• Review •

Corneal blindness and current major treatment concern-graft scarcity

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Abstract

• According to World Health Organization, the global prevalence of blindness in 2010 was 39 million people, among which 4% were due to corneal opacities. Often, the sole resort for visual restoration of patients with damaged corneas is corneal transplantation. However, despite rapid developments of surgical techniques, instrumentations and immunosuppressive agents, corneal blindness remains a prevalent global health issue. This is largely due to the scarcity of good quality corneal grafts. In this review, the causes of corneal blindness, its major treatment options, and the major contributory factors of corneal graft scarcity with potential solutions are discussed.

• KEYWORDS: corneal blindness; keratoplasty; corneal graft; corneal donation; eye banking

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INTRODUCTION

Corneal disease is a leading cause of visual impairment[1-2], currently ranking as the fourth commonest cause of global blindness after cataract, glaucoma and age-related macular degeneration[3-5]. According to World Health Organization (WHO), among the 39 million people who were blind, 4% were due to corneal opacities[6-7]. The major causes of corneal blindness are trachoma, corneal ulcers, xerophthalmia, ophthalmia neonatorum, viral infections, traditional eye medicines, onchocerciasis, leprosy, and ocular trauma[8]. Most of the causes of corneal blindness are preventable if timely treatment or better access to healthcare is provided[8-9]. Unfortunately when many of these conditions were left untreated in the acute stage, the only treatment option remaining for patients with a damaged cornea is corneal transplantation[2].

Since 1961, over 1 500 000 people had their sight restored through corneal transplantation[10]. In 2012, there were 283 530 corneas procured from 82 countries [41% (116 990) from United States, 14% (40 000) from India] and stored in 742 eye banks[11]. About 8% of the procured corneas (23 247) were exported from 9 countries [85% (19 546) from the United States, 9% (2000) from Sri Lanka, and 3% (600) from Italy][11]. However, almost 100 000 (35%) corneas were not selected for transplantation after quality control, which was mainly based on serology of donor blood for human immunodeficiency virus (HIV) and hepatitis B and C, and on the number and quality of corneal endothelial cells[12]. These measures aimed to reduce the risks of transmission of infection and primary graft failure, and to ensure acceptable graft survival. Finally 184 576 corneal transplants were performed in 116 countries in 2012[11]. This number however was still far from reaching the 12.7 million patients awaiting corneal transplantation in 2012[11].

Corneal Transplantation Corneal transplantation is the commonest organ transplantation in human[13]. Unlike other solid organs, tissue matching is not routinely required in corneal transplantation.

Corneal transplantation has the highest success rate among all kinds of organ transplantations, achieving up to 94% of mean 1-year graft survival rate[14]. This success is contributed largely by 1) the relatively low graft rejection rate due to its avascular nature and scarcity of immunogenic tissues; 2) relative absence of systemic disease transmitted through transplanted corneas; 3) the emerging and maturation of lamellar keratoplasty such as Descemet's stripping automated endothelial keratoplasty (DSAEK)[14] and deep anterior lamellar keratoplasty (DALK)[15]; 4) advancements of instrumentation such as viscoelastics, diamond knives, ultrasonic pachymetry, intraoperative optical coherence tomography, artificial anterior chambers, advanced microkeratomes, and femtosecond laser[15].

Among the many subtypes of keratoplasties, the commonly performed ones are penetrating keratoplasty (PK), DALK and DSAEK[16]. PK, which involves full-thickness cornea replacement, is the traditional, dominant corneal transplantation performed

over more than half a century and has successfully tackled most causes of corneal blindness[17-18]. Two decades ago, PK was the only definitive surgical treatment for pseudophakic bullous keratopathy and Fuchs endothelial dystrophy[19].

In the last two decades, lamellar keratoplasty techniques resurged. With the concept of targeted replacement of diseased layers of cornea, the wastage of graft has been minimised, as a single donor button can be utilised for more than one patient[16]. The residual donor corneoscleral rim could be further divided into four pieces and used in other ophthalmic surgeries such as glaucoma operations, or when additional corneoscleral tissue is needed (*e.g.* patching or repairs)[16,20]. Therefore, the maximum number of patients that can be benefited from one single corneal graft is increased to 6 patients[16,21].

