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DEVELOPMENT OF OCULAR ALTERATIONS IN PATIENTS WITH SEVERE COVID-19 UNDER INVASIVE MECHANICAL VENTILATION AND PROLONGED PRONATION

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ABSTRACT

This work was designed to investigate ocular alterations in patients affected by severe COVID-19 who required invasive mechanical ventilation and prolonged pronation to optimize lung ventilation areas. The study was conducted in the Intensive Care Unit of the Specialties Hospital of the XXI Century National Medical Center, Mexican Institute of Social Security. 45 patients who required hospitalization between the months of March and May 2021 were included. Both eyes were analyzed in each patient. The mean age of the patients was 60 years. 68.9 % had comorbidities. The most frequent findings in adnexa were blepharoedema and chemosis. In the ocular fundus, several alterations including cotton-wool lesions, intraretinal hemorrhages and arteriolar vasoconstriction were observed. The effect of the hours of pronation on the frequency of retinal alterations was statistically significant the group of patients without changes against those who had more than two retinal alterations. Having more than 145 hours of pronation increases the risk of having more than two retinal alterations. Intraocular pressure increased in pronation by 61 % with $P < 0.05$. The ocular alterations in patients with COVID-19 under invasive mechanical ventilation and prolonged pronation range from the ocular adnexa to the alterations in the fundus of the eye. The relevance of this study lies in the fact that the patients were examined during the most severe period of the disease, where more systemic ischemic alterations could have manifested. These results suggest the need to implement a protocol for the primary and secondary prevention of ocular complications in patients with COVID-19, but which may be useful for patients who must remain in prolonged pronation for other medical indications.

KEYWORDS: Coronavirus Infection, Intensive Care Unit, Intubation, Intratracheal Airway Management, Pronation, Ocular Damage.

1. INTRODUCTION

At the end of December 2019 in the Hubei province in Wuhan, China, the first cases of an outbreak of pneumonia of unknown cause were reported, later it was revealed that the cause was a new coronavirus. In January 2020, the infections reached different provinces of China, and later different Asian countries. In March 2020, COVID-19 was declared a pandemic.[1] The first case of COVID-19 in Mexico was reported on February 27, 2020, in Mexico City.[2]

Coronaviruses belong to the Coronaviridae subfamily, which are composed of single-stranded, positive-sense RNA with a genome of approximately 30 kilonucleotides. Within the coronaviruses, seven of them are those that can infect humans and cause respiratory conditions with different degrees of severity, three of these, MERS-CoV, SARS-CoV and SARS-CoV-2, affect the upper respiratory tract and low, and can cause severe acute respiratory syndrome (SARS). Three main modes of transmission of these viruses have been reported: 1) respiratory droplets, 2) contact transmission, and 3) aerosols.[3] The clinical manifestations are diverse, both in affection to different organs of the body, and in severity. The most common are fever, cough, myalgia, fatigue and pneumonia.[4]

1.1. Ocular manifestations

Among the ocular manifestations, both direct and indirect involvement has been documented.[5] Conjunctivitis seems to be the initial or only symptom of this pathology, other alterations in the ocular surface are chemosis, epiphora and ocular secretions.[6] In some of these patients, the presence of the virus has been detected in conjunctival swab samples, suggesting its possible transmission through the ocular mucosa, tears or fomites, however, this is controversial, because in some publications it has been reported that the swab samples can be negative, being able to relate to the viral load.[7]

Posterior segment alterations include spot or flame hemorrhages, cotton-wool lesions, and vascular tortuosity.[8, 9] Cotton-wool lesions are a marker of the severity of some pathologies since they are ischemic phenomena.[10] These manifestations occur more frequently in patients with more severe pathology.[11-15] Although previous studies have reported that the SARS-CoV-2 virus does not cross the blood-retinal barrier, the presence of SARS-CoV-2 has been documented in retinal tissue biopsies from deceased patients.[16] In addition, the expression of the angiotensin-converting enzyme 2 receptor for SARS-CoV-2 has been confirmed in retinal tissue.[17]

Imaging studies with optical coherence tomography have been performed, where hyperreflective plaques have been found in the inner plexiform layer,[18] reduced macular vascular density[19] and the nerve fiber layer. These changes may be the result of microangiopathy caused by the pathogen.[20] In addition to reports of central vein and branch retinal artery occlusion,[21,22] severe retinal ischemia,[23] multifocal chorioretinitis, Adie's syndrome,[24] and papillophlebitis,[25] associated with SARS-CoV-2 infection.

