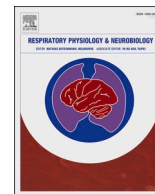




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Short communication

Low serum erythropoietin levels are associated with fatal COVID-19 cases at 4,150 meters above sea level

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ABSTRACT

Previous studies suggested that erythropoietin (EPO) may protect against severe COVID-19-induced injuries, ultimately preventing mortality. This hypothesis is based on the fact that, in addition to promoting the increase in red blood cells, EPO is an anti-inflammatory, anti-apoptotic and protective factor in several non-erythropoietic tissues. Furthermore, EPO promotes nitric oxide production in the hypoxic lung and stimulates ventilation by interacting with the respiratory centers of the brainstem. Given that EPO in the blood is increased at high-altitude, we evaluated the serum levels of EPO in critical patients with COVID-19 at "Hospital Agramont" in the city of El Alto (4150 masl) in Bolivia. A total of 16 patients, 15 men, one woman, with a mean age of 55.8 ± 8.49 years, admitted to the Intensive Care Unit were studied. All patients were permanent residents of El Alto, with no travel history below 3000 masl for at least one year. Blood samples were collected upon admission to the ICU. Serum EPO concentration was assessed using an ELISA kit, and a standard technique determined hemoglobin concentration. Only half of the observed patients survived the disease. Remarkably, fatal cases showed 2.5 times lower serum EPO than survivors (2.78 ± 0.8643 mU/mL vs 7.06 ± 2.713 mU/mL; $p = 0.0096$), and 1.24 times lower hemoglobin levels (13.96 ± 2.56 g/dL vs 17.41 ± 1.61 g/dL; $p = 0.0159$). While the number of cases evaluated in this work is low, our findings strongly warrant further investigation of EPO levels in COVID-19 patients at high and low altitudes. Our results also support the hypothesis that exogenous EPO administration could help critically ill COVID-19 patients overcome the disease.

1. Introduction

The COVID-19 pandemic, caused by the coronavirus type 2 (SARS-CoV-2), has reached alarming global dimensions. As such, health systems are being hit hard, especially in developing countries. In Latin America, preventing public and private hospital institutions collapse is an enormous challenge. This materializes in Intensive Care Units (ICU): the battlefield against disease. Despite the advances in the development of vaccines, their arrival and delivery in emergent countries is taking much longer than it was initially planned. On the other hand, regrettably, treatments to alleviate the disease, particularly in critically ill

patients, are still controversial. Thus, the most serious cases rapidly evolve into pneumolysis (lung destruction) with severe hypoxemia (Zubieta-Calleja et al., 2020), requiring the administration of oxygen and even mechanical ventilation (Ehrenreich et al., 2020). Erythropoietin (EPO) is essential to promote tissue oxygenation. Indeed, EPO is the main growth factor involved in increasing the number of red blood cells (Jelkmann, 2007). However, in addition to this "classical endocrine task", EPO fulfills several other non-erythropoietic functions. EPO counteracts pulmonary vasoconstriction by increasing the endothelial capacity to produce the vasodilator nitric oxide (NO), thus facilitating the oxygen supply to the brain, heart, and other tissues (Beleslin-Cokic

