Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 3750 - 3760
Received 25 April 2021; Accepted 08 May 2021.

COVID-19; A Review for Eye Care Practitioners

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ABSTRACT

The spread of COVID-19 is becoming unstoppable and has already reached the necessary epidemiological criteria for declaring it as a pandemic. Given the close distance between the patients and eye doctor during the examination, frequent exposure to the tears and ocular discharge, and the unavoidable use of equipment requiring the close proximity, eye doctors are at a high risk of infection with COVID-19. Based on the 60 manuscripts written about COVID-19 diseases and other coronaviruses, the basics of this new virus, signs and its relationship to the eyes, eye doctors' care procedures against the disease, hygiene measures for sanitization of the environment and ophthalmic instruments, patients' care and attention to the use of contact lens during the COVID-19 pandemic were all investigated in the present study.

KEYWORDS

COVID-19, Eye, Care Practitioners.

Introduction

The spread of coronavirus disease 2019 (COVID-19) is becoming unstoppable and has already reached the necessary epidemiological criteria for declaring it as a pandemic right now where many countries are affected by this disease.

Health care workers are also at risk for the infection with COVID-19. Over 9000 health care workers have developed the infection in the world (1). For example, in China ,as the first country affected with COVID-19, it is estimated that, 3400 health care workers have been infected and at least 22 of them have died (2, 3). Also, a previous study indicated that the healthcare workers suffered from higher risk of SARS infection in the case of unprotected eye contact with secretions (4, 5).

Eye doctors including the optometrists and ophthalmologists, as a primary healthcare provider interact with a largely unscreened population and so are susceptible to the transmission of epidemic diseases like COVID-19(6). According to the recent reports, a large number of eye doctors involved in the diagnosis and treatment of the disease accidentally acquired the COVID-19 daily (7). One of them was Dr. Li Wenliang, an ophthalmologist at Wuhan Central Hospital. In early January, he contracted the COVID-19 from a patient with asymptomatic glaucoma and succumbed to the disease one month later (1, 8, 9). Also in Iran, an optometrist has died because of this disease.

According to the Centers for Disease Control and Prevention (CDC), COVID-19 has an incubation period of 2–14 days; however, studies have also shown a shorter incubation period of 5.2 days (10-13). Ophthalmic services may be the first line of transmission of COVID-19 as it can be spread by aerosol contact with conjunctiva (5, 9, 14).

Furthermore, since ophthalmic consultations often include multiple examinations, such as evaluating the visual acuity, measurement of intraocular pressure, pupillary dilatation, and others, it is not uncommon that the patients have prolonged stay in the clinic to complete the whole examination (8).

While the COVID-19 transmission route is still unknown, countries have prepared the measures based on past experiences with the coronaviruses namely SARS-CoV and MERS-CoV (15). In this paper, COVID-19 as an epidemic disease is studied, and necessary steps to prevent the spread of this disease in primary eye care practices are presented. Considering the available evidence in research papers and according to the authorities in the centers for disease control and prevention around the world, there are main areas to know the COVID-19 and its related preventative actions applicable in the ophthalmic practices to minimize the transmission of COVID-19 including the COVID-19 basics, the relationship between eye discharges and COVID-19, eye doctors' care procedures, patient management, equipment disinfection, disinfection of contact lens equipment and system.

COVID-19 Manifestation

Coronaviruses (CoV) belong to the Coronavirinae subfamily and the order of Nidovirales, in the Coronaviridae family (16). They are classified into four genera: Beta, Alpha, Gamma, and Delta coronavirus (16). It is a single-stranded virus with a positive sense of RNA (17). Mutation rates of RNA virus are higher than DNA viruses, and they indicate a more successful survival adaptation cycle (16, 17).

Fig. 1 shows the virus structure (18, 19).

