Dilemma of donor testing before corneal retrieval in the COVID-19 era

In the wake of the COVID-19 pandemic, the entire health care system has undergone restructuring to cope with the widespread morbidity and mortality caused by the novel SARS-CoV-2 virus. Elective health care services have temporarily taken a backseat, and eye-banking and keratoplasty services have come to a near-standstill.[1] As we learn to live with the pandemic and move forward, there is a need to revise existing norms and guidelines in order to optimize eye-banking services and effectively tackle the growing backlog of routine keratoplasty procedures.

Challenges in Eye Banking and Donor Cornea Retrieval

The dual challenge of having to maintain a sufficient supply of donor tissues while ensuring adequate safety in the wake of the pandemic has compelled us to continually adjust and adapt the guidelines pertaining to corneal tissue retrieval, storage, and processing in accordance with the improved understanding of COVID-19 pathophysiology.[2]

In addition to the potential threat of viral transmission via donor corneas, there also remains the issue of potential infection transmission to eye-bank technicians involved in donor retrieval and processing. Adequate personal protective equipment, double betadine cleaning of the eyes before tissue retrieval, nasopharyngeal swabs from cadaveric donors for RT-PCR, and quarantining the harvested ocular tissue for 48 hours are some of the measures that have been devised to safeguard technicians and potential recipients. Eye donation counselors face the mammoth task of counseling the next of kin in accord with the COVID-19 norms and eliciting pertinent history to ascertain donor eligibility.

Extensive research has been undertaken in the past two years to confirm the presence of coronavirus in the ocular tissues of COVID-19-infected patients as well as to ascertain the plausibility of coronavirus transmission via ocular fluids and tissue. Ocular involvement in COVID-19 is relatively uncommon, with conjunctivitis being the most frequently reported manifestation; however, the presence of SARS-CoV-2 RNA has been reported in the tears and conjunctival secretions of patients both with and without conjunctivitis, raising concerns regarding potential ocular transmission.[3,4] Post-mortem studies evaluating the presence of viral RNA in the ocular tissue of COVID-19-infected patients are not conclusive, with some studies reporting the presence of viral RNA in cornea, sclera, and retina and other studies reporting the absence of any viral RNA in ocular tissues.[5-11] The variability observed in different studies can be attributed to the extremely low prevalence of the virus in ocular tissues, the relatively small number of samples analyzed, and the lack of a validated diagnostic test for use in post-mortem settings.[9,11]

Currently, there is limited evidence to support direct ocular infection or transmission of SARS-CoV-2 through tissue or cell transplants; however, considering that viral RNA has been detected in tear film and the necessary viral cellular integration machinery exists within ocular surface tissues, the possibility cannot be discounted completely.[4,9] Moreover, the potential source of viral material in ocular secretions is unlikely to be systemic infection as the virus does not appear to enter the bloodstream, further suggesting that direct ocular infection may be possible.[11] Recent studies reporting the presence of SARS-CoV-2 antigens in the ocular surface of deceased COVID-19 patients with evidence of cadaveric ocular surface cells getting infected on exposure to the virus reinforces this theory.[12]

Routine Donor Testing: Weighing the Pros and Cons

The utility of universal testing of donor tissue for SARS-CoV-2 remains a matter of debate. Table 1 details the current evidence for universal donor testing for SARS-CoV-2 and post-mortem detection of viral RNA/proteins in ocular tissues of COVID-19-positive donors. Nasopharyngeal RT-PCR test for detecting SARS-CoV-2 RNA is performed most commonly, with antigen testing or donor serum antibody testing performed less frequently. The sensitivity of RT-PCR ranges from 35%–77% for oropharyngeal samples, 59%–94% for nasal samples, and 92%–100% for nasopharyngeal samples. The reported specificity of RT-PCR is high and ranges from 99%–100%.[13]

International eye bank associations such as the Eye Bank Association of America (EBAA) and Global Alliance of Eye Bank Associations (GAEBA) do not prescribe mandatory RT-PCR testing of all potential donors, citing insufficient evidence for ocular transmission of the virus. Other arguments against universal testing include the additional cost of testing, the delay in releasing the tissue to the surgeon, and the limited sensitivity of the test, which may cause false-negative results. The EBAA screening guidelines take into consideration clinical factors such as the presence of signs/symptoms of COVID-19, the presence of an alternative plausible diagnosis if symptomatic, close contact with an infected individual, and the vaccination status of the donor.[14]

