Clinical Ophthalmology

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REVIEW

Effect of Covid-19 on Eye Banks and Corneal Transplantations: Current Perspectives

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic exerted a great impact on medical practice, which was reframed according to the actual needs. Ophthalmological services and procedures including corneal transplantation did not represent an exception. The adoption and implementation of new standard operating procedures as well as of new technologies for remote consultation and smart-working reshaped daily activities of both eye bankers, physicians, researchers, and patients. Regulatory restrictions were issued redefining corneal donor eligibility criteria, as well as handling and harvesting procedures of donor ocular tissues. Surgical schedules underwent an abrupt contraction with prioritization of urgent procedures. Local lockdowns and confinement strategies resulted in both a reduction and redirection of research activities. The evaluation of SARS-CoV-2 colonization of ocular tissues, long-term corneal storage techniques, new disinfection strategies, split corneal transplants and cell-based therapies for the treatment of corneal disease peaked in the pipeline. Aim of this article is to summarizes the overall impact of the pandemic on the corneal transplantation machinery, and the current and future perspectives for the corneal transplant community.

Keywords: SARS-CoV-2, COVID-19, eye bank, cornea, cornea transplantation, cornea transplant, basic sciences

Introduction

From March 11, 2020, when coronavirus disease 2019 (COVID-19) was declared a pandemic, the rapid spread of SARS-CoV-2 severely challenged health systems worldwide.[1,2] In this context, issues regarding donor procurement and screening, as well as the general reorganization of health care services exerted a profound negative impact on the delivery of organs and tissues for transplantation.[2,3]

Corneal transplantation was not an exception. In fact, while no conclusive evidence is available regarding SARS-CoV -2 transmission via corneal transplantation, current recommendations in several countries advice for dismissing tissues from donors recently infected with or exposed to COVID-19.[3–6] Indeed, both the European Eye Bank Association (EEBA), and the Global Alliance of Eye Bank Associations (GAEBA) have recommended to exclude potential donors diagnosed with COVID-19 in a 14-day window prior to death.[7,8]

Meanwhile, the redirection of the health care, human and economic resources towards COVID-19 departments, resulted in the disruption of the ophthalmic services in many institutions.[3,9–12] As a consequence, the Eye Bank Institutions worldwide have been facing unprecedented and unforeseeable operational challenges, with a considerable reduction in the number of both procured and distributed corneoscleral buttons, as well as with an increased proportion of discarded corneas due to non-use.[13] For instance, the Eye Bank Association of America (EBAA) reported for the 2020 a ~20% reduction in tissue procurement (54,740 donors in 2020, compared with 68,759 in 2019).[14,15] An exacerbation in the shortage of corneal donors, and a reduction in the donor-to-recipient ratio might derive, thus aggravating the condition of an already vulnerable system (e.g., in 2016 it was reported one cornea available every 70 needed).[16] This aspect is crucial considering the profound human, social, and economic costs associated with corneal diseases, which represent the third leading cause of blindness worldwide.[17,18]

Received: 13 October 2022
Accepted: 22 December 2022
Published: 30 December 2022

To counterbalance these difficulties, a profound reassessment of the Eye Bank System (including eye bankers, corneal surgeons and ophthalmic basic scientists) has already commenced and new techniques aiming to improve the efficiency of the corneal transplant machinery have been proposed. Nonetheless, technological innovations for tissue engineering and tissue preservation are on their way from bench to bedside, with a direct impact on eye bankers, corneal surgeons and basic scientists.

All of these will be analyzed one-by-one in this review, which aims to investigate how the corneal transplant community responded to the global health crisis of the century.

COVID-19 and Eye Banking

As we previously reported, the Eye Bank organization works as a complex structure responsible for recovery, evaluation, preservation, and distribution of corneal tissues.[3] Thus, not only donation, but also tissues harvesting, and preservation are critical steps of the process.[13]

During the pandemic, a general reduction in the amount of cornea donors was registered as a consequence of several factors including restrictive recommendations from regulatory bodies, logistic issues (e.g., tissues recovery staff safety and limited hospital access), and temporary reduction or cessation of the of eye bank activities.

