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The Osteo-Odonto-Keratoprosthesis (OOKP)

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ABSTRACT The osteo-odonto-keratoprosthesis (OOKP), although described over 40 years ago, remains the keratoprosthesis of choice for end-stage corneal blindness not amenable to penetrating keratoplasty. It is particularly resilient to a hostile environment such as the dry keratinized eye resulting from severe Stevens-Johnson syndrome, ocular cicatricial pemphigoid, trachoma, and chemical injury. Its rigid optical cylinder gives excellent image resolution and quality. The desirable properties of the theoretical ideal keratoprosthesis is described. The indications, contraindications, and patient assessment (eye, tooth, buccal mucosa, psychology) for OOKP surgery are described. The surgical and anaesthetic techniques are described. Follow-up is life-long in order to detect and treat complications, which include oral, oculoplastic, glaucoma, vitreoretinal complications and extrusion of the device. Resorption of the osteo-odonto-lamina is responsible for extrusion, and this is more pronounced in tooth allografts. Regular imaging with spiral-CT or electron beam tomography can help detect bone and dentine loss. The optical cylinder design is discussed. Preliminary work towards the development of a synthetic OOKP analogue is described. Finally, we describe how to set up an OOKP national referral center.

KEYWORDS keratoprosthesis, OOKP, surgery, dry eye, allografts, electron beam tomography, ciclosporin, optics

Osteo-odonto-keratoprosthesis (OOKP) surgery is a technique used to replace damaged corneae in blind patients for whom cadaveric corneal transplantation is doomed to failure. It was developed some 40 years ago by Strampelli and uses the patient's own tooth root and alveolar bone to support an optical cylinder.[1] After a long interval the technique is finally gaining widespread recognition by corneal surgeons worldwide as the treatment of choice for patients with end stage inflammatory corneal disease. In the case of a dry eye, no other device will work nearly as well.

HISTORICAL REVIEW

Keratoprosthetics, replacing damaged and opaque corneae with an artificial implant, dates back more than 200 years to Pellier de Quengsy, a French ophthalmologist who proposed implanting a glass plate into an opaque cornea.

The first surgical case in a human was performed in 1855 with a quartz crystal implant developed by Nussbaum. The prosthesis remained in the eye for six months. Over the next 50 years, more attempts were made to develop different keratoprostheses (KPros) and techniques (von Hippel 1877, Dimmer 1889, and Salzer 1895). Almost all the implants were extruded and in the early twentieth century, interest in keratoprostheses waned with the introduction of penetrating keratoplasty. The early pioneers in the field of penetrating keratoplasty included Elshnig in Prague (1914), Filatov (1924), and Tudor-Thomas, who introduced the technique to the United Kingdom (1936). Penetrating keratoplasty went from strength to strength with Stocker in the 1950s and was accompanied by the introduction of steroids and fine needles and sutures. Though more diseases became suitable for penetrating keratoplasty, there were still conditions where the prospect of successful grafts was hopeless and so interest was renewed in keratoprostheses. Many pioneers were involved in developing new KPros (Gyorffy, Sommer, Vodovozov, Stone and Herbert, Macpherson and Anderson, Binder and Binder, Fyodorov, Puchkovska, Krasnov, Cardona, Castroviejo, de Voe, Choyce, Lund, Dohlman, Casey, Donn, Buxton, Girard, Maroz, Pintucci, Marchi, Legeais, Lacombe, Worst, Polack, Aquavella, Waring, Bertelson, Singh, Mohan, Yakimako, Caldwell and Barraquer).[2]

WHAT IS THE IDEAL KERATOPROSTHESIS?

In developing a KPro, the ideal device should be able to surpass the natural cornea by having an improved optical quality, with decreased aberrations and a specifiable power. It should have excellent biointegration, provide resistance against infection and last the lifetime of the patient. It should also replicate some of the qualities of the cornea such as drug penetration and allowing intraocular pressure measurement.[3,4] The types of KPros currently available vary in design, especially regarding the support for the optical cylinder. Most models use a non-biological skirt that is often porous e.g. all PMMA (Choyce, Dohlman-Doane [now known as the Boston KPro]), Dacron (Pintucci), hydroxy-apatite (Leon-Barraquer), expanded PTFE (Legeais) and hydrogel (AlphaCor). KPros with biological skirts were also developed, as they were thought to be closer related to the corneal tissue so that they would intergrate better and be more compatible, such as the Strampelli OOKP using autologous tooth root and alveolar bone as a support for a PMMA optical cylinder, cartilage (Casey) and tibial bone (Temprano).