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et al., 2011). Other studies in mice demonstrated that EPO protects against acute lung injury induced by renal ischemia-reperfusion, playing a key role in suppressing pulmonary edema and attenuating inflammation of alveolar epithelial cells (Moeini et al., 2013; Zhu et al., 2019). In neural pathological contexts, studies in animal models of ischemic stroke and head trauma have shown that EPO is a potent neuroprotective factor that activates anti-apoptotic, anti-inflammatory, anti-cytotoxic, and antioxidant molecular mechanisms (Gassmann et al., 2003; Ghezzi and Brines, 2004). Studies in our laboratory have shown that EPO stimulates normoxic and hypoxic ventilation by interacting directly with the respiratory centers in the brainstem (Ballot et al., 2015; Khemiri et al., 2011; Soliz, 2013; Soliz et al., 2020). In the context of the COVID-19 pandemic, it was suggested that treating critically ill patients with EPO could be highly beneficial (Hadadi et al., 2020; Soliz et al., 2020; Zubieta-Calleja and Zubieta-DeUrioste, 2020; Zubieta-Calleja et al., 2020). In fact, within high altitude medicine, the altered lung gas exchange has similarities between High Altitude Pulmonary Edema (HAPE) and COVID-19 (Zubieta-Calleja et al., 2020). An attenuated stimulation of the neural circuits that control respiration has also been suggested to occur in COVID-19 (Soliz et al., 2020). HAPE, however, is rapidly reversible under treatment, leaving no sequelae whereas COVID-19 can result in pulmonary fibrosis due to pneumolysis (Zubieta-Calleja and Zubieta-DeUrioste, 2021). Furthermore, it was reported that prophylactic injections of EPO could at least partly prevent Acute Mountain Sickness (AMS) within 14 days prior to ascent (Heo et al., 2014). On the other hand, a blunted erythropoietic response (evidenced by anemia) has been reported to be rather common in critically ill patients, regardless of the disease type that led to that condition (Rogiers et al., 1997). In addition, recombinant human EPO was used as a final treatment option for an 80-year-old COVID-19 patient who recovered from the severe stage. In this case, one week before therapy, the patient was already hemoglobin deficient, further decreasing as the disease progressed. With the EPO treatment, her hemoglobin levels finally improved to physiological levels, with evident clinical, laboratory, and radiological improvement. An accelerated reversal of acute respiratory distress due to SARS-CoV-2 infection was also described (Hadadi et al., 2020). Finally, an increasing number of clinical reports show that SARS-CoV-2 infections can also cause kidney and heart failure due to a general excessive inflammation (cytokine storm) (Alert et al., 1988; Wang et al., 2021). In this context, EPO could prevent and/or protect against tissue damage and inflammation in several tissues (Nairz et al., 2012). EPO-mediated anti-inflammatory effects have been demonstrated in chronic inflammatory diseases and infectious diseases, including stimulation with bacterial lipopolysaccharide (LPS) and *Salmonella* sp. infection (Cuzzocrea et al., 2005; Nairz et al., 2012; Yuan et al., 2008). In addition, it has been shown that there is a positive effect of EPO in patients suffering from a critical systemic infection (Corwin, 2007; Napolitano et al., 2008). Taking into account that EPO is physiologically increased in high-altitude residents (Basu et al., 2007), we reasoned that the evaluation of EPO levels in critically ill COVID-19 patients could shed light on the protective effects of EPO mentioned above. This study was carried out in COVID-19 critically ill patients admitted to the "Hospital Agramont" in the city of El Alto (4150 masl) in Bolivia.

2. Methods

2.1. Study design

We conducted an observational, descriptive, and transversal study at Hospital Agramont's Intensive Care Unit (exclusive for COVID-19 adult patients) in El Alto city (4,150 m above sea level), La Paz - Bolivia.

2.2. Ethics declaration

The study was approved by the Bioethics Institutional Committee of

the hospital and carried out in accordance with the Helsinki declaration.

2.3. Patients

Sixteen patients were studied based on the following inclusion parameters: 1) 18 years old or older, 2) high-altitude permanent residents (no history of migration from lower lands during the last year), 3) "pneumonia" diagnosis due to SARS-COV-2 infection, 4) admitted to ICU. Patients with one or more of the following criteria were not considered: 1) non-COVID-19 related pneumonia diagnosis, 2) hematological disease (including anemia), 3) blood transfusion during the last six months.

2.4. Computed tomography (CT)

All the patients underwent chest CT prior to ICU admission. The percentage of lung involvement, the tomography severity score, and the COVID-19 Reporting and Data System (CO-RADS) score were calculated from the imaging data. Patients were categorized into one of six categories, from very low to very high (CO-RADS 1 to CO-RADS 6) probability of being COVID-19 positive ((Özel et al., 2021).

2.5. Determination of EPO levels

Blood samples were taken from patients prior to UCI admission and were analyzed by the standard ELISA methods using the DRG EPO ELISA EIA3646 kit (DRG Instruments, Marburg-Germany) in the MR-96A microplate reader (Mindray, Shenzhen-China) to read the EPO levels. Analyses were performed in the clinical laboratory of "Hospital Agramont".

