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Original article

Living on High Altitudes Associated with Reduced Requirements of Exogenous Erythropoietin in Patients on Chronic Hemodialysis

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Abstract

Introduction: During the last decades the use of erythropoiesis stimulating agents has significantly diminished the prevalence of anemia in patients receiving chronic hemodialysis. Currently, residing at higher altitudes is associated with higher levels of endogenous erythropoietin.

Keywords: Chronic hemodialysis, erythropoietin, high altitude, low altitude, renal replacement therapy, chronic kidney disease.

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Objective: This study aims to analyze how residing at higher altitudes influences the requirements of exogenous erythropoietin in patients receiving hemodialysis as renal replacement therapy.
Methodology: Descriptive observational cross-section, including adult patients from three Ecuadorian centers, receiving chronic hemodialysis, between January and June 2020. Patients were classified into two groups regarding the altitude of residence: those living at low-lying regions (<2000 masl, Santo Domingo de los Tsachilas and Tena) and those living at high altitude (>2000 masl, Quito).
Results: We included 580 patients, 45.5 % in the high-altitude group and 54.5 % at low-lying regions. Median exogenous erythropoietin dose was higher in low-lying regions (22000 international units) versus high altitude (17333.3 international units) (P=0.00003) and the proportion of patients without erythropoietin requirement was higher in high altitude (21.6 %), compared to low regions (1.0 %) (P<0.01). The multivariate analysis associated residing in low regions (HR 58.9, P<0.01), age (HR 0.98, P=0.03) and Kt/V (HR 38.5, P<0.01) with higher exogenous erythropoietin requirements. Additionally, among patients who required erythropoietin, residing in lower altitudes was linked with a need for exogenous erythropoietin doses exceeding 15000 international units per week (HR 1.92, P=0.001).
Conclusion: In Ecuadorian patients receiving hemodialysis, living at high altitude is associated with a reduced requirement of exogenous erythropoietin compared with those patients residing in low-lying regions.

Vivir en altitudes elevadas asociado a requerimientos reducidos de eritropoyetina en pacientes con hemodiálisis

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Resumen

Introducción: durante las últimas décadas, el uso de agentes estimulantes de la eritropoyesis ha disminuido significativamente la prevalencia de anemia en pacientes que reciben hemodiálisis crónica. En la actualidad, residir a mayor altitud se asocia a niveles más elevados de eritropoyetina endógena.
Objetivo: este estudio pretende analizar cómo influye la residencia a mayor altitud en los requerimientos de eritropoyetina exógena en pacientes que reciben hemodiálisis como tratamiento renal sustitutivo.
Metodlogía: estudio transversal observacional descriptivo, que incluyó pacientes adultos de tres centros ecuatorianos, que recibían hemodiálisis crónica entre enero y junio de 2020. Los pacientes se clasificaron en dos grupos en función de la altitud de residencia: los que vivían en regiones de baja altitud (<2000 msnm, Santo Domingo de los Tsachilas y Tena) y los que vivían a gran altitud (>2000 msnm, Quito).
Resultados: se incluyeron 580 pacientes, el 45,5 % en el grupo de gran altitud y el 54,5 % en regiones de baja altitud. La mediana de la dosis de eritropoyetina exógena fue mayor en las regiones de baja altitud (22000 unidades internacionales) en comparación con las de gran altitud (17333,3 unidades internacionales) (p=0,00003) y la proporción de pacientes sin necesidad de eritropoyetina fue mayor en las regiones de gran altitud (21,6 %), en comparación con las de baja altitud (1,0 %) (p<0,01). El análisis multivariante asoció la residencia en regiones bajas (HR 58,9, p<0,01), la edad (HR 0,98, p=0,03) y el Kt/V (HR 38,5, p<0,01) con mayores requerimientos de eritropoyetina exógena. Además, entre los pacientes que precisaron eritropoyetina, residir en altitudes más bajas se relacionó con una necesidad de dosis de eritropoyetina exógena superior a 15000 unidades internacionales por semana (HR 1,92, p=0,001).
Conclusión: en los pacientes ecuatorianos que reciben hemodiálisis, vivir a gran altitud se asocia a una menor necesidad de eritropoyetina exógena en comparación con los pacientes que residen en regiones de baja altitud.

