alfa), duration of ESA application, and ESA doses were calculated in international units (IU) per month and kilograms (kg) per week. For dose equivalence, epoetin zeta and epoetin alfa were considered equivalent (16). Darbepoetin alfa doses were converted to IU, assuming 1 μg of darbepoetin alfa was equivalent to 200 IU of epoetin zeta/alfa (17). IV iron usage, duration, and monthly doses were recorded. The dialysis was considered adequate if the single-pool Kt/V was greater than 1.2 (18).

Statistical Analysis: Descriptive data were recorded as frequencies and percentages for categorical variables, while continuous variables were presented as medians, ranges (minimum-maximum), and mean±standard deviation (SD). The normality of data was tested using the Kolmogorov-Smirnov and Shapiro-Wilks tests, which indicated a non-normal distribution. Continuous variables from two independent groups were compared using the Mann-Whitney U test. Fisher's exact test was employed for comparing categorical variables. Statistical analyses were performed using IBM SPSS for Windows v.22 software, and the results were reported with 95% confidence intervals. Values of $p<0.05$ were considered significant.

Results

A total of 184 patients were included in the study (HAG: 108 patients and LAG: 79 patients). The study cohort was divided into two groups based on altitude: HAG, representing 1,730 meters (5,765 feet), and LAG, signifying sea level. Patients living at high altitudes were comparatively older (HAG: 59.9±15.4 years vs. LAG: 53.9±15.9 years; p=0.011). In the HAG, diabetes mellitus was the predominant cause of CKD, whereas hypertension held this distinction in the LAG (p<0.001). The preponderance of HD vascular access comprised arteriovenous fistulas in both groups, with tunneled central venous catheters more prevalent in the LAG (p=0.014). Mean arterial pressure was higher in the LAG (LAG: 100 mmHg vs. HAG: 97 mmHg; p=0.02). Notably, the single-pool Kt/V value of the LAG was significantly higher than the HAG (LAG: 1.66 vs. HAG: 1.38; p<0.001). However, the rate of patients who underwent effective HD, accepted as single-pool Kt/V >1.2, was similar (LAG: 84% vs. HAG: 75%; p=0.11). The prevalence of patients retaining residual urine was higher in the LAG (LAG: 71% vs. HAG: 0%; p<0.001). Gender distribution, BMI and duration of hemodialysis were similar (Table 1).

White blood cell, albumin, and PTH levels of the patients in the LAG were higher than those in the HAG. Moreover, Hgb values were statistically significantly higher in the HAG compared to the LAG (HAG: 11.5 g/dL vs. LAG: 11.3 g/dL; p=0.04), and ferritin levels exhibited the same pattern (HAG: 749 pg/L vs. LAG: 543 pg/L; p<0.001). Although the incidence of patients with hemoglobin values ≥10 g/dL was greater in the LAG, no statistically significant discrepancy emerged between the two groups (p=0.06). Meanwhile, transferrin saturation was lower in the LAG (LAG: 30% vs. HAG: 26%; p=0.004) (Table 2).

ESA and IV iron usage characteristics of the patients are shown in Table 3. ESA usage, type of ESA used, and duration of use were similar in both groups (p=0.69, p=0.14, and p=0.94, respectively). ESA dosing was statistically significantly lower in the HAG than the LAG (HAG: 53 IU/kg/week, 12000 IU/month vs. LAG: 100.6 IU/kg/week, 24000 IU/month; p<0.001). Furthermore, the frequency and duration of IV iron use were significantly higher in the LAG (HAG: 208.3±151 mg/month vs. LAG: 364.9±300.8mg/month; p=0.002) (Table 3).

Discussion

This study marks the pioneering exploration of the interrelation between altitude and anemia in HD patients in Turkey. Our findings illuminate a distinctive trend: patients residing at high altitudes (1,730 meters/5,765 feet) exhibit improved anemia outcomes compared to their low-altitude counterparts (sea level). In our study, HD patients living at high altitudes needed lower doses of ESA and IV iron compared to those living at low altitudes, while had higher Hgb levels. Our results are consistent with previous studies demonstrating the curative effect of altitude on anemia, IV and IV iron doses (10-12, 19).

We conventionally know that patients who live at higher altitudes experience elevated Hgb values compared to those at sea level. Although the hypothesis that high-altitude patients would produce more endogenous EPO and require less exogenous EPO was used to explain our results, an interesting aspect in our patient group is the absence of residual urine in the high-altitude group. ESA is more likely to cause a better response at higher altitudes. However, prolonged stays at high altitudes are known to cause a higher ESA response (10-12).

