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Literature review of conjunctivitis, conjunctival swab and chloroquine effect in the eyes: A current updates on COVID-19 and ophthalmology

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ABSTRACT

This overview briefly describes current literature findings in ophthalmology related to coronavirus disease 2019 (COVID-19) that become a worldwide pandemic. It included the current updates related to conjunctivitis that believed as the early sign of COVID-19, the effectiveness of conjunctival swab in detecting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) compared to naso- or oropharyngeal swab and the long-term side effect of chloroquine use to the eyes. The analysis from four current published literatures revealed, overall sensitivity of conjunctivitis was 2.42% (CI 95%: 0.79-5.55) and conjunctival swab was 2.90% (CI 95%: 1.07-6.20). There were no current COVID-19-related literatures discussing the side effect of chloroquine to the eyes, however, previous literatures revealed there were potential long-term harmful effects of chloroquine treatment to the eyes.

ABSTRAK

Tinjauan pustaka ini menjelaskan secara singkat temuan-temuan literatur terbaru di bidang oftalmologi terkait dengan *coronavirus disease* 2019 (COVID-19) yang menjadi pandemi di seluruh dunia. Tinjauan ini mencakup temuan terbaru pada konjungtivitis yang dipercaya sebagai tanda awal COVID-19, efektivitas *swab* konjungtiva dalam mendeteksi *severe acute respiratory syndrome coronavirus* 2 (SARS-CoV-2) dibandingkan dengan *swab* naso atau orofaring dan efek samping jangka Panjang penggunaan klorokuin pada mata. Analisis dari empat publikasi terbaru menunjukkan sensitivitas konjungtivitis adalah 2,42% (CI95%: 0,79-5,55) dan *swab* konjungtiva adalah 2,90% (CI95%:1,07-6,20). Tidak ada literatur terbaru terkait COVID-19 saat ini yang membahas efek samping klorokuin pada mata, namun kajian sebelumnya mengungkapkan ada potensi efek jangka panjang pada mata yang membahayakan akibat penggunaan klorouin.

Keywords:
conjunctiva;
coronavirus;
COVID-19;
ocular;
chloroquine;

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INTRODUCTION

Many experts believed that conjunctivitis as the early sign of coronavirus 2019 (COVID-19). It based on the findings that some cases of COVID-19 may have conjunctivitis manifestation and upon conjunctival swab of the patients, several of them yielded positive results for COVID-19 viral nucleic acid.[1] Conjunctival congestion was among the least common symptoms occurring at only 0.8% even lower than diarrhea occurring in 3.8% of the population.[2]

There were attempts to find an easier way to collect sample of severe acute respiratory syndrome 2 (SARS-CoV-2) other than from naso- or oropharyngeal swab. Conjunctival swab technique has been used to obtain conjunctival specimens from patients suspected infected by SARS-CoV-2. This technique aims to collect tears and conjunctival secretions from patients. The examiner should open the lower lid of each patient and wipe the conjunctiva of the patient's lower eyelid fornix using a disposable sampling swab without anesthesia.[1]

COVID-19 is a new emerging viral disease and no antiviral treatments have been approved. However, there were several attempts have been proposed to treat this disease such as lopinavir/ritonavir (400/100 mg every 12 h) as well as the administration of chloroquine (500 mg every 12 h) or hydroxychloroquine (200 mg every 12 h). Therefore, the safety issue regarding those regiments to the eyes has raised. This study aimed to decipher how sensitive is conjunctivitis as a sign of COVID-19 and conjunctival swab in detecting SARS-CoV-2 as well as to inform the potential long-term harmful effect of chloroquine use to the eyes.