For instance, Thuret et al, analyzing the impact of COVID-19 on corneal transplantation and ensuing response by health authorities, reported a nearly 50% reduction in cornea procurement during the first peak of the pandemic in Europe (i.e., February to May 2020). This significant contraction strongly correlated with the stringency of national donor selection algorithms.[19] In other words, the more stringent the criteria for cornea donation, the lower the number of procured tissues suitable for transplantation.[19] However, as reported by the authors, many of these recommendations had been established as precautionary measures at the beginning of the pandemic, before the severity of SARS-CoV-2 infection was known, and the potential ocular involvement by the virus confirmed.[19]

Based on these assumptions, it must be noted that regulatory bodies around the globe issued guidelines for deeming any deceased organ donors suitable for organs explantation. For instance, as reported by Ang et al, some centers in China recommends performing CT scans of the lungs in selected potential donors.[17] On the other hand, the Eye Bank Association of Australia & New Zealand and European Centre of Disease Control advised against routine exclusion of donors on the basis of tests which are not validated for use in deceased patients.[20,21] The EBAA and the Global Alliance of Eye Bank Associations, in compliance with the food and Drug Administration and the Center for Disease Control and Prevention, have recommended excluding donors recently infected with COVID-19, or those at high-risk such as a in the presence of a significant contact history. Further studies on the validity of SARS-CoV-2 PCR tests on deceased donors are needed to inform policy decisions on donor testing requirements.

To mitigate the risk of discarding tissues, the dramatic decline in requests for corneas from stakeholder, secondary to the ramped down elective procedures, resulted in many corneal bank facilities deciding for a temporary contraction of corneas procurement.[18–20] For instance, Busin et al reported a reduction of corneal button procurement up to 60% of normal rated.[13,22–24]

However, the risks of donor–recipient transmission, and potential financial losses, should be equipoised against the profound human, social, and economic burden of corneal blindness. An estimated 13 million persons globally await corneal transplantation, and the greatest disparities in access to this sight-restoring procedure exist in low-to-middle-income countries.[25,26] In the context of an already low proportion (~2%) of eligible cornea donors, COVID-19-related restrictions on donor eligibility and contracted tissue procurement might further reduce an already slim donor pool, thus jeopardizing cornea transplant programs in countries relying on tissue imports.[16,19]

Being the transmission of SARS-CoV-2 in working environments a recognized route, in the early phases of the pandemic Eye Bank Institutions around the globe were forced to rearrange their working strategies.[27] For instance, Thuret et al reported two Eye Banks in Europe having completely halted their activities and several others reorganizing their teams due to confinements, with limited personnel present on site.[19] Similar situations were reported virtually in the entire globe, including India, Germany and Canada.[24,28,29] Both AlShaker et al and Acharya et al reported Eye Bank Staff to have been trained to the appropriate and constant use of personal protective equipment, and exposure risk analysis

strategies (e.g., questionnaires, body temperature check, nasopharyngeal swab, etc.) to have been implemented to minimize the risk of in bank SARS-CoV-2 transmission.[24,29]

Standardized operating procedures (SOP) needed to be revised, too. An increasing number of checkpoints were added to avoid unnoticed potential exposure to SARS-CoV-2 (e.g., checklist for double-checking donor medical history and a detailed tissue tracker), according to the experience of Acharya et al.[29]

In addition, as suggested by the EBAA, double disinfection of cornea donors with povidone iodine before removal and preparation of the eye globe was confirmed or adopted in daily practice.[30] In fact, Sawant et al noted none of the povidone iodine pre-treated cornea donor resulting positive for SARS-CoV-2 RNA.[31,32] Similarly, polyvinylpyrrolidone solution (0.23–7.5%) was reported to be capable of up to 99.99% inactivation of viruses such as SARS-CoV, within 15–60 s at room temperature on inanimate surfaces.[33] While both these methods seem promising, more research regarding the disinfection potential against SARS-CoV-2 both in vitro and in vivo are warranted. However, the lack of any corneal toxicity mediated by the two compounds substantiate their immediate potential adoption in current SOP.[17]