With the advancements of surgical techniques and instruments for keratoplasty[15,22-23], rapid evolution of eye-bank preparation of corneal tissue[24], and continuous emergence of novel effective immunosuppressive agents (*e.g.* tacrolimus, cyclosporine, sphingosine 1-phosphate receptor agonists[25-29]), the overall life expectancy of a corneal graft has increased, and the safety, effectiveness and visual outcomes of lamellar keratoplasty are now comparable to, if not better than, standard PK[14,17,30-31].

Persistent Treatment Concern of Corneal Blindness-graft Scarcity In 2012, it was estimated that only 1 cornea was available for 70 people in need[11]. Approximately 53% of the world's population had no access to corneal transplantation, while only 35.7% had satisfactory access[11]. The median waiting time for receiving a corneal transplant was 6.5mo (interquartile range=1-24mo), whilst the waiting time in 53% of the world's populations could not be estimated because most patients in those countries never received a graft[11].

Among the 12.7 million patients awaiting corneal transplantation in 2012 globally, there were 7 million in India, but only 25 000 transplants were performed in the same year[11]. China had 2 million patients on the waiting list, but fewer than 8000 corneal transplantations were performed in 2012[11]. In Hong Kong, there were about 7.3 million people (by December 2015) but on average only 239 pieces of corneas were donated each year[32]. The number of patients on the waiting list in Hong Kong as on December 31, 2014 was almost twice the number of annual supply[32]. Despite active promotion of organ donation by government and relevant organisations, Hong Kong had approximately 8 times lower corneal donation rate per capita than United States in 2014. Meanwhile, Malaysia, Indonesia, Vietnam and Korea were unable to procure more than 20 to 30 corneas per year[33].

Around the world, there are 742 eye banks identified[11]. There are 28 countries which only have 1 eye bank each, while 30 countries have 2 to 5 eye banks each, and only 16 countries have more than 5 eye banks each[11]. The number of corneas received annually by each eye bank ranged from 1 to 7000 (median=168, interquartile range: 58-377)[11].

The situation of the generally unfavourable organ donation rate was aggravated by a high selective refusal to eye donation. The fact that eyes are not simply biologic but have much deeper and wider meaning towards each individual, has contributed to the high reluctance to donation[13]. The rationales underlying the reluctance are complex[34]. Macroscopic factors such as international, national, local governmental and institutional policies and eye-banking systems exert variable influences on the ease of cornea donation, procurement, exportation or importation, storage, distribution and transplantation. The knowledge, awareness, attitude and beliefs of potential donors and their families regarding corneal donation and transplantation influence their willingness and decision to donate. Organ donation rates are also affected by communication skills of healthcare providers with potential donor families, legislation, presumed consent system, donor availability, transplantation system organisation and infrastructure, wealth and investment in healthcare[35].

Factors of Corneal Graft Scarcity and Respective Recommended Solutions

Government, legislation and hospital policies The lack of efficient notification system has led to wastage of potential grafts due to suboptimal timing of raising corneal donation request. In 1998, the United States Health Care Financing Administration (HCFA, now the Centers for Medicare and Medicaid Services) amended the federal Conditions of Participation (COP)[36]. Since then, hospitals had been required to notify their local organ procurement organisation (OPO) about individuals who decease or whose death is "imminent"[36]. This is to ensure timely offering of eye, tissue and organ donation option to the families, because the decision to accept donation request also depends on the time elapsed from death or the time of grave prognosis to the time of raising corneal donation request[37].

In Hong Kong, since the establishment of Transplant Coordination Service in August 1988 under the Hospital Services Department, the organ procurement rate increased from below 10% to above 40%[38-39]. This service was strengthened in 1994 by cluster-based regional coordinators to better coordinate different disciplines during the period of organ procurement and transplantation[38-40]. These coordinators not only approached and convinced the families to consent for organ donation, but also promoted the public awareness to organ donation[38,40]. According to legislation of Hong Kong, one can only donate his/her tissues or organs with the consent of family. According to the transplant coordinators in Hong Kong, family disharmony was one of the main reasons of refusal[38]. Moreover, Hong Kong is among the 45% of cornea-procuring countries and regions that practise the opt-in system, which has

significantly lower donation rate than the opt-out system[11,38]. A survey revealed that only 28% of respondents in Hong Kong agreed to presumed consent for organ donation, meanwhile 66% objected[38,41]. This might be attributed to the traditional Chinese belief to preserve body integrity after death[38,42].