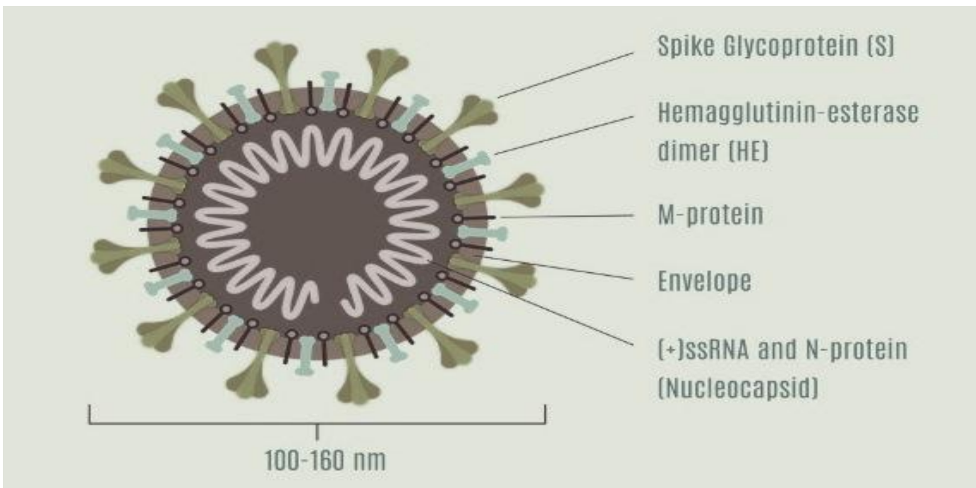

Figure 1. The structural proteins of Coronavirus

Particulates of the coronavirus possess four major structural proteins including the Spike (S), Membrane (M), Envelope (E), and Nucleocapside (N) proteins, all encoded within the 3′ end of the viral genome (20). The S protein (almost150 kDa) uses an N-terminal signal sequence to get access to the Endoplasmic Reticulum (ER), and is crucially N-linked glycosylated (20). Homotrimers of the S-protein encoded virus form the distinctive spike structure on the virus surface (21). The glycoprotein trimeric S as a class I fusion protein mediates the binding to the host receptor (22). In the majority but not in all the coronaviruses, S is divided into two different polypeptides by a host cell furin-like protease called as S1 and S2. S1 constitutes the broad S-protein receptor-binding domain while S2 forms the stalk of the spike molecule (22, 23).

The M protein is the most plentiful structural protein in the virion. It is a protein (almost 25–30 kDa) with three transmembrane domains and is thought to be responsible for formation of the virion (24). It has a low glycosylated ectodomain at N-terminal and a much bigger endodomain at C-terminal extending about 6–8 nm into the viral particle (22). While they are inserted co-translationally into the ER membrane, many M-proteins have no signal sequence (25). Recent studies have suggested that the M protein occurs in the virion as a dimer and can follow two different configurations to facilitate the membrane curvature and bind to the nucleocapside (23).

The E protein (maybe 8–12 kDa) is present in the virion in small quantities (23). E coronavirus protein is widely divergent but has an architecture similar to the others (26). Topology of the E-protein membrane is not fully resolved but based on the most findings it is a transmembrane protein (26). The E protein has an ectodomain N-terminal and an endodomain C-terminal and is active in the ion channels (26). Unlike other structural proteins, recombinant E-protein viruses are not always lethal, although it depends on the type of virus (27). The E protein promotes the assembly and release of the virus (See Section on the Assembly and Release of Coronavirus), but it also has other functions (27). For example, the operation of ion channels is not needed for viral replication in SARS-CoV E protein but is important for pathogenesis (28).