The interruption in corneal transplant activity during the peaks of the pandemic, has resulted in a variable number of disqualified corneas, due to non-use, as variably reported in the literature.[3,9] In fact, corneal tissues maximum storage time depends on the preservation technique used, but it does not generally exceed 34 days.[3] Specifically, various methods have been proposed over the years for long term corneal tissues depot, with glycerol preservation, lyophilization, and gamma irradiation being the most promising ones.[34–36] It must be noted that, with differences, these approaches are validated and that clinical results and indications per each of them are already available.[34]

COVID-19 and Corneal Surgery

The aforementioned described reduction in corneal tissue distribution resulted as a consequence of a decreased demand by corneal surgeons and by the movement restrictions imposed to the general population by local quarantine regulations.

For instance, we previously described a nearly 60% reduction in the number of keratoplasties performed during the COVID-19 lockdown period in Italy, as compared with the same timeframe of the previous two years.[3] Similarly, Roy et al, based on the results of national survey conducted in India, reported 66% corneal surgeons not having performed any procedure between April and June 2020.[37] Eventually, according to Das et al, a 29.5% decline in the total number of keratoplasties was registered during the COVID-19 period as compared to the average of the previous three years.[38]

In this context, Pallavi et al also described the COVID-19 pandemic indirectly impacting on the corneal transplant machinery in the form of a delayed presentation of patients to healthcare facilities as per their hesitance to visit hospitals due to fear of contracting COVID-19, or per the lack of transport as a sequelae of the lockdown related restrictions.[39]

A revision of SOPs was also required in the context of corneal transplant procedures. The use of COVID-19 triage checklists at the patient admittance and the universal adoption of personal protective equipment in healthcare facilities became the new standard.[37,40,41] In addition, the adoption of standardized follow-up schedules, the implementation of telemedicine services as the standard of care for follow-up visits, and the creation of COVID-19 restricted and COVID-19 free pathways were common strategies variably adopted in several centers to minimize the risk of contagion, still allowing a continuous corneal transplant activity.[37,40,41] Accordingly, two main considerations should be made. First, given the COVID-19 pandemic curve still far from being settled, it is probable that many of the aforementioned procedures are or will be included in daily SOPs even in the aftermath of the pandemic. Furthermore, it should be reckoned that the main aim for the adoption of these strategies was to continue the corneal transplantation activity, to limit the number of discarded corneas due to non-use.[40] As such, keratoplasty should be considered as an urgent procedure, strictly dependent on the availability of corneal tissues from deceased donors, which at present cannot be preserved ad libitum.[34] Hence, the availability of safe and standardized strategies to ensure continuity of care in the corneal transplant activity is crucial for both the present and the future.

In the actual scenario of an unsustainable donor-to-recipient ratio, optimization of the available resources remains the key for success in corneal surgery. Accordingly, several options had already been proposed, the COVID-19 pandemic representing the occasion for both their adoption and implementation.[42]

For instance, in 2007, Vajpayee et al performed the first one-cornea multi-transplant procedure.[43] Working on a single cornea-scleral buttons, they were able to perform a deep anterior lamellar keratoplasty (DALK) in a patient with macular

corneal dystrophy, a Descemet stripping automated endothelial keratoplasty in an eye affected by bullous keratopathy and a cadaveric limbal stem cell transplantation in a 5-year-old boy with total limbal stem cell deficiency secondary to alkali burns.[43]

However, some concerns exist regarding the idea of splitting, in the operating theatre, one single corneal button in two topographically distinct portions (i.e., anterior and posterior). In fact, the risk of accidental macroperforation of the recipient Descemet membrane during DALK may imply the conversion of the procedure into penetrating keratoplasty, thus requiring a back-up cornea available, that is two corneas for two separate procedures.

However, Heindl et al reported a success rate of 97% when a single donor cornea was used for 2 recipients (47 of 50 cases).[44] The authors also suggested that the broader the experience of the surgeon in "split cornea transplantation", the higher the success rate. Nonetheless, although rare, the risk of infectious-related post-operative complications in two recipients cannot be excluded.

