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Eye care in intensive care in COVID-19 era: a prospective observational study from Turkey

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Abstract. – OBJECTIVE: There has been an increase in intensive care applications due to respiratory failure of COVID-19 infection. Management of respiratory failure includes a range of additional interventions, including high-flow nasal oxygen, noninvasive and invasive ventilation and prone position. These interventions contain risk factors for the development of ocular complications. This study aimed to elucidate the ocular pathologies that occurred in COVID-19 patients hospitalized in the intensive care unit.

PATIENTS AND METHODS: Patients who completed 24 hours in the intensive care unit were included in the study. Age, gender, duration of hospitalization before intensive care unit, comorbid diseases and APACHE 2 scores of COVID-19 patients admitted to intensive care unit were recorded. SOFA scores, presence of sedation and muscle relaxant, oxygen therapy (conventional oxygen therapy, high flow nasal oxygen therapy, noninvasive ventilation, invasive ventilation) and presence of prone position were recorded. All patients were evaluated daily for ocular findings. Routine eye care protocol was applied to all patients.

RESULTS: Seventy patients were followed for a total of 596 days in the intensive care unit. Pathological ocular findings were observed during hospitalization in 59 of the patients followed. The incidence of chemosis in patients who underwent IMV was significantly higher compared to other methods (*p*<0.001).

CONCLUSIONS: In this study, we observed that despite our routine eye care protocols, invasive mechanical ventilation applications predispose corneal surface damage in patients followed up in the intensive care unit with COVID-19 infection.

Key Words:
COVID-19, Eye care, Intensive care.

Introduction

The use of sedative and neuromuscular drugs impairs consciousness in intensive care unit (ICU) patients[1]. A substantial negative effect of this procedure is Bell's phenomenon and corneal reflex deterioration due to the relaxation of the periocular muscles[2,3]. With the deterioration of the protective mechanism of the eyelids and the evaporation of tears, the ocular surface defense is impaired. Corneal epithelial disorders, exposure keratopathy, conjunctival chemosis and infections can occur[4].

In ICU patients, ocular surface disorders usually occur within 48 hours to 1 week after hospitalization[5], and prolonged hospitalization and sedation can increase the risk of developing corneal damage[2]. In previous studies[5,6], the corneal damage rates have ranged from 3.3% to 22%, but this rate could reach up to 60% in patients who have been sedated for longer than 48 hours. Every new complication that will occur in the patient will increase the workload and the cost of treatment[7]. However, precaution and preventive treatments against ocular surface diseases are easy and inexpensive. Eye care should not be neglected in intensive care units[8-10].

Previous studies[8,9] showed that the incidence of corneal abrasion was around 50%. According to Dawson et al[10], the incidence of ocular diseases was found to be between 37.5% and 60%. Imanaka et al[9]. detected eye related disorders in the 20% of patients who were administered mechanical ventilation for at least 48 hours in their study (n=143)[9]. Girgin et al[11] diagnosed conjunctival hyperemia in 70.8% of the patients, keratopathy in 25%, keratitis 12.5%, chemosis 12.5% and keratoconjunctivitis 12.5% in patients due to exposure treated at the intensive care unit. Hilton et al[12] have conducted 18 months of study in three ICUs and detected ten different groups of nosocomial eye infections. Smulders et al[13] have identified *Pseudomonas aeruginosa* in respiratory tract samples in 36% of the patients who had been mechanically ventilated for more than three days.

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The ocular infection has been developed with the same agent in 11% of these patients.

After the corona virus disease 2019 (COVID-19) pandemic, there has been an increase in intensive care admissions. During the COVID-19 treatment process, noninvasive ventilation (especially high flow nasal oxygen treatment), mechanical ventilation, and prone positions constitute several risk factors for developing ocular complications. As a result, there may be an increase in ocular complications during the treatment processes of COVID-19 related ICU admissions. Therefore, increased awareness of eye care in the ICU will help prevent these complications and maintain quality of life in patients recovering from COVID-19[13,14].

The direct ocular effects of COVID-19 infections remain unclear. In addition, the effects of treatments applied to increase oxygenation of patients on the eye also remain unclear.

This study aimed to elucidate the ocular pathologies occurring in COVID-19 patients hospitalized in the intensive care unit.

Patients and Methods

This study had a prospective observational nature. Patients admitted to ICU between 1 June 2021 and 31 October 2021 have been enrolled in this study. The Ethics Committee approval has been granted at 28.04.2021 and protocol number: 2011 – KAEK – 25 2021/04 – 06. Written informed consent was obtained from the patients participating in the study.