The N protein is the only protein found in nucleocapsid (29). It is consisted of two distinct domains, an N-Terminal Domain (NTD) and a C-Terminal Domain (CTD), both are able to accomplish the *in -vitro* RNA binding but each domain uses different mechanisms to bind the RNA (29). It has been recommended that ideal RNA binding needs assistances from both domains. N protein is also greatly phosphorylated and phosphorylation has been proposed to cause a structural variation promoting the affinity of viral RNA against non-viral RNA (29). N protein links to the viral genome together in a beads-on - a-string type of conformation. Two different RNA substrates have been identified for N protein including the Transcription-Regulating Sequences (TRSs) and the genomic packaging signal (20). The genomic packaging signal was found precisely bound to the second or C-terminal RNA binding domain (26). In addition, N protein binds to the nsp3, a key component of the replicase complex, and M protein (21). Such protein interactions probably help in binding the viral genome to the Replicase-Transcriptase Complex (RTC) and then packing the encapsidated genome into viral particles (30). Also, Hemagglutinin-Esterase (HE) as a fifth structural protein is found in the subset of β-coronaviruses (31). This protein functions as a hemagglutinin, binds to the sialic acids on the surface of glycoproteins and includes the activity of acetyl esterase (31). Such behaviors are thought to enhance the S protein-mediated cell entry and the spread of viruses through the mucosa (31). Curiously, HE improves neurovirulence of the Murine Hepatitis Virus (MHV); however, it is selected against in tissue culture for unknown reasons (32).

Prior to the outbreak of SARS-CoV, coronaviruses were thought to only cause mild, self-limiting respiratory tract infections in the humans (32). The α-coronaviruses (HCoV-229E and HCoV-NL63) are two of these human coronaviruses and β-coronavirus (HCoV-OC43 and HCoV-HKU1) are the other two human coronaviruses. HCoV-229E and HCoV-OC43 were isolated almost 50 years ago and HCoV-NL63 and HCoV-HKU1 were only recently identified following the outbreak of SARS-CoV (33). These viruses are native to the humans and cause 15-30 % of respiratory tract infections annually (34).

They cause more severe disease in the neonates, the elderly, and people with underlying diseases, with an increased incidence of lower respiratory tract infection in these people. HCoV-NL63 also causes the acute laryngotracheitis (croup) (35).

The emerging 2019 novel coronavirus (2019-nCoV) has forced several countries (particularly China, Iran, Italy, etc.) to announce the emergency situation (36). The potential transfer of 2019-nCoV by conjunctiva is controversial and has significant implications for public health (36). The 2019-nCoV has ignited the global alarm about the possibility of an outbreak such as the 2003 Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), which infected more than 8,000 people and killed 774 people (37, 38).

While the transmission route for 2019-nCoV is still unknown, countries have prepared some preventative steps based on past experiences with coronaviruses, namely SARS-CoV and MERS-CoV (39). These viruses can be mainly spread through the droplets and other body secretions. In the field of ophthalmology, health care workers may be especially vulnerable to these infections (40).

COVID-19 Ocular Presentation

The role of the eye in the transmission of COVID-19 is still under discussion, since there are considerable controversies in this regard (41). There are increasing reports suggesting that a few COVID-19 cases developed the conjunctivitis as the initial symptom following the contact with confirmed patients and wearing no protective goggles (5).

Xia et al., investigated 30 confirmed COVID-19 patients, and showed that virus was present in the tears and conjunctival secretions of the patients with conjunctivitis and there was no virus in the conjunctival sac of the patients without conjunctivitis. In this research, some patients had no obvious fever or respiratory manifestations (7).

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Seah et al., evaluated 17 confirmed COVID-19 patients and concluded that the risk of SARS-CoV-2 transmission is low through tears (42).
Zhou et al., investigated 76 confirmed COVID-19 patients. Among the cases enrolled in this study, one was positive for the conjunctival sac COVID-19 test and two cases were suspicious to be positive. None of these three patients had ocular symptoms. One anesthesiologist was presented with conjunctivitis as the first symptom but had a negative conjunctival sac COVID-19 test.

In another study, Wu et al., investigated 38 confirmed COVID-19 patients. They suggested that among patients with this disease, 31.6% (95% CI, 17.5-48.7) of them had ocular abnormalities, while most of them had more severe systemic manifestations or abnormal findings on the blood Tests. They found only one patient presenting with conjunctivitis as the first symptom (43).