1.2.Management of patients with severe COVID-19. Pronation

In patients with severe pneumonia, pronation optimizes the areas of pulmonary ventilation, which contributes to improving body oxygenation, which is why it is a maneuver that is part of the treatment for patients with severe pulmonary involvement, in addition to this, use is made of the invasive mechanical ventilation. Patients remain in this position generally for more than 16 hours. Prolonged pronation time increases the risk of ocular involvement due to direct contact with the eyeball and the pressure exerted on the orbit. Several complications have been observed, among them; papillophlebitis, retinal hemorrhages, retinitis, microangiopathies, and orbital compression syndrome,[26] even ocular perforation has been documented.[27]

Invasive mechanical ventilation is related to damage to the ocular surface in different degrees of severity, due to ocular exposure and lack of awareness of eye protection measures, an example of this is bacterial keratitis that can lead to blindness.[28]

In the COVID-19 pandemic, the use of intensive care units, prolonged pronation, and invasive mechanical ventilation in the management of complicated patients increased greatly. Treatments that collectively subject the eyeball to increased intraocular pressure that can result in severe damage.

This work was designed to investigate the ocular alterations produced in patients positive for COVID-19 with the use of invasive mechanical ventilation and who, due to medical indications, remained in pronation for more than 16 hours.

2. MATERIALS AND METHODS

The study design was descriptive, prospective and cross-sectional, it was carried out during the months of March and May 2021. All patients over 18 years of age, of both sexes with a positive test (PCR) for COVID-19, who had the diagnosis of severe pneumonia associated with SARS-CoV-2 who were under invasive mechanical ventilation and who had more than 16 hours of pronation. Exclusion criteria were diagnosis of diabetic retinopathy, optic neuropathy, use of ophthalmological eye drops excluding lubricants, underlying hematological or oncological diseases, family history of glaucoma, superimposed bacterial, fungal or parasitic infection.

A total of 90 eyes of 45 patients diagnosed with critical COVID-19 who were hospitalized in the Intensive Care Unit of the Specialties Hospital of the XXI Century National Medical Center of the Mexican Institute of Social Security were studied.

Various data that included age, sex, date of onset of symptoms, progression of symptoms, date of hospitalization in the Intensive Care Unit, result of the COVID-19 diagnostic test, personal pathological and ophthalmological history, laboratory studies (Procalcitonin, Fibrinogen, D-dimer, Ferritin and PCR), chest X-ray results, were collected through electronic files.

The classification as cases of COVID-19 with a critical stage was made in accordance with the "Diagnosis and Treatment Protocol for Pneumonia due to the New Coronavirus Version 7" issued by the National Health Commission and National Administration of Traditional Medicine of China (March 3, 2020). Critical cases included patients with respiratory failure requiring invasive mechanical ventilation, shock and organ failure requiring hospitalization in the Intensive Care Unit.

The procedures were performed by health personnel with full use of protective equipment. A macroscopic ophthalmological review was performed, the characteristics of the ocular adnexa, anterior segment, intraocular pressure in the supine and prone position, as well as the eye fundus under dilation, were evaluated. Sodium fluorescein strips were used for the evaluation of corneal epithelial defects. Intraocular pressure was measured in the supine position, while in the prone position, the intraocular pressure of the eye that was not in contact with the bed was documented. After training the health personnel, a previously calibrated Schiotz tonometer was used. The fundus of the eye was evaluated using a 20 D lens, indirect ophthalmoscope and a smartphone camera. For pupil dilation, 1 drop of 1% tropicamide was used in both eyes when in the supine position, after having completed a minimum of 16 hours of pronation. A video of the eye fundus was taken, which was later analyzed by an independent researcher (retinologist), who was unaware of the personal pathological history of the patients, laboratory studies, eye in contact with the bed in the pronated position.