MATERIALS AND METHODS

A systematic literature search was undertaken during the period of April-May 2020 from PUBMED database and other additional sources (i.e: Google Scholar). PICO framework was used to identify the research problems related to conjunctivitis, conjunctival swab, and chloroquine for literature review (TABLE 1). Keywords for schematic review were conjunctivitis OR ocular AND COVID-19 OR SARS-CoV-2; Conjunctival swab OR ocular AND COVID-19 OR SARS-CoV-2, chloroquine OR hydroxychloroquine AND COVID-19 OR SARS-CoV-2 (FIGURE 1). Papers were examined in terms of percentages of conjunctivitis and positive conjunctival swab in COVID-19 as well as current findings of chloroquine administration in COVID-19. Percentages of conjunctivitis and positive conjunctival swab from current literature (January 2020-current) were analyzed for sensitivity and specificity diagnostic tests.

TABLE 1. PICO framework for identifying the research problems

Variable	Patients/ Population	Intervention	Comparison	Outcome
Conjunctivitis	COVID-19	N/A	Naso- or oropharyngeal swab	Diagnostic value of conjunctivitis
Conjunctival Swab	COVID-19	N/A	Naso- or oropharyngeal swab	Diagnostic value of conjunctival swab
Chloroquine	COVID-19	Chloroquine	Other treatment for COVID-19	Retinotoxicity or other ophthalmic side effects

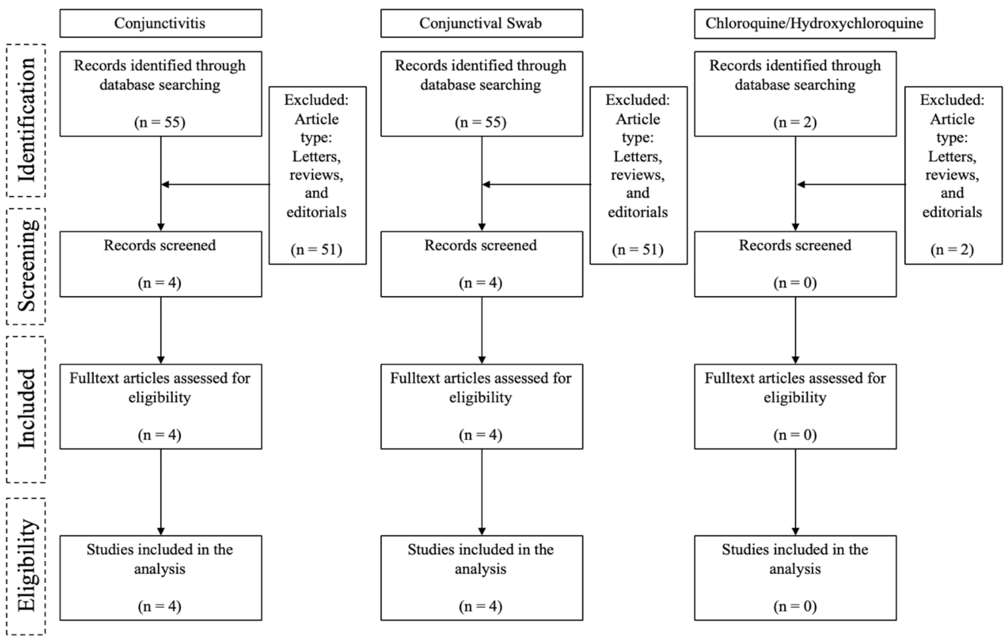

FIGURE 1. PRISMA chart of systematic review

RESULTS

Diagnostic characteristics analysis of conjunctivitis and conjunctival swab were sensitivity, specificity, positive, predictive value (PPV), negative predictive value (NPV), and accuracy. TABLE 2 shows the sensitivity and specificity of conjunctivitis as the sign of COVID 19, and was revealed that overall sensitivity and specificity were 2.42 (0.79-5.55) and 100 (91.59-100), respectively.

TABLE 2. Diagnostic analysis of conjunctivitis in COVID-19.