Zhou et al., evaluated the 67 confirmed or suspected COVID-19 patients and showed that, in the early stage, it appears as common conjunctival hyperemia along with fewer secretions and this kind of conjunctivitis has no specific manifestation, and can present in one eye or two eyes. It is watery and akin to the thin mucus. Occasionally, small pieces of conjunctival hemorrhage were seen. The ocular symptoms of the patients were mild and tended to be self-healing. There was great variation between the patients (5).

As the evidence regarding the ocular transmission has not been well studied and due to the novelty of the virus, there is a need to use the findings of studies about other coronaviruses like SARS and MERS. Also, similar to SARS-CoV, COVID-19 enters into the host cells through recognizing and binding to the potential receptor of its host, Angiotensin-Converting Enzyme 2 (ACE2), distributed among various tissues and cell types including the conjunctiva (5, 44).

Belser et al., in a study showed that the SARS-CoV is spread through direct or indirect contact with mucous membranes in the eyes (45).

Loon et al., detected the coronavirus in the tears of the patients infected with SARS, although they concluded the detection rate of coronavirus was low in the conjunctival sac (46).

Hui, in a study detected the SARS coronavirus in the respiratory tract secretions, urine, feces, and tears of some patients infected with SARS coronavirus infection (47).

Thus, it can be said that, the COVID-19 can cause the conjunctivitis and till completion of the related studies and publishing more reliable results, it should be noted that, ocular secretions and tears from the infected patients may contain the viruses and can be a source of transmission.

Staff Health Care

Personal protection is one of the most important issues in preventing the spread of the diseases. In addition to the eye doctors, they often express their concern about family transmission. Therefore, it is of utmost importance to prevent any further spread in the public and healthcare settings (2, 48). Transmission in healthcare settings can be successfully prevented when appropriate measures are consistently performed (48, 49).

For preventing the spread of the disease, the practitioners should use protective equipment and follow the healthcare and hygiene protocols. Also, if respirator is worn, users must be trained about its proper use including advice on proper fitting, maintenance and sanitization, re-use protocols, and proper disposal of the used respirators (50, 51).

Eye doctors should use the personal protective equipment including a disposable cap, gown, gloves, mask especially N95 respirator mask and eye protection, or face shield to ensure minimal risk of infection while treating the patients with COVID- 19 based on the previous experiences on MERS-CoV and SARS-CoV outbreaks. It is noteworthy that, eyeglasses or contact lenses are not considered as eye protection and surgical masks are not considered a substitute for an N95 mask and they can be used only if there is no alternative (2, 5, 6, 41, 52-55).

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Routine personal hygiene measures include frequent hand washing with soap and water after patient contact, which is a prudent means for reducing the spread of disease. It is recommended that the healthcare workers wash their hands using a combination of chlorhexidine with ethanol and cetrimide, or alcohol-based hand-rub solutions, and routinely clean the "high-touch "surfaces after visiting each patient (56). Avoiding to touch the eyes, nose, or mouth is also recommended (12, 51, 57, 58). Also, according to the WHO, it is recommended to apply alcohol-based hand rubs for decontamination of the hands, e.g., after removing the gloves (48).

All the clinical staff is required to report their temperature and any related symptoms like cough, breathlessness before work, and also their travel history (8, 12).

Finally, eye doctors need to apply the protocols while arriving at home and coming back to their families. These protocols include the protective planning for the home such as separation of living spaces and bathrooms and when such separation should be implemented. Protocols related to routine home arrival after duty will be a point of discussion including the benefits of taking off the shoes, removing and washing the clothes, and immediately taking a shower (2).

Environmental and Instrumental Hygiene

The aim of protective actions for the environment and instruments is preventing the spread and reducing the concentration of infectious droplets in the ambient air such as the healthcare clinics (8).

The coronavirus is known to live on the surfaces for hours or days (12, 59). It can remain infectious for 2 hours up to 9 days on different types of materials (48).