3. STATISTICAL ANALYSIS

Statistical analysis was performed using the R.v.3.6.2 program (R Core, team, 2020). The Shaphiro-Wilk test was used to check the normality of the variables, the Fligner-killeen test to determine the homoscedasticity of the variables. The non-parametric Kruskall-Wallis equivalent was used to compare the groups and investigate whether there were differences in eye fundus changes depending on the hours of pronation. If there was a significant difference between the groups studied, Dunn's posthoc test was continued. to see in which of them was the difference.

To analyze the change in intraocular pressure from supine to prone, since these were repeated measurements, the Wilcoxon test was used. Fundus changes were compared with inflammatory laboratory markers using the Kruskal-Wallis test. $P < 0.05$ was considered statistically significant.

4. RESULTS

A total of 90 eyes of 45 patients were reviewed. The mean age was 60.66 ± 11.89 years. 68.9 % had comorbidities, first, systemic arterial hypertension (44.4 %), followed by diabetes (28.89 %) and overweight or obesity (26.7 %). 31.1 % had no comorbidities. Concomitant diseases included: chronic kidney disease, chronic liver disease, neoplasms, multiple sclerosis, history of cerebrovascular disease and acute myocardial infarction, and mood disorders. In the electronic files and indirect questioning, no ophthalmological history was recorded. All patients had a positive PCR test for COVID-19, in addition to being hospitalized in the Intensive Care Unit for critical COVID-19 under invasive mechanical ventilation (endotracheal intubation) and prolonged pronation (more than 16 hours).

4.1. Clinical manifestations

The average time from symptom onset to ophthalmologic examination was 20.9 days. Among the most frequent clinical findings in ocular adnexa was blepharoedema (N=36; 79.98 %) and in the anterior segment it was chemosis (N=37; 83.32 %) (Table 1, Figure 1).

Table 1: Ocular manifestations in Adnexa and Anterior segment.

Ocular manifestations in adnexa and anterior segment (N=45, 100%)		
Annexes	Blepharoedema	36 (79.98)
	Scales on eyelashes	25 (55.55)
	Dermabrasion	7 (15.55)
Anterior segment	Epithelial defects	19 (42.22)
	Conjunctival chemosis	37 (83.32)
	Conjunctival hiperemia	3 (6.66)
	Subconjunctival hemorrhage	11 (24.44)