Oganesyan et al further extended the concept of one donor cornea for multiple recipients, proposing the idea of five keratoplasties from one single donor.[45] After stripping Descemet and endothelium (i.e., Descemet membrane endothelial keratoplasty or DMEK), they divided the graft in four quarters, to be implanted into four different recipients with primary endothelial dysfunction. The remaining corneal button was used for a DALK in patient with keratoconus.[45]

The idea of smaller and split DMEK grafts derives from the observation of primary endothelial conditions, such as Fuchs endothelial corneal dystrophy, often affecting the central cornea only in the early disease process.[26] Nonetheless, it is worth considering that the endothelial density is greater in the periphery of a DMEK graft, and as a consequence, a partial DMEK will still contain a sufficient amount of healthy endothelial cells.[46] Thus, a large diameter DMEK graft might not always be essential.

In this context, the role of the Eye Banks appears crucial. In fact, several pieces of evidence nowadays suggest pre-cut and surgeon-cut tissues to present similar biological features and comparable clinical outcomes.[47,48] Based on this assumption, the eye banks could be responsible not only for the corneal tissues harvesting but also for its splitting into the desired number of grafts. These would be delivered to different centers according to the demand, with a considerable resource-saving, while ensuring full traceability.[49,50]

COVID-19 and Basic Sciences

The impact of the COVID-19 pandemic on the world of research and basic sciences has been severe, too. While it is difficult to estimate the direct long-term consequences of COVID-19 related restrictions on this field, some drawbacks are noticeable. Among them, the slowdown of all research activities (specifically non-COVID-19 related) is of interest.[51]

Of note, Nassisi et al reported that in a large ophthalmic research center in France three main measures were adopted to hamper viral transmission and contagion, including the reduction and control of employees simultaneously allowed in the facilities, the prohibition to start any new bench experiments, and the implementation of software to allow remote working.[52] Researchers permitted to enter the facilities were required to wear PPEs, and any face-to-face contact was strictly forbidden.[52] In addition, specific regulations were released for both animal and cell culture facilities. For instance, each team was asked to reduce the number of animals housed, and the protocols of animal maintenance was revised to extend the time for cage cleaning, bedding renewal and feeding.[52] For the cell culture facilities, most of the cultures were frozen with few authorized exceptions for stem cell research requiring long protocols of differentiation and maturation.[52] As a result, a major impact mainly on short-term basic science projects was registered by the authors.[52]

In October 2020, the National Institute of Health (NIH) conducted two large surveys to objectively document the impact of the COVID-19 on extramural research activities.[53] Based on the response of 45,348 participants, some concerns about research functions, research productivity, and financial status were reported by the majority of respondents.[53] Intriguingly, early-career scientists and those conducting laboratory-based research emerged as being most likely to report concerns about career trajectory, with lower job productivity described by nearly the entire cohort.[53] Finally, almost 50% of respondents reported that caretaking responsibilities made it substantially more difficult to be productive.[53]

Similarly, Hogg et al, in a UK survey, described 79.8% of 148 active researchers reporting an overall negative impact of the COVID-19 pandemic on their research activities, with main drawbacks being the unavailability or shortage of

funding opportunities, lack of necessary human and physical resources, and redeployment of research staff.[54] Three main consequences derived. First, 92.3% participants to the survey described delay or full termination of their research projects.[54] Second, observational research seemed to prosper along with research activities that could continue or were made more efficient by the culture shift toward using virtual platforms.[54] Third, a small number of researchers decided to reframe their activities to include aspects addressing questions specifically related to the COVID-19 pandemic.[54]