For environmental control, firstly, air ventilation should be used in different sections of the clinic. For this purpose, the windows should be opened and fresh air dampers are needed in the air handling equipment to achieve a higher fresh air rate with improved air dilution. High Efficiency Particulate Air (HEPA) units are recommended in order to augment the total air change rates in waiting areas where needed (8, 12, 51, 60).

Disinfection of work environment, surfaces, and objects that might be touched by the patients (e.g., doorknobs and chair handles) is a prudent method for preventing the spread of infectious agents (6, 12, 51, 59). There is a need to ensure that environmental cleaning and procedures for disinfection of the surfaces are followed consistently and correctly. Thoroughly cleaning environmental surfaces with water and detergent and applying commonly used hospital-level disinfectants (such as sodium hypochlorite) are effective and sufficient procedures. The typical use of bleach is recommended at a dilution of 1:100 of 5% sodium hypochlorite resulting in a final concentration of 0.05% (48). Also, various types of biocidal agents such as hydrogen peroxide, alcohols, sodium hypochlorite, or benzalkonium chloride are used worldwide for disinfections mainly in the healthcare settings (48, 61). For disinfection of small surfaces, ethanol (62e71%; carrier tests) has been shown to have a similar efficacy against coronaviruses. The use of 70% ethanol is also recommended by the WHO for disinfecting the small surfaces (48). Table 1 demonstrates how the Coronaviruses inactivates by different types of biocidal agent (48).

Table 1. Inactivation of coronaviruses by different types of biocidal agents

Biocidal agent	Concentration	Type of Virus	Exposure time	Reduction of viral infectivity (log10)
Sodium hypochlorite	0.1%	MHV	10 min	2.3- 2.8
	0.2%	CHV	10 min	0.3
	0.21%	MHV	30 s	≥4.0
Hydrogen peroxide	0.5%	HCoV	1 min	> 4.0
Formaldehyde	1%	SARS-CoV	2 min	> 3.0
Povidone iodine	7.5%	MERS-CoV	15 s	4.6
	4%	MERS-CoV	15 s	5.0
	1%	MERS-CoV	15 s	4.3
Benzalkoniumchloride	0.02%	HCoV	10 min	0.0
Ethanol	95%	SARS-CoV	30 s	≥ 5.5

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 3750 - 3760
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	85%	SARS-CoV	30 s	≥ 5.5
	80%	SARS-CoV	30 s	≥ 4.30
SARS ¼ Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; MHV: mouse hepatitis virus; CCV: canine coronavirus; HCoV: human coronavirus.				

Clinical staff should clean and disinfect the workspaces and personal items such as computers, keyboards, telephones, and other medical equipment using the alcohol-based disinfectants and wrap them with plastic sheeting such as cling wrap (2, 6).

On the other hand, as, the close proximity between the eye doctors and patients during examination puts them at risk of infection, and the droplets from a cough or sneeze can travel up to six feet and stay on the ophthalmic equipment for hours to days (8, 12, 56, 59), and also the use of non-contact tonometer spraying a gas during examination, and producing a large amount of aerosols in the local area (7). it is needed to install the protective shields on the equipment such as slit lamp, ophthalmoscope, and retinoscope to reduce the risk of transmission between the doctors and patients, and these instruments are required to be disinfected according to local disinfection guidelines (8, 12, 60) (figure 2). Various types of biocidal agents such as alcohols, hydrogen peroxide, sodium hypochlorite, or benzalkonium chloride are used mainly for infection control against coronaviruses (48, 61-63).

Figure 2. Protective shield on slit lamp

There is a potential possibility on the transmission of the viruses to other patients through the use of reusable ophthalmic equipment such as trial frames, trial contact lenses, handheld occluders, and other devices coming in close contact with the patient's eyes, thus they should be disinfected after visiting each patient, especially the Goldmann applanation prism tip should be rinsed with tap water to remove any organic manner, soaked for 20 minutes at room temperature in the 6% sodium peroxide, thoroughly rinsed with saline solution ,and air dried before every use (6, 46).