Recent studies have reported a significant RT-PCR positivity rate of nasopharyngeal swabs obtained from presumed COVID-19-negative potential donors, ranging from 4.8% to as high as 18.64%.[1,15,16] Arora *et al*.[15] also reported a high viral load (Ct < 25) in 54.54% of the positive cases, suggestive of high risk of disease transmission to the health personnel handling the tissue. These results emphasize that clinical screening measures alone may not be sufficient in capturing all COVID-19-positive donors, and RT-PCR testing is an important supplement to detect asymptomatic carriers (who have a high prevalence) or those who remained positive despite the resolution of undiagnosed COVID-19.[15] These observations are in agreement with our own, which reinforces the inadequacy of relying on symptoms and history alone for screening potential donors.[17]

The infectivity of SARS-CoV-2 in tissues of deceased RT-PCR-positive COVID-19 patients has been reported to be maintained up to 7 days post mortem, which underlines the

Table 1: Current evidence for universal donor testing for SARS-CoV-2 and post-mortem detection of viral RNA/proteins in ocular tissues of COVID-19 positive donors

Universal Testing of Deceased Donors for SARS-Cov-2			
Author (Year)	**Setting**	**Methodology**	**Outcomes**
Trigaux *et al* (2021)	26 eye banks in Germany	RT-PCR of 200 post-mortem viral swabs (NP + C or NP) performed	None found positive for SARS-CoV-2 RNA
Ballouz *et al* (2021)	Single Eye Bank (Michigan, USA)	RT-PCR of 314 post-mortem viral swabs (NP) performed within 72 h of death	15/314 (4.8%) tested positive ; 6/15 had a negative PCR premortem (ranging from day 4-13)
Arora *et al* (2021)	Single Eye Bank (India)	RT-PCR of 59 post-mortem viral swabs (NP)	11 donors (18.64%) were positive; 6/11 donors had Ct value of E gene less than 25; suggestive of a high probability of COVID-19 transmission.
Post-Mortem Detection of Viral RNA/Proteins in Ocular Tissues of COVID-19 Positive Donors			
Author (Year)	**Setting**	**Methodology**	**Outcomes**
Casagrande *et al* (2021)	Single Hospital (Germany)	Ocular tissues of 11 deceased viraemic patients tested for the presence of SARS-CoV-2 RNA.	RNA was identified in 6/11 corneas; subgenomic RNA was detected in 4/6 positive corneas, suggestive of viral replication. No virus was isolated from tissues.
Araujo-Silva *et al* (2021)	Single Hospital (Brazil)	Immunofluorescence and transmission electron microscopy performed in retinal tissue of 3 deceased COVID-19 patients	Presumed SARS-CoV-2 viral particles in various layers of the human retina
Bayyoud *et al* (2021)	Single Hospital (Germany)	Histopathological examinations and qRT-PCR-testing were carried out for retinal tissues and vitreous fluids in 10 eyes of 5 deceased COVID-19 patients	No significant level of SARS-CoV-2-RNA detected in retina and vitreous. No morphological sign of damage to retinal vasculature or tissue.
Sawant *et al* (2021)	Singe Centre (USA)	RT-PCR for 132 ocular tissues samples from 33- surgical-intended donors who were eliminated from surgical use per Eye Bank Association of America donor screening guidelines or medical director review or positive COVID-19 test (*n*=10).	RT-PCR positivity rate for SARS-CoV2 RNA- 13% (17/132). COVID-19 RT-PCR positive donor- 17% scleral rim positivity and 11% corneal positivity with RT-PCR Donors with signs and symptoms but not tested- 12% scleral rim and 15% corneal positivity with RT-PCR . Donors with close contact with cases- 0% scleral rim/corneal positivity with RT-PCR No viral antigens noted in corneas treated with povidone-iodine
List *et al* (2020)	Single Centre (Austria)	Aqueous and vitreous humor samples from 16 confirmed COVID-19 infection positive donors were tested (qRT-PCR) post-mortem	No aqueous humor or vitreous samples showed presence of SARS-CoV-2
Bayyoud *et al* (2021)	Single Hospital (Germany)	Corneal, conjunctival and aqueous samples from 5 (10 eyes) confirmed COVID-19 infection positive donors were tested (qRT-PCR) post-mortem.	No viral RNA detected in cornea, conjunctiva and aqueous humor.
Casagrande *et al* (2020)	Single Hospital (Germany)	RT-PCR performed in retinal tissue of 14 eyes of 14 deceased COVID-19 patients	3/14 eyes (21%) positive for SARS-CoV-2 viral in the retinal tissue