To ameliorate the local corneal donation rate, Hong Kong modified the corneal donation eligibility criteria. Since February 2013, all solid or metastatic cancer patients (except intraocular cancers) are eligible to donate their corneas[43]. Furthermore, in addition to conventional paper application, a user-friendly website (https://www.codr.gov.hk/codr/Internet.do) has been launched to encourage people, especially the younger generations, to register as corneal donors.

Eye banking services One main cause of graft scarcity is the lack of large professional eye banks that can effectively perform the four key eye bank functions: approach and consent, recovery, processing, and distribution[44-45]. India, the country with second largest number of people with blindness (8075 million in 2010 according to WHO)[7], has the highest number of eye banks (238) in the world[11]. This is followed by United States (84). However, there was a huge contrast in the annual number of procured grafts per bank between India (168) and United States (1393)[11].

The barriers of underdevelopment of eye banking systems include the lack of trained staff, inefficient operations, affordability (for equipment and storage media), sociocultural perceptions related to eye donation, restrictive political laws, and poor distribution, utilization and adherence to medical standards[44-46].

The implementation of efficient corneal distribution program has resulted in great increase of corneal donation and utilization rates. The establishment of a non-profit global health organisation such as SightLife, could allow excess corneas that are not used in the United State to be sent to other countries in demand[47]. The joint effort between Eye Bank Association of India and SightLife, *i.e.* EBAI-SightLife Cornea Distribution System, has led to an increase in cornea utilization rate by 379% from 2325 in 2009 to 11 143 in 2013[45,47].

The development of professional eye bank managers and Hospital Cornea Recovery Programs (HCRP) has further increased the supply of corneal grafts[44]. The training programs of efficient eye-banking skills provided by SightLife and Ramayamma International Eye Bank (RIEB-Asia's largest eye bank in India) have greatly improved graft donation and utilisation around the world[47-48]. HCRP involves trained eye donation counsellors, who are stationed in large hospitals to offer grief counselling and directly motivate potential donor families to gain consent[44]. This contrasts to the typical Indian eye bank operation, which uses a "voluntary" program that relies on general public awareness and realization of one's social responsibility towards the corneal blindness[44]. According to the Eye Bank Association of India, the overall Indian eye bank tissue utilization increased from 38% through primarily voluntary collection to 72% after the adoption of HCRP model in 8 eye banks[44]. Of the tissues recovered from 13 012 donors by RIEB between 1991 and 2014, 67% was achieved through the motivational approach of eye donation counsellors[48].

The availability of expertise to pre-cut tissues in eye banks is important to reduce wastage of corneal grafts and maximise the supply of cornea tissue. Many eye banks have started to provide pre-cut tissues for local utilization and international tissue sharing, however such expertise would require advanced eye bank training[45].

The high costs of equipment and storage media such as McCarey-Kaufman (MK) media (Bausch & Lomb), Optisol GS (Bausch & Lomb), and LIFE4℃ (Numedis) have contributed to the affordability issue in the operation of an eye bank. One alternative may be to adopt a less expensive storage medium, such as Cornisol (Aurolab, Madurai, India) which is estimated to perform similarly to Optisol GS at approximately 65% of the cost[45].

Knowledge and attitude Both knowledge and attitudes affect the willingness and commitment to organ donation[49-52]. The attitudes towards organ donation are inconsistent across different countries and populations. The attitudes had been found favourable among the public, *e.g.* United States[49,53], South Africa (urban populations)[54] and Saudi Arabia[55], healthcare providers/ professionals (HCP) in Canada[56-57] and Croatia[58], and students in New Zealand[59]. However, the contrast was observed in non-blood-donors in Hong Kong[50,60], Turkish students of healthcare-related courses[61], rural populations in Saudi Arabia[50], minority ethnic groups in the United Kingdom and North America[62], and Turkish mosque imams[63-64].