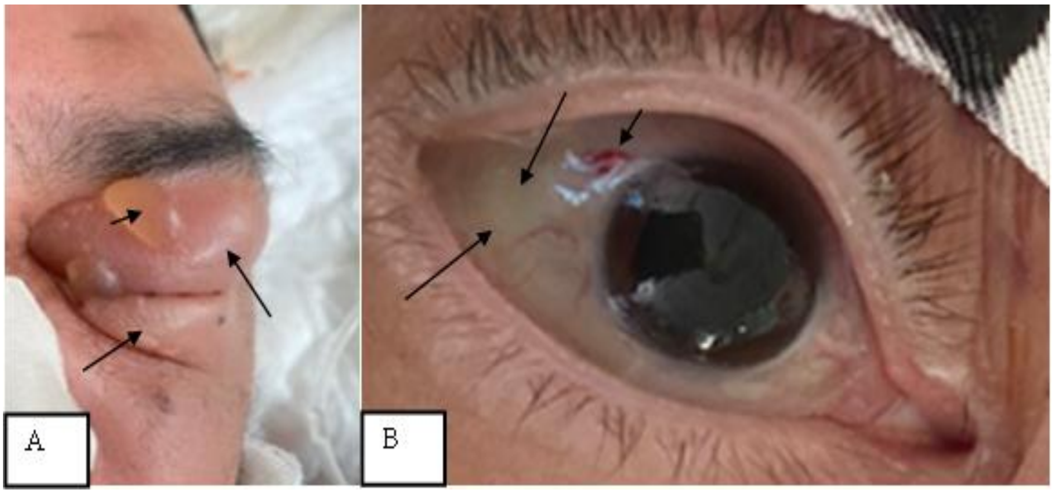


Figure 1: Main clinical manifestations in ocular adnexa and anterior segment in patients hospitalized for critically ill COVID-19 in the Intensive Care Unit. A: Clinical photograph of a male patient in the fourth decade of life after the first cycle of pronation (72 hours). Significant upper and lower blepharoedema is observed (long arrow), in addition to epidermal blisters (short arrow), and B: Clinical photograph of a male patient in the sixth decade of life after the first cycle of pronation (72 hours). Diffuse chemosis ++ (long arrow), subconjunctival hemorrhage in the upper nasal sector (short arrow) is observed.

4.2.Clinical manifestations in eye fundus

In the eye fundus review under dilation, the most frequent alterations were retinal vasoconstriction (N=19; 42.22 %), papillary hyperemia (N=9; 20 %) and intraretinal hemorrhages (N=8; 17.78 %) (Table 2, Figure 2).

Table 2: Alterations in the eye fundus.

Alterations in the eye fundus (N = 45, 100%)	
Pale papilla	3 (6.67)
Blurred papillary margins	5 (11.11)
Hyperemic papilla	9 (20.00)
Retinal vasoconstriction	19 (42.22)
Intraretinal hemorrhages	8 (17.78)
Cotton-wool lesions	7 (15.56)
Without modifications	13 (28.89)

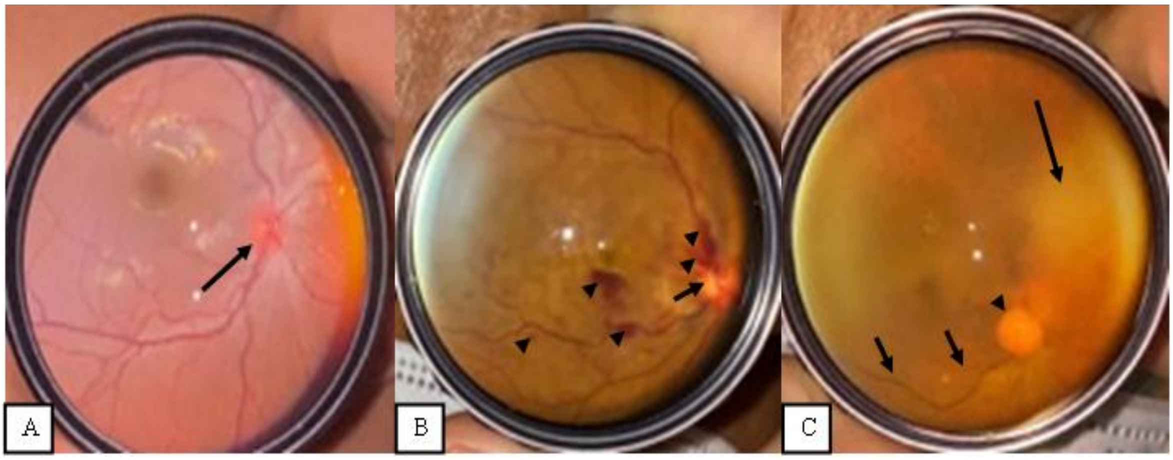


Figure 2: Clinical manifestations in the eye fundus in patients hospitalized for COVID-19 in critical condition. A: Left eye fundus image taken with a 20 D lens + Smartphone of a male in his sixth decade of life, without comorbidities, under invasive mechanical ventilation after 192 total hours of pronation and left eye intraocular pressure of 23.8 mm Hg. The hyperemic papilla is observed (arrow). B: Left eye fundus image taken with a 20 D lens+ Smartphone of a female in the sixth decade of life with a history of chronic liver disease, under invasive mechanical ventilation, after 192 total hours of pronation and left eye intraocular pressure 23.8 mm Hg. Peripapillary and perifoveolar intraretinal hemorrhages and over the path of the superior and inferior temporal arch (arrowhead) are observed, in addition to blurring of the papillary inferotemporal borders (arrow). C: Left eye fundus image taken with a 20 D lens + Smartphone of a male of the seventh decade of life with a history of obesity, under invasive mechanical ventilation, after 144 total hours of pronation and left eye intraocular pressure 25.8 mm Hg. Pale papilla (arrowhead), diffuse arteriolar vasoconstriction (short arrow), and retinal pallor in the nasal sector (long arrow) are observed.