Palabras clave: hemodiálisis crónica, eritropoyetina, gran altitud, baja altitud, tratamiento renal sustitutivo, enfermedad renal crónica.

Introduction

Anemia is a frequent complication in chronic kidney disease (CKD) being more severe as the estimated glomerular filtration rate (eGFR) declines, affecting up to 60 % of patients receiving hemodialysis as renal replace therapy (RRT), and causing an increase in morbidity and mortality, worse renal survival, and reduced quality of life [1, 2]. Different mechanisms have been described to explain the pathophysiology of anemia in CKD, including elevated levels of uremic toxins and the subsequent shortened survival of red blood cells; reduced erythropoietin (EPO) production secondary to a loss in the functioning renal parenchyma; hypo responsiveness to EPO; iron deficiency and, finally, chronic inflammation [3–5]. Over three decades ago, since the development of erythropoiesis stimulating agents (ESA), the red blood cell transfusion requirements reduced significantly in the patients under hemodialysis [6–8]. In this context, the current guidelines on ESA use in hemodialysis recommends its use to achieve a hemoglobin target between 10.0 and 11.5 g/dl [9].

Residing on high altitude (HA) is extensively documented as a factor linked to elevated endogenous levels of EPO, hemoglobin and hematocrit [10,11]. Individuals in such environments develop compensatory mechanisms that persist even in the renal pathology, which decreases exogenous EPO requirements during RRT. Although the relationship between endogenous EPO levels and HA is known, the behavior of hemoglobin levels in CKD and RRT with respect to the two variables mentioned is not clear. Moreover, the available data for Latin America are limited, and the references found in the literature are outdated. The objective of this study is to analyze and update the data available in the Latin American literature on how living in HA influences EPO requirements and hemoglobin levels in patients with terminal CKD receiving hemodialysis as RRT.

Methodology

This is a descriptive observational cross-section study, which included 580 adult patients with a diagnosis of end-stage CKD who received intermittent hemodialysis three times a week as RRT between January and June 2020. Three Ecuadorian centers of the Public Health System support network participated in the study. The participating centers are located at different altitudes in the cities; Santo Domingo de los Tsáchilas at 625 meters above sea level (m.a.s.l.), in Quito at 2850 m.a.s.l. and in Tena at 510 m.a.s.l. The analysis encompassed all patients meeting the inclusion criteria at each respective center.

Inclusion criteria

Adult patients undergoing hemodialysis three times per week, diagnosed with stage 5 CKD, who have been on hemodialysis for more than three months. Additionally, only individuals with comprehensive information on the variables considered in the analysis were included. Exclusion criteria were patients under 18 years of age, and those with incomplete information.

Data extraction and variables

Data were extracted from the medical records in each institution. The variables included in the analysis encompassed demographic information (sex, age, and place of residence), blood laboratory findings (hemoglobin and hematocrit), exogenous erythropoietin dose and requirement (users and non-users), systolic blood pressure (SBP), diastolic blood pressure (DBP), median blood pressure (MBP), parathormone levels (PTH), and hemodialysis efficacy defined by Kt/V.

Study groups

Patients were classified into two groups regarding their residential altitude. Locations with an altitude $\geq$2000 m.a.s.l. were considered HA, whereas locations with an altitude <2000 m.a.s.l. were considered LR. In this context Quito was classified as HA, while Santo Domingo de los Tsachilas and Tena were categorized as LR.

Outcomes

The main outcomes of this study include firstly, the requirement of exogenous EPO defined as the need for ESA to attain internationally recommended hemoglobin levels. Secondly, the median dose administered to those patients receiving exogenous EPO.