With this regard, the main debate in the literature concerned whether the disease could be accompanied by ocular disorders.[4,5,55] Several reports have described a plethora of different ophthalmological disturbances in COVID-19 patients, with an involvement of structures of both the anterior and the posterior segment of the eye.[56] Specifically, the identification of the virus in the conjunctival sac and in the tear sample of infected patients was the hint for the investigation of COVID-19 screening tests alternative to the more invasive and bothersome nasopharyngeal swab.[5,57,58] Interestingly, several techniques for the collection of the tears (e.g., conjunctival swabs,[57] Schirmer strips,[57,59] capillary tubes[60]) and various commercial kits for the execution of real time-polymerase chain reaction have been adopted in different studies. However, no standardized protocol exists to date, thus rendering this diagnostic approach not recommended. To our knowledge, one group is currently trying to test a safer and less painful way to collect patient tear samples and a new test, using faster diagnostic technology, that would help providers repeat tests to track the lifespan of an active virus in COVID-19 patients.[61]

Notwithstanding the amelioration of surgical techniques and the introduction of modern surgical tools rendering corneal transplants able to guarantee optimal visual recovery to treated patients, the lack of tissues suitable for transplantation remains an unmet need.[62–65] For this reason a growing area of research has focused on the development of corneal substitutes aimed at reducing reliance on human donor tissues, especially for the low-risk cases comprising the majority of corneal transplantations performed worldwide. Specifically, two developments that have the potential to result in major changes in surgery for corneal disease are the development of artificial or bioengineered cornea, and cell-based therapies as an alternative to transplantation (for a comprehensive review see Griffith et al[66] and Mobaraki et al[67]).

Concerning bioengineered cornea, a cell-free, cross-linked collagen-based biosynthetic corneal substitute was implanted in a Phase 1 clinical study in 10 patients with significant visual loss, with the aim of facilitating endogenous tissue regeneration without the use of human donor tissue.[68,69] The implants remained integrated and avascular for four years after surgery, with suboptimal visual acuity improvement.[68,69] No episodes of rejection were registered without the need for long-term use of the steroid immunosuppression. In the long term, biocompatible engineered corneas may represent a valid alternative for donor derived keratoplasties, or to the plastic artificial corneas currently used in keratoprosthesis (Kpro) surgery (e.g., Boston Kpro, osteoodontokeratoprosthesis, AlphaCor, etc.).

Nowadays, Kpros play a role in cases of multiple failed corneal transplants or ocular surface disease for which corneal transplants are likely to fail.[70] It is fair to say that in spite of substantial effort, progress in this field has been slow. In fact, substantial complications still exist with the adoption of Kpros, including infection, and extrusion of the device, melting and inflammatory reactions of the surrounding tissues, and glaucoma.[71–73] Thus, the need for a totally safe device remains, so that it is unlikely Kpros might replace traditional transplant in the near future.[71,72]

On the other hand, substantial improvements in cell-based approaches have been recorded in recent years. Corneal epithelial replacement using stem cells is now a routine clinical procedure in many centers.[74–76] Limbal Epithelial Stem Cells (LESCs) are used to treat patients who suffer Limbal Stem Cell Deficiency as a result of limbal damage or specific corneal diseases.[76] Notwithstanding the differences between diverse approaches (e.g., simple limbal epithelial transplantation, cultivated limbal epithelial transplantation, kerato-limbal allograft, cultivated oral mucosal epithelial transplantation), LESCs transplantation is nowadays able to guarantee success rate of ~80% up to 10 years.[75]

More intriguing is the idea to expand human corneal endothelial cells (hCECs) in cell culture. The evidence of corneal clarity restoration in bullous keratopathy monkey-model eyes after the inoculation of cultured corneal endothelial cells represented the theoretical basis for the conduction of clinical trials in human.[77–81] Kinoshita et al, in a single-group study involving 11 people with a diagnosis of bullous keratopathy receiving intra-cameral injection of cultured hCECs, reported increased corneal clarity, reduced central corneal thickness, and improved visual acuity in more than 80% of treated eyes.[77] The adoption of Rho kinase inhibitors was proven useful to enhances the adhesion and proliferation of

cultured hCECs and to suppresses their apoptosis.[82,83] Thus, the use of cultured cells, either as a monolayer or by injection into the anterior chamber, may become a reality for clinical applications soon.