2.6. Hemoglobin (Hb) concentration

From the same blood samples, the concentration of hemoglobin was measured using an automated spectroscopic system (Coulter Hematology Analyzer, Brea CA, U.S.A.).

2.7. Data and statistical analysis

For each patient, the following data were collected at the moment of UCI admission: age, comorbidities, lung compromise percentage, tomography severity score, CO-RADS score, number of days of COVID-19 evolution, EPO levels in the blood, and hemoglobin concentration. The number of days in ICU was accounted for each patient at the moment of discharge or death. The final data set, including the final outcome for each patient (survival or deceased), was anonymized entirely for statistical analysis. Two subsets of data were formed separating the survivors ($n = 8$) and the deceased ($n = 8$) patients. Differences in the percentage of lung involvement, tomography severity score, CO-RADS score, days of evolution of COVID-19 before admission to ICU, days in ICU, levels of EPO, and hemoglobin concentration, between surviving and deceased patients were evaluated by Mann-Whitney U tests in GraphPad Prism version 9.1 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com. Test significances were set to $p < 0.05$. Values are presented as mean \pm S.D. unless stated differently.

3. Results

The study recruited 16 patients (1 woman and 15 men), all adults (46–75 years old). The most common comorbidities found in the cohort were overweight/obesity (62 %), systemic arterial hypertension (18.75 %), diabetes mellitus type 2 (6.25 %), and pulmonary tuberculosis sequelae (6.25 %). By the end of the study, 50 % (8/16) of the patients survived.

When comparing surviving versus deceased patients, no differences

were found in the number of days of evolution of COVID-19 before UCI admission ($U = 22, p = 0.31$) or the number of days patients remained in ICU ($U = 31.5, p = 0.971$) (Table 1).

3.1. Lung involvement and injury severity

The percentage of lung involvement and the tomography severity score were lower (better) in patients who survived compared to those who died (Fig. 1A, B; Table 1). However, the CO-RADS score was not different between both groups (Fig. 1C; Table 1).

3.2. EPO and hemoglobin levels

The average EPO level in the deceased patients was roughly 2.5 times lower than in the survivors (Fig. 2A; Table 1). Similarly, the mean hemoglobin concentration was 25 % lower in the deceased compared to the survivors (Fig. 2B; Table 1).

4. Discussion

In the present study, we have investigated the potential involvement of EPO in the survival of critically ill COVID-19 patients at high-altitude (4150 masl, El Alto-Bolivia). Taking into account that EPO is physiologically increased in high-altitude residents and that EPO is an ubiquitous protective factor against inflammation, the main findings of the present report are that: (i) the serum level of EPO (and hemoglobin) in all tested patients is significantly lower than standard values reported for this altitude, (ii) serum EPO levels (and hemoglobin) in deceased subjects was about 2.5 times lower than in survivors, and (iii) lung involvement was significantly higher in deceased subjects than in survivors.

Several works (Cano-Pérez et al., 2020; Quevedo-Ramírez et al., 2020), including ours (Arias-Reyes et al., 2021, 2020; Zubieta-Calleja et al., 2020) clearly suggested that the virulence of SARS-CoV-2 decreases significantly with altitude. In a first report, we showed that at global and region specific scale (Tibetan Autonomous Region of China, Bolivia and Ecuador) COVID-19 cases were notably decreased at high altitudes (above 2500 masl) (Arias-Reyes et al., 2020). Later, we expanded this information through the epidemiological analysis of 23 American countries. Our results showed that both the incidence, the transmission capacity and the severity of COVID-19 significantly decrease with altitude, with a turning point that begins at 1000 masl (Arias-Reyes et al., 2021). Although the causes of this effect could be related to environmental and physiological factors, we proposed that high levels of EPO (naturally increased at altitude) could be one mayor factor. Indeed, apart from stimulating the production of red blood cells in the bone marrow, the non-hematopoietic effects of EPO are present in a ubiquitous manner. As such, by activating anti-apoptotic, anti-cytotoxic, anti-oxidative, and anti-inflammatory molecular pathways EPO promotes development, maintenance, protection and repair in