Patients Health Care

When the patients have close contact with recovered individuals in common areas such as reception areas and examination rooms, then the viruses can be transmitted from person to person (51). The starting point for transmission is not clear, although it has been reported that the transmission occurs during the asymptomatic incubation phase (8, 10, 12, 64). Therefore, there is a need to reduce the communication and increase the distance between the people in the health care clinics. Also, cessation of elective care with telemedicine implementation under

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suitable eye conditions further reduces the crowding in the clinics (1). Emergency surgeries and services should be maintained (8).

Active screening of all the patients and having very limited number of companions along with the patients can be performed through a targeted questionnaire and non-contact temperature checking at the time of entering the clinic (1).
In the case of a patients' attendance for an appointment, it is important to evaluate the potential risk of transmission by the patient, such as checking the patients who have travelled to outbreak areas within past 14 days, patients with upper respiratory tract infection (e.g., cough), and those with the conjunctivitis. Those patients who are suspected to have the symptoms of COVID-19 should be rapidly triaged and separated from the general population ideally in a well-ventilated space with a distance of at least 6 feet from others until they can be taken in an isolation room (2, 58).

After check-in examinations, healthy patients should be asked to wait in open spaces or in their cars for cellular phone notification, as well as increasing the spacing between the patients in office waiting rooms (1). Placing a facemask on the asymptomatic patient at the time of arrival, supplying the tissues, promoting the cough etiquette, and providing for regular hand hygiene are considered as important steps (1, 2).

Also, the use of telemedicine including home visual function testing, transmission of image and video and face-to-face interactions through the widely available applications can provide the eye doctors with opportunities to provide limited care and counseling (1, 65).

Contact Lens and COVID-19

Contact lens practice can be particularly exposed to these modalities of transmission. Indeed, contact lens practice involves face-to-face communication, close examination of the patient, and the need to directly touch the patient's eyelids. Finally, some contact lenses are still fitted using the trial sets, which should be cleaned thoroughly after visiting each patient (58).

Thoroughly cleaning the instruments used in the CL practice such as trial frame and ophthalmic lenses, chin rest and head rest of the instruments like slit lamp, auto refractometer, and keratometer can be performed effectively using the water and detergent and applying commonly used hospital- level disinfectants (such as sodium hypochlorite, 70 % alcohol, or an alternative disinfectant) (58).

In the case of fitting the specialty contact lens such as the Rigid Gas Permeable (RGP) lenses in keratoconus, Ortho-K and Scleral lenses, where a trial set of contact lenses is used, it becomes very important to ensure that the contact lenses are disinfected well after visiting each patient. In these cases, rigorous infection control measures must be followed when trial lenses are reused (58, 66).

Notably, during the patient examination, practitioner must avoid touching their own face, nose, mouth, and eyes. The message concerning following the hygiene instructions should be reinforced for the patients. They should be reminded to wash their hands thoroughly before touching their own eyes and their contact lenses. Patients should also be reminded to clean their contact lenses correctly, ensuring complete disinfection between applications and not using disposable contact lenses longer than they are intended. Patients should seek for the doctors' advices if they are sick and discontinue the use of contact lenses if they have any malaise (58, 66).

Also, telemedicine should be applied as an alternative for reminding the use of medicines, consulting with the patients about symptoms and checking the images of eyes and contact lenses (67).

Conclusion

Due to the novelty of this disease, more studies are needed on its origin, transmission and treatment. More comprehensive studies are also needed on the presence of COVID-19 in tears and the possibility of transmission through the eyes. In the end. It is necessary to follow the

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recommended health protocols, in order to protect the staff, patients and the clinical environment from the disease. These protocols must be fully considered until the features of the virus are better discovered.

Conflict of Interest

Conflicts of Interest: Kangari H, None; Shahcheraghi S H, None; Ayatollahi A, None; Mirfendereski S A, None.

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