Variable	Xia *et al.*[1]	Zhou *et al.*[5]	Wu *et al.*[6]	Deng *et al.*[7]	Overall
Sensitivity	4.0 (0.10-20.35)	1.54 (0.04-8.28)	10.71 (2.27-28.23)	0 (0-4.02)	2.42 (0.79-5.55)
Specificity	100 (39.76-100)	100 (15.81-100)	100 (69.15-100)	100 (85.75-100)	100 (91.59-100)
PPV	100	100	-	-	100
NPV	14.29 (13.33-15.29)	3.03 (2.94-3.12)	28.57 (26.03-31.26)	21.05	17.21 (16.91-17.52)
Accuracy	17.24 (5.85-35.77)	4.48 (0.93-12.53)	34.21 (19.63-51.35)	21.05 (13.98-29.69)	18.88 (14.21-24.3)

Note: All data were in percentage (CI95%); PPV: positive predictive value;
NPV: negative predictive value.

TABLE 3 shows the sensitivity and specificity of conjunctival swab as the sign of COVID-19. The sensitivity and specificity were 2.90 (1.07-6.20) and 100 (91.59-100), respectively. A very low sensitivity means that there were many false negative results, and thus many cases of COVID-19 were missed when using conjunctivitis as sign of COVID-19 as well as conjunctival swab for SARS-CoV-2 detection.

TABLE 3. Diagnostic analysis of conjunctival swab in COVID-19

Variable	Xia *et al.*[1]	Zhou *et al.*[5]	Wu *et al.*[6]	Deng *et al.*[7]	Overall
Sensitivity	3.85 (0.10-19.64)	4.76 (0.99-13.26)	7.14 (0.88-23.50)	0 (0-4.02)	2.90 (1.07-6.20)
Specificity	100 (39.76-100)	100 (36.76-100)	100 (69.15-100)	100 (85.75-100)	100 (91.59-100)
PPV	100	100	100		100
NPV	13.79 (12.90-14.73)	6.25 (5.93-6.58)	27.78 (25.76-29.89)	21.05	17.28 (16.95-17.62)
Accuracy	16.67 (5.64-34.72)	10.45 (4.3-20.35)	31.58 (17.50-48.65)	21.05 (13.98-29.69)	19.28 (14.57-24.73)

Note: All data were in percentage (CI95%); PPV: positive predictive value; NPV: negative predictive value.

There were no current clinical trials investigating the potential side-effect of chloroquine treatment for COVID-19 to the eyes.

DISCUSSION

Is conjunctivitis the early sign of COVID-19?

From four current literature, the diagnostic test analysis revealed that conjunctivitis showed a very low sensitivity. Therefore, many cases of COVID-19 might be missed when conjunctivitis is used as sign to diagnose COVID-19. A case report of a 30 y.o patient with confirmed COVID-19 developed bilateral conjunctivitis on day 13 with a positive conjunctival swab for COVID-19.[3] Another case reported ocular manifestation of keratoconjunctivitis occurred as the initial medical presentation of COVID-19. The patient's main symptoms were red eye with watery discharge and upon conjunctival swab, the result yielded positive for COVID-19. Despite the positive COVID-19 result, the patient had a mild respiratory symptom without fever.[4]

It was also found that conjunctiva and corneal epithelial also expressed ACE2 although the expression was only slight. It was likely caused the binding of COVID-19 which explains the ocular findings of COVID-19 viral nucleic acid.[8] Peng and Zhou[9] concluded that COVID-19 is less likely transmitted via conjunctiva which means the detection of COVID-19 in tears and conjunctival secretions in patients exhibiting symptoms of conjunctivitis is a coincident event rather than causative of COVID-19 infection of the conjunctiva.[9]

Is conjunctival swab effective in detecting SARS-CoV-2?

Conjunctival swab technique is used to obtain conjunctival specimens which consists of tears and conjunctival secretions samples taken from lower eyelid fornix. In the present literature review, similar as the conjunctivitis result low sensitivity in conjunctival swab suggested that conjunctival swab diagnostic value was very low for SARS-CoV-2 detection. Furthermore, low negative predictive value reveals that when conjunctival swab yielded no virus detected, the patient still has very high probability having COVID-19.