several organs, including the heart, lung, kidney, liver and brain tissue (Rabie and Marti, 2008). The way in which each of these properties of EPO can help palliate COVID-19 was described somewhere else (Soliz et al., 2020; Zubieta-Calleja et al., 2020). In line, these observations are strongly supported by clinical reports that suggested that: 1) EPO treatment could be highly beneficial for the treatment of COVID-19 critically ill patients (Hadadi et al., 2020); 2) EPO may prevent and/or protect against tissue damage and inflammation in several tissues (Nairz et al., 2012); and 3) EPO has positive effect in patients suffering from a critical systemic infection (Corwin, 2007; Napolitano et al., 2008). Moreover, the two first factors of the oxygen transport triad are seriously compromised in COVID-19: pneumodynamic pump (ventilation), the hemodynamic pump (heart and vessels). Therefore, the third factor (hemoglobin), becomes the crucial life-sustaining factor, also dependant on EPO (Zubieta-Calleja et al., 2020).

Inhabitants of high-altitude cities (between 2500 and 5000 masl), particularly in South America, have a 2- to 4-fold increase in serum EPO levels and hemoglobin concentration compared to residents of the lowlands (Beall et al., 2002). In fact, this difference in the level of serum EPO was evidenced in subjects exposed, for short and long periods of time, to 3450 masl: 14.23mU / ml and 21.68 g / dL in citizens acclimatized to high altitude; and 11.18 mU / ml and 18.31 g / dL in adapted people (natives) to high altitude, compared to 8.5 mU / ml and 13.86 g / dL at sea level (Basu et al., 2007). Remarkably, the EPO levels reported in all COVID-19 patients in this work are alarmingly low compared to that mean. In fact, at the time of their hospitalization, the surviving patients showed serum EPO levels between 2 and 3 times lower than the physiological mean, and the deceased patients, between 4.6 and 7.3 times below those values. The data collected in this work does not allow understanding the reason of such decrease. In any case, these results suggest that EPO should be a routinely parameter evaluated in all critical patients with COVID-9 both at sea level, and especially at high altitude. It is also difficult to say whether these patients showed a significant decrease of serum EPO (and anemic picture) prior to their infection with COVID-19, or whether such EPO reduction occurred due to infection with the SARS-CoV-2 virus. In addition, our data show that the pulmonary involvement of deceased patients is significantly higher than that of survivors. These data allow us to suggest that EPO in surviving subjects (decreased, but not drastic), could have contributed to the fact that this organ does not degenerate into a condition that contributes to a negative outcome. On the other hand, our data clearly show that those patients with extremely low levels of EPO and hemoglobin failed to defeated the disease. From this perspective, and in a context in which there are still mostly ineffective treatments for COVID-19, it is tempting to suggest that the administration of exogenous EPO seems to be a reasonable strategy to optimize hemoglobin concentration values and, therefore, improve arterial oxygen content in COVID-19 patients. This treatment should, however, be accompanied by the administration of thromboprophylaxis /anticoagulation factors since an increase in blood density could lead to thrombotic phenomena (Phrommintikul et al., 2007) and/or phenomena of arterial hypertension, hyperviscosity, tumor progression, and cellular aplasia (Kakavas et al., 2011).

In conclusion, to the best of our knowledge, our work is the first to report dramatically decreased EPO and hemoglobin values in critical patients with COVID-19 at high altitude. The results of this work strongly praise the further investigation of EPO levels in critically ill patients with COVID-19, both at sea level and at altitude. Our findings strongly support the hypothesis that exogenous EPO administration should be considered in critically ill patients with COVID-19 for humanitarian reasons, and if the results are good to do a research using it.

Author statement

Antonio Viruez-Soto. Participated in the recruitment of patients, experimental design, blood sampling, experimentation, data analysis and contributed to the writing of the article

Table 1

Parameters studied in the COVID-19 patients admitted to ICU.