Statistics

We used Statistical Package for Social Sciences (SPSS) v.25 for statistical analysis. Descriptive statistics included quantitative and qualitative variables; quantitative variables were represented with median and interquartile range (IQR), or mean and standard deviation, depending on the normality of distribution determined by the Kolmogorov-Smirnov test. Qualitative nominal or ordinal variables were represented as percentages or proportions.

To compare quantitative variables, we used nonparametric methods (Mann-Whitney U or Kruskal-Wallis H) or parametric methods (t-test or ANOVA), as corresponds. The comparison of proportions was performed with the chi-square test. Risk association was estimated using binominal logistic regression. Significance was presented with p-values being significative if P<0.05, along with 95 % confidence intervals (95 % CI).

Results

580 patients were included with a median age of 59 years (IQR 22), with males representing the 52.2 %. The percentages of patients classified by city of residence were Quito 45.5 %, Tena 21.9 %, and Santo Domingo de los Tsachilas (32.6 %), which corresponds to 45.5 % of patients residing in HA, and 54.5 % residing in LR (Table 1).

Table 1. Characteristics of the patients included in the study

	n	**%**
Total	580	100.0
Males	303	52.2
Females	270	46.6
City of residence		
Quito	264	45.5
Tena	127	21.9
SDT	189	32.6
Altitude of residence		
HA	264	45.5
LR	316	54.5
Quantitative variables		
	Median	IQR
Age	59	22
EPO	20000	15000
Kt/V	1,7	0.4
HB	11.5	1.6
SBP	130	20
DBP	70.8	10.7
MBP	93.3	14.2
BMI	24.6	5.5

Note: BMI, body mass index; EPO, erythropoietin dose (UI); DBP, diastolic blood pressure (mmHg); HA, High altitude; HB, hemoglobin level (g/dl); Kt/V, renal urea clearance; MBP, median blood pressure (mmHg); SBP, systolic blood pressure (mmHg).
Source: The authors.

Characteristics of patients residing in HA

The median values and IQR for each variable were as follows: age 63 years (IQR 23), exogenous EPO dose weekly 17333 UI (IQR 16000), BMI 24.5 (IQR 4.9), Kt/V 1.6 (IQR 0.3), and hemoglobin 11.26 g/dl (RIC 1.2). Regarding gender, 53.8 % and 46.2 %, corresponded to males and females, respectively.

Characteristics of patients residing in LR

The median values and IQR for each variable were as follows: age 57 years (IQR 20), exogenous EPO dose weekly 22000 UI (IQR 13857.2), BMI 24.7 (IQR 6.1), Kt/V 1.7 (IQR 0.6), and hemoglobin 11.6 g/dl (RIC 2.2). Regarding gender, 50.9 % and 49.1 %, corresponded to males and females, respectively.

Comparison between populations residing in HA and LR

When comparing the quantitative variables between the analyzed groups using the Mann-Whitney U test, the statistically significant differences correspond to age (P=0.0002), exogenous EPO dose (P<0.001), and SBP (P<0.001). On contrast, the non-significative differences included hemoglobin levels (P=0.20), DBP (P=0.62), MBP (P=0.29) BMI (P=0.05), Kt/V (P=0.05), and PTH levels (P=0.63). The proportion of patients that do not required EPO was significatively higher in the HA group (21.6 %) compared to LR (1.0 %) (chi-square 66.1, P<0.01).

Risk of EPO requirement

Through the use of a univariate binominal logistic regression, we found that residing in LR was associated with an increased risk of requiring exogenous EPO (HR 28.8, 95 % CI 8.9 to 93.0, P<0.01). This finding remained consistent in the multivariate analysis, which included residing in LR (HR 58.9, 95 % CI 13.9 to 249.5, P<0.01), age (as quantitative variable) (HR 0.98, 95 % CI 0.96 to 1.00.0, P=0.03), BMI (HR 1.0, 95 % CI 1.00 to 1.00.0, P=0.97), Kt/V (as quantitative variable) (HR 38.5, 95 % CI 7.53 to 196.52, P<0.01), and gender (HR 1.59, 95 % CI 0.74 to 3.40, P=0.23). The detailed values obtained in the equation are presented in Table 2 . Additionally, in those patients who required exogenous EPO, living in LR was associated with a need of exogenous EPO doses higher than 15000 UI weekly (HR 1.92, 95 % CI 1.32 to 2.78, P=0.001).