Although there are recommendations for increasing the anemia limit in patients living at high altitudes, it has not been routinely applied to clinical practice (20, 21).

In a study by Brookhart et al. (10) involving 341,737 HD patients in the USA from 1995 to 2004, altitude was categorized into five groups: <250 ft, 1,999 ft, 2,000-3,999 ft, 4,000-5,999 ft, and >6,000 ft. The research revealed that patients living above 6,000 ft. experienced a 1.1 increase in hematocrit levels (35.7% vs. 34.6%) while requiring 19% less ESA (12,900 vs. 15,900 IU/week) compared to sea-level residents. The same study showcased that higher hematocrit levels correlated with lower ESA doses, even after adjusting for confounding variables like CKD etiology, age, gender, and race. Our study also supports the achievement of higher hematocrit levels with lower ESA doses, a main finding of our research. However, the ESA dose in the high-altitude category in our study was 3000 IU/week, approximately 25% of the ESA dose highlighted in Brookhart et al.'s study. This finding reflects the revolving ESA dose reduction policies over the years, where higher Hgb targets have been associated with increased mortality rates (22-25). Another finding of Brookhart et al.'s study is the decrease in ESA resistance with the increase in

Table 1. Baseline Demographic and Clinical Findings of The Patients

			Groups by altitude status		
		Whole group (n=184)	High-altitude (n=105)	Low-altitude (n=79)	p
		Mean±SD (median) / n (%)	Mean±SD (median) / n (%)	Mean±SD (median) / n (%)	
Male sex		112 (61)	63 (60)	49 (62)	0.780
Age		57.3±15.9 (60)	59.9±15.4 (63)	53.9±15.9 (52)	0.011*
CKD etiology	Diabetes mellitus	72 (39)	50 (48)	22 (28)	
	Hypertension	50 (27)	27 (26)	23 (29)	
	Chronic glomerulonephritis	4 (2)	2 (2)	2 (3)	<0.001
	Polycystic kidney	6 (3)	0	6 (7)	
	Urologic problems	10 (5)	9 (8)	1 (2)	
	Other	5 (3)	0	5 (6)	
	Unknown	37 (21)	17 (16)	20 (25)	
HD vascular access	Arteriovenous fistula	149 (81)	89 (85)	60 (76)	
	Arteriovenous graft	5 (3)	5 (5)	0	0.014
	Tunneled central venous catheter	29 (16)	11 (10)	18 (24)	
BMI		24.9±5.8 (24)	25.01±6 (24)	24.9±5.5 (24)	0.900*
Mean arterial pressure (mmHg)		96.5±13.7 (97)	95.5±7 (97)	97.9±19.2 (100)	0.020*
Hemodialysis duration (months)		70.8±65.8 (48)	607±49.1 (48)	84.3±81.6 (60)	0.110*
Kt/V		1.5±0.3 (1.42)	1.4±0.3 (1.38)	1.63±0.3 (1.66)	<0.001*
Dialysis efficacy	Kt/V >1.2 (effective)	146 (80)	79 (75)	67 (84)	0.110
Residual urine volume (mL/24h)		429.5±532.2 (175)	88.3±66.4 (50)	901.9±534.1 (1000)	<0.001
Residual urine	≥500 mL	23 (12)	0	23 (29)	<0.001

BMI: body mass index, CKD: chronic kidney disease, HD: hemodialysis, SD: standard deviation
*Mann-Whitney U test

altitude (11). Their investigation demonstrated that when HD patients living at low altitudes were moved to higher altitudes, ESA doses decreased and Hgb values increased. This effect was especially pronounced with greater altitudes and longer stays at those altitudes, gradually intensifying after 6 to 12 months. These findings were also supported by Sibbel et al.'s study (12).