Numerous studies have previously found no superiority of conjunctival swab compared to nasopharyngeal swab. For instance, a cross-sectional study of 72 patients with laboratory confirmed COVID-19 RT-PCR assay showed only 2 patients had the ocular manifestation of conjunctivitis and only one patient had positive COVID-19 upon conjunctival swab.[10] From the experience of SARS-COV, there was a prospective interventional case series study that was conducted to identify the SARS-CoV virus in tear secretions and conjunctival cells of patients that is confirmed positive SARS-CoV in Prince of Wales Hospital, Hongkong. The study result showed that 17 patients are confirmed positive after being tested with paired convalescent sera. Then, the specimen sample including nasopharyngeal aspirate and stool, tear swab, and conjunctival scraping were taken from these patients. Among these 17 patients, there were five samples from nasopharyngeal aspirate and stool specimens that were tested positive using RT-PCR, but there were no specimens from tear swab and conjunctival scraping that are tested positive. This could be caused by the RT-PCR test itself. RT-PCR is known to be very specific but lacks sensitivity, so the negative test result can be false negative and do not exclude the presence of the virus. The study could not completely exclude the presence of virus in tear secretion, but it was clear that conjunctival swabs and conjunctival scraping are not useful samples for confirming or excluding the diagnosis of SARS-CoV.[11]

Although the risk of ocular infection of COVID-19 was low, the transmission of COVID-19 through the ocular surface must not be ignored. The infectious droplets may easily contaminate the conjunctival epithelium. It was also recommended for all ophthalmologists to wear protective eyewear in examining suspected cases.[12]

Is chloroquine as COVID-19 treatment is safe for eyes?

Chloroquine is a medication used to prevent and cure malaria but now is only used in areas where malaria remains sensitive to its effects and use as prophylaxis in areas that are resistant to this medication.[13] Besides the antimicrobial effect, chloroquine was found to be efficient in inhibiting virus replication cycles such as rabies virus, poliovirus, HIV, hepatitis A virus, hepatitis C virus, influenza A and B viruses, influenza A H5N1 virus, Chikungunya virus, Dengue virus, Zika virus, Lassa virus, Hendra and Nipah viruses, Crimean–Congo hemorrhagic fever virus and Ebola virus, as well as various DNA viruses such as hepatitis B virus and herpes simplex virus.[14]

Chloroquine has multiple mechanisms on the virus, especially in coronavirus. By interfering with viral particles binding to their cellular cell surface receptor. Chloroquine can inhibit a step of the viral cycle life. Chloroquine can also interfere with the post-translational modification of viral proteins. Besides interfering with the life cycle of the virus, chloroquine can impair the proper maturation of viral protein by pH modulation.[14] *In vitro* study found evidence of the ability of chloroquine to inhibit SARS-CoV-2 activity.[15]

The empirical evidence for the effectiveness of chloroquine in COVID-19 is currently very limited but the first clinical trial data were published on the March 17th 2020. The study showed all patients who were treated with a combination of chloroquine and azithromycin tested negative on day 6. The authors argued that this finding speaks to the effectiveness of chloroquine and a potential synergistic effect of its combined treatment with azithromycin.[16]

It is not fully clear how chloroquine caused toxicity in the eye. In one study, high doses have an acute effect on retinal cell metabolism. Studies have shown that the drug affects the metabolism of retinal cells and also binds to melanin in the retinal, which could explain the persistent toxicity after discontinuation of the medication.[17] This can happen because chloroquine binds to melanin within retinal pigment epithelial cells, and it is resulting in long term damage to macula photoreceptors (FIGURE 2). These mechanisms may lead to clinically characteristic "bull's eye" maculopathy after chronic exposure to both agents even in the safe dose, in early stages is reversible but leads to irreversible loss of central vision in long term, reduced visual acuity, scotoma formation, and/or color vision deficits.[18] Bull's-eye maculopathy caused by a ring of parafoveal retinal depigmentation that spared a foveal island.[19]