Patients aged >18 years and positive for nasopharyngeal swap reverse transcriptase-polymerase chain reaction test (RT-PCR) for SARS-CoV-2 (severe acute respiratory syndrome- Corona virus-2) were included. Patients with ocular pathology and history of ocular surgery or trauma (except cataract surgery) were excluded from the study.

Patients who completed 24 hours in the intensive care unit were followed daily. Age, gender, hospitalization time before ICU, comorbid diseases and APACHE 2 (acute physiologic and chronic health evaluation) scores of COVID-19 patients admitted to intensive care unit were recorded. SOFA (sequential organ failure assessment) scores, presence of sedation and muscle relaxant, oxygen therapy [conventional oxygen therapy, high flow nasal oxygen therapy (HFNO), noninvasive mechanical ventilation (NIV), invasive mechanical ventilation (IMV)] and presence of prone position were recorded on a daily basis.

Eye care protocol was implemented to the patients: care 1 – artificial tears, eye closure; care 2 – artificial tears, lubricant ointment, eye closure; care 3 – artificial tears, lubricant ointment, corticosteroid drops; care 4 – if an additional infection is considered, the antibiotic ointment has been added.

Eye related symptoms were followed daily by the ICU team during the ICU stay. Periorbital edema, subconjunctival hemorrhage, degree of lagophthalmia, chemosis, conjunctival hyperemia, secretion, corneal epithelial defect (CED), keratitis, punctate keratopathy and presence of infection was evaluated. An ophthalmologist consulted every patient with ocular signs. The type of discharge from the intensive care unit (dead, service) was recorded. Sedation and neuromuscular blockade drugs used were recorded.

Patient follow-ups were performed daily (including on weekends), considering that clinical findings and oxygenation requirements could affect ocular findings.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY, USA) package program. Frequency and percentage were given for categorical data and median, minimum and maximum descriptive values for continuous data. "Kruskal Wallis H-Test" was used for comparisons between groups, and "Pearson Chi-square or Fisher's Exact Test" was used for the comparison of categorical variables. The results were considered statistically significant when the *p*-value was less than 0.05.

Results

There were 262 admissions to the COVİD-19 intensive care unit during the study period, and 73 patients included the study and 70 patients completed the study.

Three patients (conjunctival bleb was observed in one patient due to previous glaucoma surgery, two with visual impairment) were later noticed and discontinued from the study. At least one pathological eye finding was observed in 59 of the 70 patients followed. The distribution of demographic and clinical findings of the cases was given in Table I.

Mucormycosis (one kidney transplant history and two diabetes mellitus) were detected in 3 pa-

Table I. Baseline demographics of the study population.

Characteristics (N=70)	Median (Min-Max)
Gender	
Male	34 (48.6)
Female	36 (51.4)
Age, years	**61 (25-88)**
Total hospital stay, days	7 (2-35)
Hospitalisation before ICU, days	**3 (1-14)**
Obesity	8 (11.8)
Diabetes Mellitus	**22 (31.4)**
Renal Failure	13 (18.6)
Cardiac Disease	18 (25.7)
Hypertension	29 (41.4)
Cerebrovascular Disease	**6 (8.6)**
Pulmonary Disease	14 (20.0)
Rheumatoid Disease	**6 (8.6)**
Malignancy	2 (2.9)
APACHE-2	**21 (10-45)**
Final Status	
ICU	6 (8.6)
Discharged (service)	27 (38.6)
Deceased	37 (52.9)

ICU: Intesive care unit; APACHE 2: acute physiologic and chronic health evaluation score

tients. In the follow-up of 140 eyes, 8% periorbital edema, 4.2% subconjunctival hemorrhage, 2.1% eyelid defect, 26.7% mild chemosis, 12.3% moderate chemosis, 8.2% severe chemosis, 62.8% conjunctival hyperemia, 7.1% secretion were detected. With the corneal staining test performed by the ophthalmologist, 14.8% of the patients had punctate keratopathy, and no corneal epithelial defect was observed. Microbial infection was not seen.

Within the scope of the study, 70 individuals hospitalized in the intensive care unit were followed up for a total of 596 days. Patients in the intensive care unit received different oxygen support on different days. Oxygen therapy was not given to the cases for only 20 days in the 596 days of follow-up. In 576 days of oxygen therapy, HFNO 140 days, IMV 341 days, NIMV 20 days and N–O_2 or R–O_2 (nasal or reservoir oxygen) 75 days have been applied to the patients. The distribution of oxygen treatments applied according to clinical findings is given in Table II. When the table was examined, the relationship between all parameters except subconjunctival hemorrhage, SCE, secretion, corneal staining was found statistically significant among oxygen treatments. Chemosis has been statistically significantly higher in IMV group where most of the cases were mild to moderate. The secretion was serous in all patients.