Moreover, research indicates that substituting treatment at higher altitudes not only holds curative effects on anemia parameters but is also associated with reduced mortality (12-15). However, a contrasting perspective exists in the literature, suggesting that such substitution might not necessarily confer additional benefits (26). It has been postulated that utilizing lower-dose ESA at higher altitudes, juxtaposed with higher-dose ESA at lower altitudes, could potentially correlate with mortality reduction. In 2011, policy shifts were proposed, advocating for drastic reductions in ESA doses due to concerns about the adverse impact of higher hemoglobin targets on mortality

Table 2. Laboratory Outcomes of The Patients

		Whole group (n=184)	Groups by altitude status: High-altitude (n=105)	Low-altitude (n=79)	p
		Mean±SD (median) / n (%)	Mean±SD (median) / n (%)	Mean±SD (median) / n (%)	
White blood cell count (103/mm3)		6628.1±2291.5 (6380)	5965.4±2113 (5460)	7511.6±2233.1 (7075)	<0.001*
Hemoglobin (g/dL)		11.4±1.4 (11.4)	11.6±1.4 (11.5)	11.1±1.3 (11.3)	0.040*
Thrombocyte (103/mm3)		197±69 (197)	188±62 (184)	209±75 (205)	0.080*
Transferrin saturation (%)		31.6±17.4 (27)	27.9±11.9 (26)	36.5±21.9 (30)	0.004*
Ferritin (pg/L)		708.6±382.7 (614)	800.3±387 (749)	586.3±342.5 (543)	<0.001*
Albumin (g/dL)		3.9±0.3 (3.9)	3.8±0.3 (3.9)	4.1±0.3 (4.2)	<0.001*
Parathyroid hormone (ng/L)		410.6±414 (283)	380.7±461.7 (251)	450.4±339.2 (349.5)	0.005*
C-reactive protein (mg/L)		9.1±9.9 (5.9)	8.3±9.4 (5.6)	10.0±10.6 (6.5)	0.230*
Hemoglobin (g/dL)	≥10 mg/dl	159 (86)	95 (90)	64 (81)	0.060*
	<10 mg/dl	25 (14)	10 (10)	15 (19)	

SD: standard deviation
*Mann-Whitney U test

Table 3. ESA and IV Iron Usage By Altitude

		Whole group (n=184)	Groups by altitude status: High-altitude (n=105)	Low-altitude (n=79)	p
		Mean±SD (median) / n (%)	Mean±SD (median) / n (%)	Mean±SD (median) / n (%)	
ESA					
Used in		140 (76)	81 (77%)	59 (75%)	0.690
Type	Darbepoetin alfa	45 (32)	30 (37%)	15 (26%)	0.140
	Epoetin zeta/alfa	95 (68)	51 (63%)	44 (74%)	
Duration of use (months)		12.4±6.3 (13)	12.4±6.1 (12)	12.3±6.7 (13)	0.940*
Dosing	IU/kg/week	71.1±39.6 (63.2)	54.7±31.5 (53)	93.9±39.5 (100.6)	<0.001*
	IU/month	17784.1±10405.6 (16000)	12839.5±7056.6 (12000)	24689.6±10439.8 (24000)	<0.001*
IV iron					
Used in		117 (64)	60 (57)	57 (72)	0.030
Duration of use (months)		6.2±3.9 (6)	4.7±3.7 (4)	7.9±3.5 (7)	<0.001*
Dosing (mg/month)		284.6±247.9 (200)	208.3±151 (200)	364.9±300.8 (200)	0.002*

ESA: erythropoiesis-stimulating agent, IV: intravenous
*Mann-Whitney U test.

(22-25). Sibbel et al. (12) study in 2012, the period after radical changes in ESA doses in the USA, HD patients were evaluated in 5 different altitude groups (0-1499 ft, 1500-2999 ft, 3000-4499 ft, and >4500 ft). The positive effect of altitude on mortality in previous studies is important to observe in this study, despite the changing ESA policies. The relationship between altitude and IV iron is presented for the first time in this study. Supporting previous studies, the highest altitude category (>4,500 ft) exhibited Hgb levels higher than the sea-level category (0-1,499 ft), concurrently requiring lower doses of ESA and IV iron. Ferritin levels were higher in the low-altitude group than in the high-altitude group (low-altitude: 790 ng/mL vs. high-altitude: 694 ng/mL; $p<0.001$). Our study supports these data.

Our study had some limitations. The presence of only two altitude categories and the small number of patients in these categories did not allow for a subgroup analysis. Due to the short follow-up period, we could not examine the relationship between mortality and altitude. Finally, the divergence in healthcare practices between the two distinct centers should also be considered in the interpretation of results.

In conclusion, our study echoes the existing literature, corroborating the beneficial impact of residing at high altitudes on anemia parameters compared to low-altitude living. This advantageous effect is underscored by the attainment of higher Hgb levels while necessitating reduced doses of ESA and IV iron. This study constitutes a pioneering endeavor within our country, marking the first exploration of this domain.

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