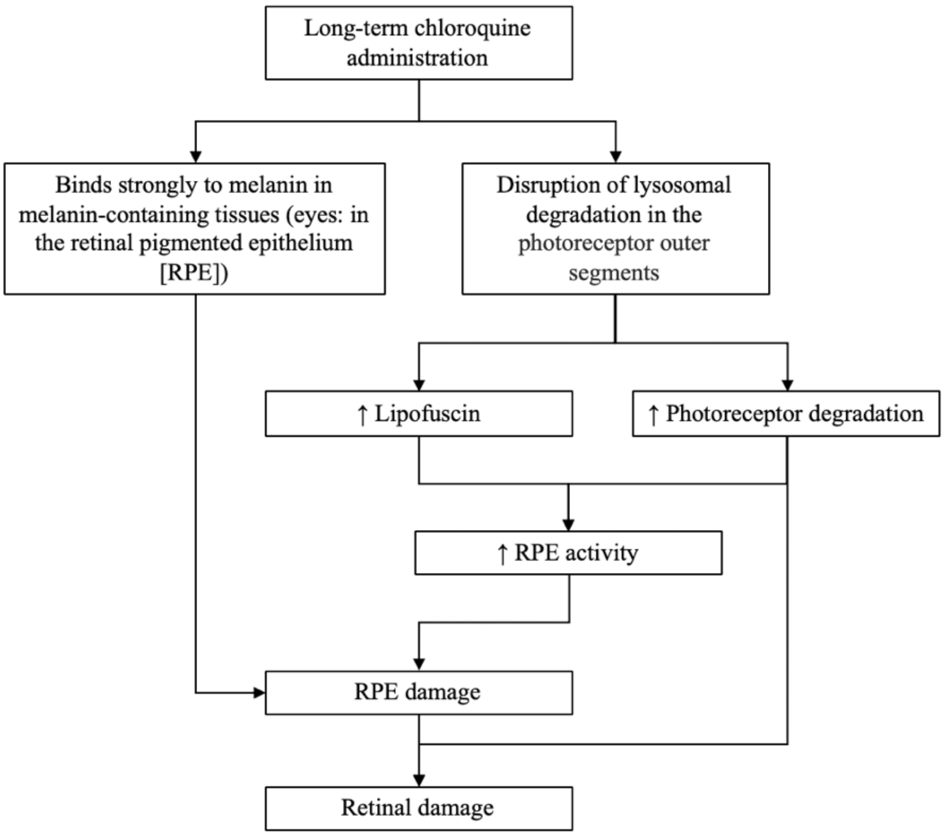

FIGURE 2. Proposed pathophysiology in chloroquine retinal toxicity[17-19]

American Academy of Ophthalmology reported that the most significant major risk factors for chloroquine retinal toxicity are high dose and long duration of use.[19] The maximum daily dose of chloroquine is ≤2.3 mg/kg of real body weight. But various treatment guidelines worldwide are well beyond the recommended dosage regimen.[20] Although the fact that doses for chloroquine exceed the recommended dosage regimen, the treatment may still be considered relatively safe for retinal toxicity. This is because irreversible retinal damage and visual loss, requires exposure for a long period, generally above five years. The recommendation suggested for the screening for retinal toxicity from chloroquine is within the first year of use and after a year of use for chloroquine and screening should be conducted sooner if the major risk factors are present.[21] In this pandemic condition, routine baseline ocular examination for patients with COVID-19 is not absolutely necessary but should be considered if the number of medical personnel is adequate. But it is necessary to take a history of ocular disease in patients who are older than 50 years before giving a treatment, especially macular disease.[20]

CONCLUSION

The analysis from the present literature review revealed that from four current published literatures, the overall sensitivity of conjunctivitis and conjunctival swab are very low. There are no current COVID-19-related literature discussing the side effect of chloroquine to the eyes, although previous literature suggested there is potential long-term harmful effect of chloroquine treatment for COVID-19 to the eyes.

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