Studies have consistently shown the inadequacy in the knowledge of general public and medical personnel regarding the legal and medical status of death[50,57,65-67], organ donation[1,50,57,59,67-69] and organ transplantation[1,68]. However, even if the knowledge of organ donation was known, it was mainly about kidney, liver and heart[67,69].

Lower level of socioeconomic status[34,37,70], formal education[34,37,70-72] and knowledge regarding corneal donation[72] have been associated with lower likelihood of believing the justification of corneal and organ donation and lower likelihood of corneal donation.

Earlier and more exposure to information on corneal donation may result in more favourable attitude and belief in donation, and improve the donation rate[72]. Some effective means to educate the public about corneal donation and develop more positive attitudes towards corneal donation include mass media[64], such as television[50], Facebook[73], billboards,

awareness campaigns[72,74] and leaflet distribution[58], or through HCPs[64].

The "tomorrow's donors", *i.e.* the adolescents who are at the age eligible of applying driver's license, are eligible to register for corneal and organ donation in most countries[75]. Therefore, school-based education programs for adolescents may be an effective strategy to improve corneal and organ donation rates[68]. These educational programs need additional, regular evaluations and supportive evidences to delineate their impact on affirmative donor registration and realized donations[75].

Identity and visibility The eyes represent a long tradition of visual primacy in all aspects of culture[13]. When we are engaged with an individual, the first thing that we would look at and interact with is often his or her eyes. In daily communication process, eye contact, eye movement and the messages imparted *via* the emotions of the eyes make up the main part of facial expressions.

An interview revealed how great the distortion of one's image in the heart of relatives if the beloved decedent has his or her eyes removed in part or in whole[76]. This is because the removal of eyes has similar meaning to the alteration of one's identity, even when the eyes are forever shut after one is deceased[76]. Therefore, the selective refusal of corneal and eye donation is prominent[13,76].

This is further aggravated by the visibility of eyes as an external organ, as opposed to the internal organs that cannot be visualized. Bodily disfigurement is often a major concern during the request of corneal donation from families, as it is relatively easier for relatives to accept the physical absence of the decedents' internal organs after procurement[76], and be less concerned about the influence on funeral arrangement[71,76].

HCPs and organ procurement staff have the responsibility to address these concerns, and explain that the operative wound is small and artificial cornea or eyeball will be replaced after procurement. Furthermore, corneal donation may be viewed as the continuity of the relationship with decedents in another manner as the decedents can continue to "see" the world through the corneal recipients by "giving a life to a dead eye"[77].

Strengthening the role of healthcare providers/professionals? HCPs were infrequently reported as the source of information on corneal and organ donation[49]. At least 90% of respondents in both rural and urban areas of a study in Saudi Arabia reported "none" or "little" contribution of knowledge about organ donation and transplantation by HCPs[50]. However, 60% of respondents would like their HCPs to provide information of donation to them[49].

The quality of explanation and clarification of the meaning of brain death affects the decision-making of donation[37,78-79]. However, in fact, many HCPs, including nurses and physicians of intensive care units, did not have adequate knowledge on organ donation in general[80-82], on brain death[82] and religious barriers to organ donation[57]. In addition, many physicians were unable to recognize the importance of decoupling the discussion of brain death from the donation of cornea and organs[83].

In comparison to solid organ donation, HCPs were less knowledgeable about the cornea donation criteria, less successful in the identification of eligible corneal donors and less efficient in the process of procurement of corneas as compared to that of solid organs[84]. Not only did many eligible corneas miss their chances to be identified, even if they were, many nurses and physicians were reluctant to approach potential organ donors and their relatives[56-57]. The lack of knowledge and natural repellence against facing negative emotions had contributed to the ambivalence in breaking news of the patient's grave prognosis or death to families and in requesting the corneal donation from them[83].

The knowledge deficit in corneal donation may be traced to the lack of such emphasis in the curricula of healthcare-related courses. A significant number (63.1%) of students of medicine, nursing, dentistry and health technician courses are not familiar with tissue and organ donation process[61]. The mean and median scores on knowledge level of organ donation among medical students are less than 50%[52,85]. In addition, low exposure to potential organ donors has led to less favourable knowledge level, attitude and professional involvement of organ donations[56].