Discussion

The adaptive physiological modifications to chronic functional hypoxia, a product of living at high altitudes, are a widely reported phenomenon which varies depending on the affected population. In the case of the Andean population, a significant adaptive mechanism involves an elevation in erythroid mass.

Table 2. Variables in the equation in the binominal logistic regression model

	B	Wald	DF	p-value	Exp(B)	95 % CI	
Variables						Inferior	Superior
Residing in LLR	4,08	30,64	1,00	0,00	58,92	13,91	249,53
Age	-0,02	4,75	1,00	0,03	0,98	0,96	1,00
BMI	0,00	0,00	1,00	0,97	1,00	1,00	1,00
Kt/V	3,65	19,26	1,00	0,00	38,49	7,54	196,52
Gender	0,46	1,43	1,00	0,23	1,59	0,74	3,40
Constant	-3,01	5,49	1,00	0,02	0,05		

Note: LLR : low lyving regions; BMI : Body mass index; Kt/V: K: dialyzer clearance of urea, t: dialysis time, V: volume of distribution of urea; Wald: Wald Chi-Squared Test); B : bachelor statistics
Source: The authors.

Even in renal impairment, these adaptive conditions seem to persist, as we found in this study. Ecuadorian patients living at high altitudes (HA) exhibit a significantly higher frequency of individuals who do not require erythropoietin (EPO). Furthermore, the dosage needed to achieve a hemoglobin target was also inferior compared with the patients residing in LR.

The geographical higher altitudes are well known for the hypobaric and hypoxic conditions [12]. These environmental factors, particularly in the case of Andean highlanders, are associated with lower resting ventilation and hypoxic ventilatory response. In addition, these individuals exhibit higher oxygen saturation and higher hemoglobin concentration when compared with Tibetans [13].

The increased hemoglobin levels and hematocrit observed in HA residents as a compensatory mechanism in response to hypoxia is associated with higher levels of endogenous EPO when compared with LR residents [14]. However, the increased production of EPO, is a consequence of the hypoxia-inducible factor (HIF) pathway. HIF is a heterodimeric transcription factor constituted by two subunits, one of them called beta subunit which is expressed constitutively, whereas the alpha subunit (HIF-1α, HIF-2α, and HIF-3α) is synthesized and degraded constantly during normoxia. This degradation is facilitated by the action of prolyl hydroxylase domain (PHD) enzymes and von Hippel–Lindau tumor suppressor protein (VHL), leading to the ubiquitination of hydroxylated HIF causing its proteasomal degradation. However, during hypoxia the activity of VHL and PHD enzymes is blocked causing a higher availability of HIF1/2 alpha. This enables their translocation to the nucleus where along with HIF-β and p300/CBP, they facilitate the transcription of hypoxia response elements (HRE), such as *Epo, Tf, Tfr1*, and *Fpn* genes [15].

EPO is mainly produced by interstitial fibroblast-like cells that surround the renal tubules. However, it has been observed that in CKD, pericytes undergo transdifferentiation into myofibroblasts surrounded by extensive extracellular matrix deposition and fibrosis, along with epigenetic silencing by DNA methylation [16].

In our study, the reduced requirement of EPO observed in hemodialysis patients residing in HA could be explained by a higher intrinsic production of EPO by remaining normal pericytes, which may be sufficient to achieve the hemoglobin target between 10 and 11.5 g/dL recommended by the KDOQI guidelines [17]. However, the biological answer to this phenomenon is out of the scope and methodology of the current study.