Discussion

There are various disrupting factors on patients' ocular health at the intensive care unit. These can be elaborated as inadequate tear production, dry eye keratitis, corneal epithelial disorders, chemosis, infection[6], impaired eyelid movements, impaired epithelial conjunctival immune

Table II. Evaluation of Clinical Eye Findings According to Oxygen Treatments.

Characteristics (n=596 days)	Total (n=596) n (%) or median (Min-Max)	HFNO (n=140) n (%) or median (Min-Max)	IMV (n=341) n (%) or median (Min-Max)	NIMV (n=20) n (%) or median (Min-Max)	N-O_2 or R-O_2 (n=75) n (%) or median (Min-Max)	*p*-value
Periorbital edema	46 (8)	0 (0)	40 (11.7)	0 (0)	6 (8)	<0.001
Subconjunctival hemorrhage	24 (4.2)	2 (1.4)	16 (4.7)	0 (0)	6 (8)	0.090
Lagophthalmia	30 (5.2)	0 (0)	30 (8.8)	0 (0)	0 (0)	<0.001
Chemosis						<0.001
Light	154 (26.7)	20 (14.3)	114 (33.4)	5 (25)	15 (20)	
Middle	71 (12.3)	1 (0.7)	68 (19.9)	0 (0)	2 (2.7)	
Severe	47 (8.2)	1 (0.7)	46 (13.5)	0 (0)	0 (0)	
Conjunctival hyperemia	362 (62.8)	70 (50)	253 (74.2)	8 (40)	31 (41.3)	<0.001
Secretion	41 (7.1)	4 (2.9)	34 (10)	0 (0)	3 (4)	0.014
Corneal staining	4 (0.7)	0 (0)	4 (1.2)	0 (0)	0 (0)	0.427
Epithelial defect	3 (0.5)	0 (0)	0 (0)	0 (0)	3 (4)	<0.001
Keratitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Punctate keratopathy	85 (14.8)	4 (2.9)	74 (21.7)	0 (0)	7 (9.3)	<0.001

HFNO: High flow nasal oxygen IMV: Invasive mechanical ventilation NIMV: Noninvasive mechanical ventilation N-O_2: Nasal oxygen R-O_2: Reservoir mask oxygen.

functions, and protective mechanisms. These conditions even deteriorate with the use of certain medications in addition to the invasive procedures required for the diagnosis and treatment[1,4,6].

The local ocular infections predominantly occur in the eyelids and eyelashes. These infections can both originate from flora microorganisms or outer species. Regular cleansing plays a crucial role in the prevention of ocular infections. Mela et al[15]. reported that bacterial ocular colonization occurs in subjects who were hospitalized for longer than one week. They also stated that 77% had at least one bacterium other than those usually found (mostly *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Staphylococcus epidermidis*), and 40% of the patients underwent long term sedation[15]. Şahin et al[16] published that *Staphylococcus aureus* and *Neisseria* species have been observed in the intensive care unit patients following seven days. A recent study by Oncul and Yektas[17] elaborated that individuals who stayed in the ICU for a longer period had ocular problems, definitely setting to an infectious environment. In this study, no infection related symptoms were observed. In cases where we have remained in doubt, it was not recommended to take a tear culture by excluding microbial infection with eye consultation. Respiratory secretions are thought to be the main source of ocular surface infection, in conjunction with aerosols from tracheal aspiration and direct contact from aspiration catheters. This might be attributed to the utilization of broad-spectrum antibiotic treatment and closed aspiration systems to prevent contamination in the COVID-19 era. In the literature, a low rate of SARS-CoV-2 nucleotides is mentioned in the conjunctival samples of COVID-19 patients with severe acute respiratory distress syndrome[18]. However, it is currently unclear whether the conjunctival epithelium is also susceptible to SARS-CoV-2 and therefore may serve as a replication site for SARS-CoV-2.

Remarkably, we did not have any patients we started to follow up with conjunctivitis as the first symptom. In contrast, no evidence of an ocular manifestation in humans has been found to date, except for conjunctivitis in SARS-CoV patients. The low incidence of conjunctivitis in our inpatient COVID-19 patients is most likely due to the advanced stage of the disease in the patients studied. Loffredo et al[19]. reported the overall conjunctivitis rate of 1.1%, and 3% and 0.7% in severe and non-severe COVID-19 patients, respectively. The meta-analysis showed that patients with severe COVID-19 infection had an increased incidence of conjunctivitis at hospital admission[19].