	Survivors (Mean \pm S. D.)	Deceased (Mean \pm S. D.)	Mann- Whitney U	p value
Days of evolution of COVID-19 prior admission to ICU	10.63 \pm 4.34	13.75 \pm 6.52	22	0.31
Days in ICU	11.25 \pm 3.15	11.38 \pm 4.59	31.5	0.971
Lung involvement (%)	50.00 \pm 7.56	67.5 \pm 11.65	7	0.0092
Tomography severity score (/25)	15.5 \pm 2.07	18.5 \pm 1.41	10.5	0.0186
CO-RADS score	4.625 \pm 0.52	5.00 \pm 0.00	20	0.2
EPO in blood (mU/mL)	7.06 \pm 2.71	2.79 \pm 0.86	8	0.0096
Hemoglobin concentration (g/dL)	17.41 \pm 1.61	13.96 \pm 2.56	9.5	0.016

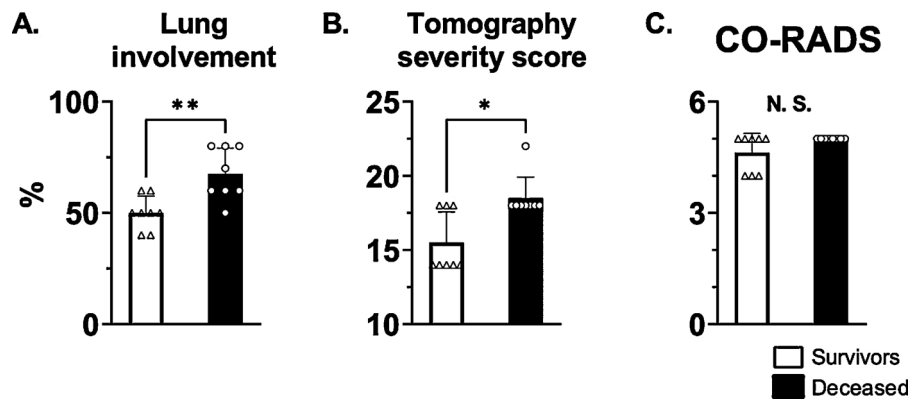


Fig. 1. Computed tomography parameters from the COVID-19 patients admitted to UCI at high-altitude (4150 m). At the moment of UCI admission, surviving patients showed lower lung involvement percentage (A) and tomography severity scores (B) compared to the patients who finally passed away. No difference was observed in the COVID-19 Reporting and Data System (CO-RADS) score between the two groups (C). *, **: $p < 0.05$ and $p < 0.01$. $n = 8$.

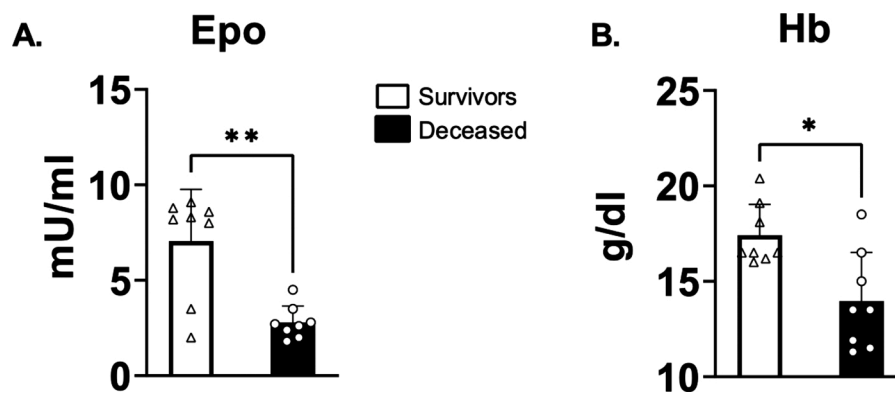


Fig. 2. Levels of EPO and hemoglobin concentration in COVID-19 patients admitted to ICU at high-altitude (4150 m). At the moment of UCI admission, surviving patients had significantly higher levels of EPO (A) and hemoglobin (B) than patients with a fatal outcome. *, **: $p < 0.05$ and $p < 0.01$. $n = 8$.

Monica Marlene Lopez-Davalos. Participated in the recruitment of patients, blood sampling, and experimentation.

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Alfredo Merino-Luna. Participated in the recruitment of patients, blood sampling, experimentation, data analysis and contributed to the writing of the article

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Natalia Zubieta-DeUrioste. Participated in the experimental design, data analysis and contributed to the writing of the article

Gustavio Zubieta-Calleja. Participated in the experimental design, data analysis and contributed to the writing of the article

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Jorge Soliz. Participated in the experimental design, data analysis and contributed to the writing of the article

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