As the vital bridge to corneal donors, HCPs need to be armed with up-to-date knowledge. Education interventions of HCPs should start from undergraduate level to build solid foundation of knowledge on corneal donation[85-86]. The organ procurement units, government or relevant organisations such as Lions Eye Bank should provide regular training programs to current and future HCPs on corneal donation, as this significantly enhances the relevant knowledge and the confidence of HCPs to approach potential donors and their families[51,80-81]. These education programs can not only promote HCPs to have greater willingness and confidence to approach decedents' families to make corneal donation request, but also motivate the HCPs themselves to explore organ donation deeper and take up subsequent interval training[81].

Many HCPs have positive attitude and support organ donation in principle[56-58,80]. However, there is significant discrepancy in the number of HCPs who support in principle and those who register themselves as organ donors[57,80]. Through education, not only can HCPs raise the corneal donation rates among patients, it also encourages HCPs to lead corneal donation with own actions[51,81].

The hospital experiences of the potential donors' families can also affect their decision-making[71,87]. During the care of patients at their end of lives, satisfactory hospital experiences and attitude towards patients and their families should be

provided in a more scrupulous, painstaking and empathic manner.

Religion Religion is an influential factor in the decision-making of organ donation[66,68]. In a survey of optometry students of University California, the leading reason of reluctance to donate cornea was religious reason[68]. Christianity had been demonstrated as a positive motivator to organ donation[66,70]. Among all cornea donors in 2012, 77.1% were Christians, 14.2% Hindus, 3.7% Muslims, and 2.6% Buddhists[11]. The remaining 2.4% cornea donors in 2012 believed in Chinese Traditional religion (1.8%), Atheism (0.4%) and Judaism (0.2%)[11].

In countries with strong religious influence, religious officials and mosque imams who are well educated on corneal donation can act as important media to encourage the members of society to donate[69,88]. Also, religious leaders can raise public discussion of issues through extensive media coverage, allowing them to promote pro-social behaviour and positively affect public health[89].

Therefore, the effectiveness in raising corneal donation may be further enhanced by the collaboration of HCPs and mass media with these influential religious figures. Focused educational program can be provided to the general or specific religious community in worship places to provide a religious support to corneal donation[88], to improve the knowledge, perceptions and beliefs about corneal donation and to clear the relevant religious misconceptions[74,90], such as the compatibility of organ donation with their religion[91].

Ethnicity & gender In multi-ethnic societies, the perception of discrimination in healthcare services exists[92]. In general, patients and relatives usually have greater satisfaction when encountering with race-concordant physicians[93]. The easier reflection of emotional context in the qualities of race-concordant voice tone, easier conveying of friendliness and social talks, and the sense of racial or social group affiliation allow deeper engagement in communication, cultivation of patient-physician relationship and development of mutual trust in race-concordant encounters[94].

It is uneasy for the doctors to achieve complete gender-neutrality[95]. It is not surprising that the gender of attending physicians also affects the patients' and families' hospital experience and satisfaction towards clinical care[96-97]. This is due to patients' gender-specific expectations of non-verbal behaviours and patterns of physicians[96]. For both genders, patients tend to expect their non-verbal behaviours to be mostly or partly congruent with their gender role[96].

Therefore, awareness of the effects of race-concordant experiences and these gender-specific expectations may have positive impacts when HCPs or organ procurement staffs approach the patients and relatives for corneal donation request.

Alternatives to National Graft Donation

Importation of corneal grafts In the past, many countries have been receiving corneal importation from the United States (up to US$ 4000 per cornea[98]) and Sri Lanka (US$ 800-1500 per cornea[98]). The United States is the world's biggest corneal provider. However, the cost incurred has been a consistent issue. While EBAA members can fulfil the demand of corneas in the United States with own donations, they can export 15 702 corneas to other eye banks (EBAA-accredited and -non-accredited) in 2014[99]. Sri Lanka International Eye Bank, and now the Eye Donation Society, had donated over 118 000 corneas to the recipients all around the world since its establishment in 1961: over 53 830 corneas exported for transplantations in 57 countries, 30 000 corneas for research and development work and the rest for Sri Lankan recipients[100]. First case of corneal exportation from Sri Lanka started was conducted with the hand-carry of graft in an ice-packed tea thermos aboard a flight to Singapore in 1964[77]. Since then, 117 towns in 57 countries had benefited from the gift of sight from Sri Lankans.