Previous studies demonstrated the reduced requirement of EPO in hemodialysis patients residing in HA. Sibbel *et al.*, demonstrated that in patients categorized by altitude of residence in four groups 0-456.9 (n = 92,490), 457-914.1 (n=3118), 914.2-1371.3 (n=1659) and $\geq 1371{,}4$ (n = 2027), the altitude $\geq 1371{,}4$ masl (vs 0-456.9 masl) was independently associated with 13.9 % (95 % CI: 12.3, 15.5 %) fewer patients treated with ESA. Additionally, in patients requiring exogenous EPO, residing in altitude higher than 1371.4 masl was associated with 723 (95 % CI: 544, 834) U/treatment lower ESA dose compared with 0-456.9 masl [18].

These results were confirmed by Brookhart MA *et al.,* in a study including 341,737 patients. The research demonstrated that residing in HA also required lower doses of EPO to achieve higher levels of hemoglobin [19].

In contrast to our study, Yue-Harn Ng *et al.*, found that altitude is inversely correlated with the probability of developing anemia, presenting an adjusted odds ratio for anemia of 0.67 (95 % CI, 0.51-0.88) for each 1-km greater elevation [20]. However, the non-significative difference between hemoglobin levels in the populations included in our study may be explained by the fact that when patients achieved the hemoglobin target, EPO administration stopped.

In Latin America, two studies including Peruvian patients did not demonstrate a significant difference between HA and LR residents in terms of survival and the dose of exogenous EPO used to for managing CKD anemia [21, 22]. Therefore, it is important to conduct further studies on this topic in the region.

Our study had limitations, such as the small number of variables included in the statistical analysis. Additionally, the absence of information on complementary evaluation of anemia, such as blood levels of ferritin, transferrin, transferrin saturation, soluble transferrin receptor, reticulocytes, folic acid, vitamin 12, inflammatory markers, serum protein electrophoresis, among others, hinders a more comprehensive exploration that could enhance the conclusions of the study. Contrastingly, the study included patients with CKD of varying durations (from months to years) which could impact EPO and hemoglobin levels. Furthermore, with the information used in this study, we were unable to gauge differences in survival and quality of life, factors that could have enriched our conclusions. However, given the limited information available regarding this issue in the region, we believe this study generates important questions to be answered: 1) What is the biological mechanism of endogenous EPO production in response to hypoxia, considering the loss of normal pericytes observed on CKD 2) Does the diminished need for exogenous EPO in HA residents, extend to other countries of the region? And 3) Is this reduced requirement of exogenous EPO in HA residents associated with an improvement in quality of life and survival?

Conclusion

In Ecuadorian patients undergoing hemodialysis as RRT, residing at HA is linked to a reduced need for exogenous EPO compared with those patients residing in LR. Also, in the multivariate analysis, we observed that age and Kt/V were significant variables associated with a higher requirement of exogenous EPO. Our results reflect that even in cases of severe kidney disease with the necessity of RRT, the compensatory mechanisms in response to the hypoxic and hypobaric environment of HA maintains its activity. However, it is essential to note that additional studies are required to validate and further explore these findings.

Contribution of authors

André Benítez: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing; David Garrido: Conceptualization, Date curation, Formal Analysis, Investigation, Writing – original draft; Andrea Banegas: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing- review & editing; Maria Belén Mena: Formal Analysis, Investigation, Supervision and Validation, Writing – original draft, Writing- review & editing; Washington Osorio: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project Administration, Software, Visualization, Writing – original draft, Writing – review & editing; Jorge Rico Fontalvo: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; Maria Raad Sarabia : Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; Rodrigo Daza Arnedo: Supervision, Validation, Visualization, Writing – original draft, Writing; Maria Cardona Blanco: Conceptualization, Formal Analysis, Investigation, Writing – original draft; Tomas Rodríguez Yánez: Conceptualization, Formal Analysis, Investigation, Writing – original draft and Liseth Sierra Torres: Investigation, Writing – original draft and Writing- review & editing.

Conflict of interest

None declared by authors.

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Ethical statement

We obtained the ethical approval of IRB Universidad Tecnológica Equinoccial (UTE) with the approval code N° PT-APH-EOB-EVA-2020. During this study, no experimental interventions were performed on the included patients.

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