In this study, three analyzes were carried out: the main one consisted of analyzing the alterations found in the fundus of the eye depending on the hours of pronation. The total population was divided into 4 groups. Group 1. Papillary alterations were grouped: hyperemic papilla, blurred papillary margins or pale papilla. Group 2. Retinal vascular alterations were grouped: thin arteriolar vascular pattern and intraretinal hemorrhages. Group 3. More than two alterations from the previous groups (papillary alteration + vascular alteration) were grouped together. Group 4. No alterations in eye fundus structures (Figure 3).

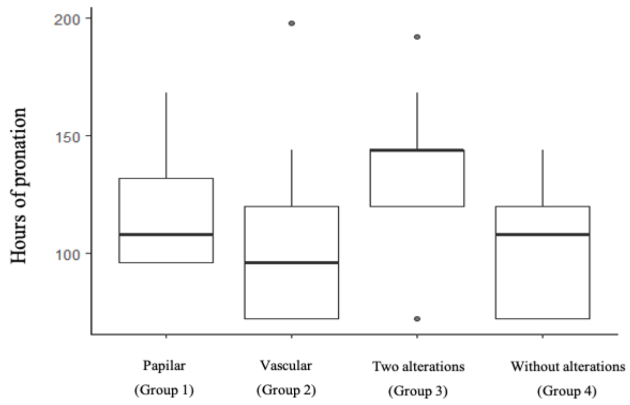


Figure 3: Differences between the alterations in the fundus of the eye of the different groups with respect to the hours of pronation.

The effect of pronation time on the frequency of retinal alterations was statistically significant P = 0.049 comparing the group of patients without alterations against those who had more than two retinal alterations. Having more than 145 hours of pronation increases the risk of having more than two retinal alterations (papillary or vascular alterations).

Subsequently, the increase in the ocular pressure of the patients when they went from supine to prone was analyzed, since the intraocular pressure measurements were taken in the same patient, these are repeated measurements. The non-parametric Wilcoxon equivalent was used. Intraocular pressure increased in pronation by 61 % with a mean supine intraocular pressure of 13.59 mm and 23 mm Hg in prone, with statistically significant differences being found with P <0.05 (Figure 4).

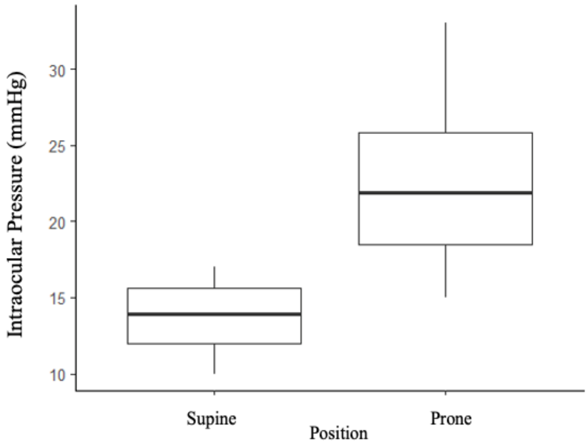
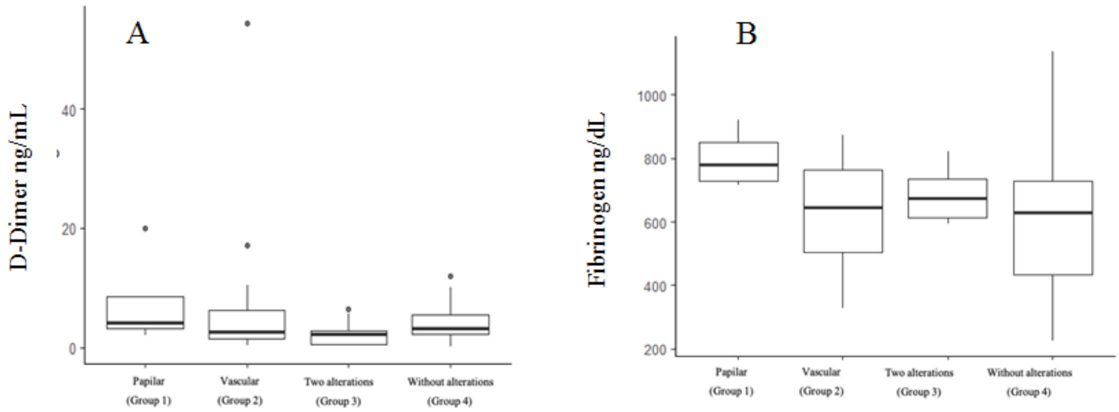