The basic expenses of corneal importation are usually the operational cost, tissue recovery, preparation, cutting, preservation and packaging cost, and courier cost. However, the quality control of grafts in Sri Lanka was discovered to be an essential issue, such as infected donor cornea[101].

In February 2011, Singapore Eye Bank had teamed up with the health authorities of Sri Lanka and set up an official alliance as the National Eye Bank of Sri Lanka (NEBSL), sited in the Colombo National Eye Hospital, to procure cornea donations from Sri Lanka's local donors, and process and distribute the high quality corneas for transplantation cost-effectively. This is achieved through modelling NEBSL after Singapore Eye Bank (SEB)[102], adoption of modified EBAA guidelines and the provision of technical and expertise support and training by SEB[103]. NEBSL has a huge, favourable potential of procuring large number of high-quality corneas a year (1072 grafts for transplants in 2014) and re-emerge as the limelight eye bank in Asia[104].

Artificial corneas, biosynthetic corneas & xenografts In view of the corneal graft scarcity, Keratoprostheses (KPros) may be an effective alternative to address the burden of end-stage ocular surface disease, failure(s) of previous corneal transplantation and high-risk corneal grafts[105-109]. Boston KPro and Osteo-Odonto-Keratoprostheses (OOKP) are the commonest adopted keratoprostheses in clinical practice. In order to reduce the financial barrier, alternative lower-cost keratoprostheses are now being manufactured[45].

However, the usage of Boston KPro is limited by an array of blinding complications especially in the long run, such as formation of retroprosthetic membrane[106]), glaucoma,

lifelong need for daily antibiotics and soft contact lens usage, endophthalmitis[106], corneal melt and implant extrusion[105-106,108-109]. On the other hand, although OOKP has higher retention rate[110] and better resilience to dryness. However the requirement of multidisciplinary, dedicated surgical units to support such complex multi-staged surgery and distortion to recipient's external appearance has limited its widespread clinical application[105,110-112].

Xenograft may be a potential alternative especially for anterior lamellar keratoplasty. However, the immunological barrier, especially the immune response against the corneal endothelial cells is the greatest hurdle[113]. Genetic engineering of pigs, clean and controlled environments for breeding and housing pigs, and decellularization techniques seem to be optimistic solutions for the immune response and the risk of transfer of potentially infectious microorganisms from pigs to humans[114-115].

Cultivated corneal endothelial cells may ease the requirement of endothelial keratoplasty in the future[116-118]. There are two approaches: 1) "corneal endothelial cell sheet transplantation" with cells grown on a type-I collagen carrier[119]; 2) "endothelial cell injection therapy" (into the anterior chamber) together with the application of Rho-kinase (ROCK) inhibitor[116,120]. ROCK inhibitor had been demonstrated to accelerate corneal wound healing and successfully regenerate a corneal endothelial monolayer with a high endothelial cell density in animal models *via* promotion cell adhesion and proliferation and inhibition the apoptosis of corneal endothelial cells[116]. However, no data on long-term safety is available to date.

With the increasing popularity and sharing of expertise in the use of keratoprostheses, the indications for KPro has expanded considerably, however the burden of drastic ocular complications and incomplete understanding of their treatment remain a hurdle for KPro to replace human corneas. On the other hand, xenografts and cell based therapy with ROCK inhibitor application seem to be holding greater potential for selected cases of corneal replacement (anterior lamella and endothelium respectively) in the future[113-116,119-120].

CONCLUSION

To date, corneal blindness still remains a major global health issue. The underlying cause of corneal graft scarcity is multifactorial and jointly contributed by the patients, families, HCPs, organ procurement organisations, eye bank systems and government factors. At this stage, the most realistic and effective way of improving graft donation could be the development of efficient and proficient eye bank services which function to maintain the provision of high quality corneal grafts and bridge the gap between demand and supply. Proactive multifaceted and multi-level approaches are warranted to tackle this predicament, with a view of improving donation rate while looking for practical alternatives.

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