Subconjunctival hemorrhage was observed in 4.2%. A recent publication[20] observed 10/28 subconjunctival hemorrhage due to systemic anticoagulant due to extracorporeal membrane oxygen therapy (ECMO) or increased coagulation disorders caused by SARS-CoV-2. In our clinic, anticoagulant (low molecular weight heparin) treatment was used following the local guidelines. In addition, no application requiring systemic heparinization was performed. That is why we thought our rates were lower than the study above.

The severity of ocular problems is definitely correlated with the patient's clinical status at the ICU[21,22]. The main reason for this is that additional diseases prolong the stay in the intensive care unit. At this stage, comorbid conditions position themselves as an essential denominator of prognosis[23]. In this study, 11.8% of the patients had obesity, 31.4% had diabetes mellitus, 18.6% had renal failure, 25.7% cardiac disease, 41.4% had hypertension, 20% had lung disease, 8.6% had connective tissue disease, 8.6% had rheumatic diseases and 2.9% had malignancy. All of our patients were hospitalized in the ICU due to respiratory failure due to COVID-19. The presence of obesity, DM, and HT caused the patients to have a severe clinical course.

Ocular surface damage can result from direct oxygen delivery or from noninvasive ventilation face masks that exert a direct drying effect on the corneal surface. Elevated venous pressure resulting from positive pressure ventilation and/or the prone position of ventilated patients can result in conjunctival edema (chemosis) and expose the surface of the eye as a result of mechanical lifting, as seen in many COVID-19 patients. Indirect damage to the unprotected corneal surface (exposure keratopathy) can lead to secondary complications with the potential for permanent vision loss, including microbial keratitis, corneal scarring, and perforation[24]. Any damage that causes scar tissue formation on the corneal surface or opacity of the cornea can reduce the amount of light entering the eye and alter the refractive power, resulting in vision loss[25]. Exposure keratopathy affects 20-42% of ICU patients. The cause of keratitis/punctate keratopathy is lagophthalmia caused by the sedatives and neuromuscular inhibitors used and insufficient valve closure due to insufficient orbicularis oculi muscle contraction. We started to apply eye closure in the early period when we started to apply sedation to the patient as a protocol in eye care; maybe that's why our exposure keratopathy rate was found to be as low as 14.8%. In patients with a suspected corneal epithelial defect, corneal staining was performed by an ophthalmologist, but no defect was detected.

The prone positioning or positive pressure ventilation in ARDS leads to conjunctival chemosis, which increases the patient's venous pressure and reduces venous return from the eye tissue. Depending on the degree of conjunctival chemosis, corneal moistening is impaired. IMV and prone position derive the risk of chemosis in ICU patients. In our study, chemosis has been statistically significantly higher in IMV group where most of the cases were mild to moderate. The most prominent risk factors regarding chemosis in our cohort could be elaborated as positive pressure ventilation, high positive end expiratory pressure and increased intrathoracic pressure attributed to the frequent use of airway pressure release ventilation (APRV) mode in our ICU.

In this study, the secretion was higher in IMV group in parallel with the previous findings. It has been recently published that COVID-19 induces small fiber neuropathy in the ocular surface[25,26] and 40% of patients had reflex tearing due to dry eye, and the majority of these improved with lubrication[26,27]. In other words, COVID-19 causes deterioration of corneal innervation and reflex hypersecretion. Even if the eyelids are closed mechanically, the decreased muscle tone in IMV may be insufficient to protect the cornea and reflex lacrimation may increase as a mechanism to protect the ocular surface[28,29].

Limitations of this study include the relatively small sample size and the inability to perform detailed slit-lamp examinations with slit-lamps due to the logistical challenges of currently managing these patients. In the literature, the most common eye complaints experienced by COVID-19 patients after extubation were stated as blurred vision and eye pain, but we could not follow-up on our patients after discharge[30]. The temperature and humidity rates of the ICU also cause dry eyes and can lead to ocular complications. Dry air and bacterial air filter system are utilized in intensive care units and if the blinking reflex of the patient is impaired, this causes the eye surface to dry quickly, thus leading to complications[14]. Finally, no data exist up to date indicating that the patients were followed up daily during the study. This is the distinguishing feature of our work.

Conclusions

The longer duration of stay in the intensive care unit, neglecting eye care due to other vital priorities may deteriorate patients' ocular health. The selection of appropriate agents and giving sufficient eye care will ameliorate this situation. In this study, it was determined that oxygenation and ventilation treatments also contributed to ocular surface damage in addition to the patients' characteristics and the clinical stages of the disease. In addition to the clinical priorities of the patients, precautions should be taken against eye damage.

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Authors' Contribution

İlkay Ceylan writing and reviewing of manuscript, Hamide Ayben Korkmaz original idea and writing of manuscript, Hafize Gökben Ulutaş writing of manuscript.

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Conflicts of Interest

The authors declare that they have no conflict of interests.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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