Figure 4: Differences between intraocular pressure in patients in the Prone and Supine position.

4.3.Markers of inflammation and fundus

The last analysis consisted of seeing differences in the changes in the eye fundus, depending on the results of inflammation markers: D-dimer, fibrinogen, ferritin, procalcitonin and C-reactive protein. Each group was compared using the Kruskall-Wallis test. It was found that, in all the groups, the markers of inflammation were the same P >0.05, that is, there were no statistical differences between the groups regarding the increase in the frequency of ocular fundus alterations.



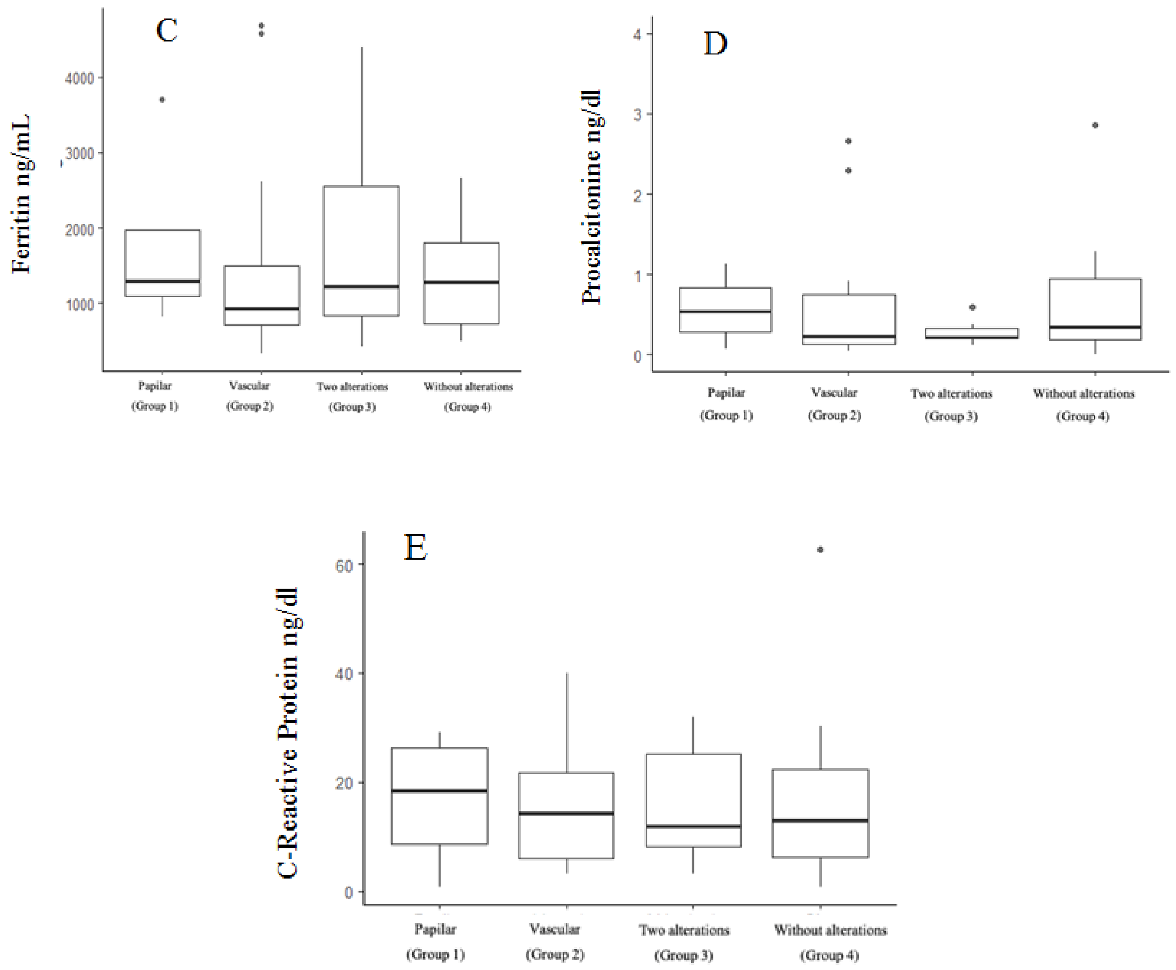


Figure 5: Comparison between ocular fundus changes and inflammation markers. A. Dimer D. B. Fibrinogen. C. Ferritin. D. Procalcitonin. E. C-reactive protein.

5. DISCUSSION

In this study, a larger number of patients was included in relation to previous studies, in order to evaluate the development of ocular alterations in both the anterior and posterior segments of the eye in patients under prolonged pronation and use of mechanical ventilation due to critical COVID-19.

71.11 % (N=32) of the patients showed some retinal alteration (pallor or hyperemia in the papilla, blurred papillary edges, retinal vasoconstriction, intraretinal hemorrhages or cotton-wool lesions). Some of these ocular manifestations are associated with other comorbidities such as diabetes or hypertension, which constitutes a limitation in the present study; however, the presence of two alterations was observed more frequently in those patients who had more hours of pronation. Papillary changes such as border blurring or hyperemia which are seen in papilledema may be related to increased orbital venous pressure during the pronated position (intraocular pressure increase: 61 %).[26]

Cotton-wool lesions were present in 15.56 % (N = 7), they are a consequence of ischemic events in the ganglion cell layer and nerve fibers, together with retinal vasoconstriction and pallor of the optic nerve, they could be secondary to thromboembolic events caused by this pathology.[10]