qRT-PCR-quantitative reverse transcriptase polymerase chain reaction; NP- nasopharyngeal; C- conjunctival; RNA-ribonucleic acid

need for careful and conscious handling of tissues by health personnel, especially in settings where universal testing is not being practiced.[18] Universal precautions, including the proper use of personal protective equipment, should be adhered to while retrieving donor tissues. The role of povidone-iodine for disinfection of donor ocular surface prior to retrieval was substantiated in a recent study wherein no viral antigens were detected in corneas treated with the solution.[7]

Our Perspective

Eye-banking services, including donor cornea retrieval and elective keratoplasty, were temporarily ceased at the National Eye Bank, RP Centre for Ophthalmic Sciences, AIIMS, New Delhi during the nationwide and later state-imposed lockdown during 2020–21. Donor retrieval was gradually restarted in accord with global norms, and potential COVID-19-positive individuals and high-risk suspects were excluded from the pool of potential donors. Donor corneas were retrieved from only presumed non-COVID-19 deceased donors, and mandatory RT-PCR testing of the deceased was performed at the time of retrieval. The donor tissues were quarantined following retrieval and used only subsequent to a confirmed negative RT-PCR report. A total of 432 donor corneas were collected in the period of July 2020–July 2021; of

these, 24 donor corneas (5.55%) were not used for keratoplasty as the RT-PCR test of the deceased donor was positive. This figure assumes even more importance when we consider the fact that all these donors were presumed to be COVID-19 negative based on the guidelines established by various global and national eye banks. In addition, one donor had previously recovered from a COVID-19 infection with a documented negative RT-PCR two months prior to death, thus highlighting the need to account for re-infection even in recently recovered donors. The evidence regarding the presence of viable viral particles in these donor tissues capable of transmitting disease remains inconclusive; however, in the absence of adequate knowledge, utilization of these tissues for keratoplasty should not be recommended.

Vaccination and Eye-Banking

Internationally, various nations are slowly easing the COVID-19 restrictions with an increase in the proportion of the vaccinated population. As the vaccination coverage further increases, the question will soon arise regarding the need for routine RT-PCR testing of vaccinated individuals for a variety of activities, including elective surgeries and organ donation. This is one aspect that needs to be addressed in the coming future, keeping in mind that no vaccine at present guarantees 100% safety from COVID-19 infection.

Conclusion

The COVID-19 pandemic is unlikely to end in the near future, and the disease may in fact become integrated in the communities with variable morbidity and mortality. The peaks of the COVID-19 wave will be associated with the pooling of all health care resources and cessation of nonemergent procedures, and the intervening quiescent phases will witness a significant backlog of elective cases, which needs to be tackled efficiently.

Eye banking and corneal transplantation need to be restored, and in fact, boosted in accordance with the new norms, to help restore sight to corneal blind patients while maintaining the safety standards. Further, the existing eye-banking and keratoplasty guidelines need to continually evolve with the emerging information and changing nature of the novel SARS-CoV-2 virus. Mandatory donor RT-PCR testing acts as a second line of defense to help exclude asymptomatic carriers who have been overlooked despite the stringent screening guidelines. Considering the high prevalence of asymptomatic infection, significant RT-PCR positivity rate reported among presumed COVID-19-negative asymptomatic donors and the recent evidence supporting the presence of virus in corneal tissue and the possibility of ocular transmission of disease, the merits of universal donor testing appear to outweigh its demerits.