Again, a pivotal role might be played in this context by the Eye Banks. In fact, as reported by Parekh et al, the hCECs pool can be increased isolating and expanding corneal endothelial cells discarded during DMEK preparation.[84,85] In the future, Eye Bank Institution may be responsible not only for corneal tissues harvesting, storing and distribution, but also for remnant grafts recollection, cell isolation, culture and expansion for another transplant using the cell culture approach.

Discussion

The COVID-19 pandemic and the associated restrictions have revealed frailties in many fields of our society. This has been especially true for corneal transplants and Eye Banking, which regardless of the health, social and economic benefit able to guarantee to treated patients, have always suffered from a long-standing and endemic lack of available tissues, and reglementary restrictions.[16,86]

However, despite the critical slide during the pandemic peaks, the Eye Bank Institutions, and the corneal transplant industry responded positively, with an immediate restoration of their activities, undoubtedly demonstrating at the same time compliance and serendipity.[3,9]

Undoubtedly harmful, the global pandemic represented an opportunity for brainstorming, thoughtful thinking, and introspection. Besides, it has provided the system with the chance to reconsider old processes and to formulate new solutions and ideas.

For instance, the introduction of new regulations for tissue handling and harvesting protocols, might guarantee a higher level of safety to the stakeholders (e.g., eye bank technicians, physicians, patients). In addition, further implementation and standardization of SOPs already adopted during the COVID-19 pandemic in both eye banks and ophthalmic practices may ensure continuity of care in the corneal transplant activity in the unfortunate case of other epidemics or pandemics.[37,40,41]

Education of patients and clinician to the adoption of telecommunication for virtual consultation might result in a more rapid screening of urgent cases and deferrals of non-urgent ones, in the pursue of a more cost-effective clinical approach.[41,87–91] Endorsement of surgeons in already available tissue sparing techniques for corneal transplant is strongly encouraged, to provide the highest efficiency of the Eye Bank/Corneal Transplant machinery, resulting in lower corneal tissues to be used for a higher number of patients.[22,42]

Nonetheless, research on the microbicidal efficacy of several compound might represent the theoretical basis for their future and widespread adoption in routine clinical practice.[31–33] The research on tear sampling techniques and more rapid and reliable -omics analyses of body fluid conducted in the context of COVID-19 might exert a profound impact on the future approach to both systemic and ocular disorders.[92–95] Finally, the actual need for available tissues might push new transplant techniques forward the bottleneck between bench and bedside.[77,78,84,85,96]

But for many of these, rapid application into clinical practice is yet to come.

While the clock is ticking, some changes are needed now. First, the COVID-19 pandemic determined a progressive contraction of grant release by both national and private funding bodies and research charities.[53,97] This resulted in a higher rate of declined funding applications otherwise successful in other years, as well as in the delay or full termination of ongoing research projects.[54] However, no innovation could be expected without scientific research. In this context, more solid and efficient funding programs for research and development are needed to accelerate the transition from preclinical to clinical settings.

In addition, adoption and implementation of new surgical techniques require appropriate knowledge, training, and experience. Nonetheless, the corneal transplant industry mainly relies on corneal tissue donation, hence on a personal, and philanthropic will. With this regard, ophthalmological and eye bank scientific committees at a national and international level should promote activities encouraging physicians to the endorsement of more efficient surgical techniques and educating the communities to tissues donation.

Finally, it is somewhat surprising that eye banking is the only field in our society not already featured by internationally accepted “efficiency indices”, or proxies. Especially during the pandemic, a number of different groups tried to analyze the impact of COVID-19 on the eye bank activity, often providing mixed or conflicting results. The

majority of the reports on the topic outlined only the raw data relative to the number of retrieved and distributed corneas, promoting such statistics as representative of the eye bank activity. The adoption of an accepted index, able to summarize efficiency and efficacy, could lead to easier and more accurate comparisons of data coming from different institutions. In addition, any single eye bank or national health service could rely on it for self-assessment and evaluation, thus helping in future strategic planning.

In a constantly changing and dynamic world, the COVID-19 obliged us to stop and to rethink our ways. Newer practice guidelines, protocols and ideas derived as a consequence, which might represent solid bases for the new, post-pandemic era.

Disclosure

The authors report no conflicts of interest in this work.

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