The presence of viral RNA in cerebrospinal fluid has been identified, in addition to RT-PCR positive biopsies in retinal tissue, leading to possible direct and indirect damage from the virus.[16] In patients in a post-COVID state, in whom studies such as optical coherence tomography have been performed, lesions in the ganglion cells and internal plexiform layer have been reported. In COVID-19 pneumonia that causes a critical state, it has been seen that there is a proinflammatory and thrombotic state and tissue ischemia due to decreased oxygen distribution, which is related to the development of multi-organ failure and this in turn is associated with retinal damage.

Serum markers of inflammation such as D-Dimer, Ferritin, and C-Reactive Protein have been correlated with the frequency of multiple organ dysfunction and COVID-19.[10] In this study, the values of the inflammatory markers were not correlated with the increase in the frequency of papillary or vascular alterations or more than two alterations in the fundus of the eye.

The relevance of this study lies in the fact that the patients were examined during the most severe period of the disease, where more systemic ischemic alterations could have manifested. Within the limitations of this study is the clinical examination in which some vascular or tissue changes cannot be accurately detected, as could be observed in imaging studies such as optical coherence tomography or fluorangiography, however, due to the conditions of the patients it was not possible to perform them. Another limitation of the study was the use of the Schiotz tonometer, in which, despite prior training and intraocular pressure measurement by different members of the team, it is not as reliable compared to other portable tonometers.

6. CONCLUSIONS

Patients with COVID-19 in critical condition and prolonged pronation had significant ocular alterations, so these patients should have a complete ophthalmological check-up. The mortality rate of this type of patients is very high, which does not make it possible to monitor these patients to assess visual acuity and its possible sequelae, however, a protocol for vision care must be developed in patients under these conditions, such as the use of ocular bearings, maintaining the position of the head above the level of the heart and performing the fundus examination.

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