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References

1. Ballouz D, Sawant OB, Hurlbert S, Titus MS, Majmudar PA, Kumar A, *et al*. Impact of the COVID-19 pandemic on keratoplasty and corneal eye banking. Cornea 2021;40:1018-23.
2. Ang M, Moriyama A, Colby K, Sutton G, Liang L, Sharma N, *et al*. Corneal transplantation in the aftermath of the COVID-19 pandemic: An international perspective. Br J Ophthalmol 2020;104:1477-81.
3. Mahmoud H, Ammar H, El Rashidy A, Ali AH, Hefny HM, Mounir A. Assessment of coronavirus in the conjunctival tears and secretions in patients with SARS-CoV-2 infection in Sohag Province, Egypt. Clin Ophthalmol 2020;14:2701-8.
4. Desautels JD, Moshirfar M, Martheswaran T, Shmunes KM, Ronquillo YC. Risks posed to corneal transplant recipients by COVID-19-affected donors. Ophthalmol Ther 2020;9:371-9.
5. Casagrande M, Fitzek A, Spitzer MS, Püschel K, Glatzel M, Krasemann S, *et al*. Presence of SARS-CoV-2 RNA in the cornea of viremic patients with COVID-19. JAMA Ophthalmol 2021;139:383-8.
6. Casagrande M, Fitzek A, Püschel K, Aleshcheva G, Schultheiss H-P, Berneking L, *et al*. Detection of SARS-CoV-2 in human retinal biopsies of deceased COVID-19 patients. Ocul Immunol Inflamm 2020;28:721-5.
7. Sawant OB, Singh S, Wright RE, Jones KM, Titus MS, Dennis E, *et al*. Prevalence of SARS-CoV-2 in human post-mortem ocular tissues. Ocul Surf 2021;19:322-9.
8. Araujo-Silva CA, Marcos AAA, Marinho PM, Branco AMC, Roque A, Romano AC, *et al*. Presumed SARS-CoV-2 viral particles in the human retina of patients with COVID-19. JAMA Ophthalmol 2021:e212795. doi: 10.1001/jamaophthalmol. 2021.2795.
9. Bayyoud T, Iftner A, Iftner T, Bartz-Schmidt KU, Rohrbach JM, Ueffing M, *et al*. Absence of severe acute respiratory syndrome-coronavirus-2 RNA in human corneal tissues. Cornea 2021;40:342-7.
10. List W, Regitnig P, Kashofer K, Gorkiewicz G, Zacharias M, Wedrich A, *et al*. Occurrence of SARS-CoV-2 in the intraocular milieu. Exp Eye Res 2020;201:108273.
11. Bayyoud T, Iftner A, Iftner T, Bartz-Schmidt KU, Ziemssen F, Bösmüller H, *et al*. Severe acute respiratory Syndrome-Coronavirus-2: Can it be detected in the retina? PLoS One 2021;16(5):e0251682.
12. Eriksen AZ, Møller R, Makovoz B, Uhl SA, tenOever BR, Blenkinsop TA. SARS-CoV-2 infects human adult donor eyes and hESC-derived ocular epithelium. Cell Stem Cell 2021;28:1205-20. e7.
13. Aldave AJ, DeMatteo J, Chamberlain WD, Philippy B, Farooq AV, Buckman N, *et al*. COVID and the cornea: From controversies to consensus: Report of the Eye Bank Association of America Medical Advisory Board Policy and Position Review Subcommittee. Cornea 2021;40:809-16.
14. COVID-19 Updates - Eye Bank Association of America [Internet]. Available from: https://restoresight.org/covid-19-updates/. [Last accessed on 2021 Aug 30].
15. Arora R, Sharda S, Sahu J, Manchanda V, Jain P, Gupta I, *et al*. Role of reverse transcriptase polymerase chain reaction in cornea donors during the COVID-19 pandemic. Cornea 2021;40:1044-7.
16. D'Souza S, Shetty R, Kundu G, Sharma N, Tandon R, Matalia H, *et al*. COVID-19 positivity rate in corneal tissue donors – A cause for concern!. Indian J Ophthalmol 2021;69:2808-11.

17. Kaur M, Nair S, Titiyal JS. Commentary: Potential transmissibility of SARS-CoV-2 infection via donor corneal tissue. Indian J Ophthalmol 2021;69:1598-9.
18. Heinrich F, Meißner K, Langenwalder F, Püschel K, Nörz D, Hoffmann A, *et al*. Postmortem stability of SARS-CoV-2 in nasopharyngeal mucosa. Emerg Infect Dis 2021;27:329-31.

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