TABLE 1 **Comparison of Devices. Clinical Studies Reported in PubMed and KPro Study Group Bibliography Including Articles in Languages Other Than English and Those not Indexed in Index Medicus (Updated May 2003)**

Device	Clinical Papers	Patients	Follow-up (Years)
Cardona	12		
Champagne Cork	10	200	
Chirila (AlphaCor)	25	38	3
Choyce	5	107	
Dohlman-Doane (Boston)	23	110	6
Fyodorov	10	15	1.5
Hydroxyapatite	2	4	2.5
Legeais (PTFE)	26	24	2
OOKP	**93**	**573**	**27**
Parel-Lacombe	13	60	10
Pintucci	20	128	19
Seoul-type	2	7	2

Comparison between the various KPros can be difficult as the published studies are often retrospective, are uncontrolled and have conflicting data for different centers. The published literature is most extensive on OOKP surgery, which was the most number of patients and the longest follow-up (Table 1). However, it must be pointed out that many of the publications are not in English, are not widely available, and several are not in indexed journals.

OOKP surgery differs in several ways from other techniques, multi-stage (usually two) surgery is required, and there is surgery both in the mouth and on the eye. Complications associated with all types of KPros are extrusion, glaucoma, retinal detachment and retroprosthetic membrane formation. The OOKP could uniquely withstand a hostile dry keratinized ocular surface. Falcinelli devised stepwise modifications to the original Strampelli technique, which have led to improved visual results and retention of the device. A biconvex larger optic, preservation of the periosteum, cryo-extraction of the lens and vitrectomy, the use of buccal as opposed to labial mucous membrane, allograft using a non-erupted tooth, joining two laminae together, and a posterior drainage tube in refractory glaucoma[5,6] are amongst Falcinelli's innovations.

REFERRAL GUIDELINES FOR OOKP SURGERY

Indications

Patients with bilateral corneal blindness resulting from severe end-stage Stevens-Johnson syndrome, ocular cicatricial pemphigoid, chemical burns, trachoma, dry eyes or multiple corneal graft failure may be considered for OOKP surgery. The better, or only, eye should have poor vision, such as PL, HM or at best CF. One eye only will be rehabilitated. In suitable cases, there would be no need to go through unsuccessful penetrating keratoplasty with or without limbal stem cells transplantation and amniotic membrane grafting beforehand.

Contraindications

Patients who are happy and managing with their level of vision, children under the age of 17, eyes that have no perception of light, evidence of phthisis, advanced glaucoma or irreparable retinal detachment should be excluded. Suitable candidates have to understand that the surgery can be prolonged–they may require multiple procedures–and that there is a significant risk of serious complications including loss of the eye. The patient must be able to commit to life-long follow-up, and not have unreasonable expectations of outcome and cosmesis.

PATIENT ASSESSMENT

Ophthalmic Assessment

In Brighton, patients referred for possible OOKP surgery attend a joint clinic headed by an ophthalmologist and maxillofacial surgeon. In the preoperative assessment we take a detailed history and determine the primary diagnosis and previous surgical interventions, especially regarding ocular perforation, glaucoma or a history of amblyopia. Preoperative examination involves determining an intact and functioning retina and optic nerve. This can be by relatively accurate light projection in all quadrants, and a normal B-scan. In some cases a flash ERG and VEP can be useful. The lids and fornices are examined, and the degree of dry eye is noted, although a severe dry eye is not a contraindication (unlike other forms of KPros). The conjunctiva and cornea are examined and evidence of stem cell failure, metaplasia, or dysplasia is noted. Thinning of the cornea and evidence of previous corneal perforation, iris adhesion, and degree of vascularization are also noted. The depth of the anterior chamber, if visible, is noted. The intraocular pressure is determined digitally and a record is made as to whether the eye is phakic, pseudophakic or aphakic.

A and B scans are used for biometry to determine the axial length, exclude pre-phthisis, confirming the lens status, exclusion of retinal detachment, and with detection of gross glaucomatous cupping.

Assessment of a patient for OOKP also involves an assessment of the general medical and psychological status of the patient. The patient must be fully informed of the procedures and risks. The "side effects" and possible complications are described below.

Oral Assessment

The oral assessment must take into account both the buccal mucosal graft donor site and a selection of an appropriate tooth to form a dentine/bone lamina.

Buccal Mucosal Assessment

Since a number of patients will need an OOKP due to muco-cutaneous diseases, the oral mucosa may be damaged. The extent of damage has never been such to affect the harvesting of a graft by us up to now but this must be borne in mind and severe scarring of the oral mucosa may compromise the successful harvest. Those who smoke should be advised to stop smoking to improve the chance of graft revascularization. Betel nut chewing will compromise tissue quality.

Dental Assessment

The procedure involves harvesting a tooth and its associated alveolar bone for fashioning a "lamina." The assessment aims to select a healthy tooth (root) with the best shape and size with good covering of alveolar bone. The surrounding anatomy is assessed to avoid possible complications and to reduce the cosmetic defect to a minimum. There also needs to be adequate space between the teeth to harvest the tooth without damage to its neighbor. There is sometimes a compromise. The assessment therefore involves careful evaluation of these factors. The overall oral health with particular reference to oral hygiene and periodontal bone loss must be assessed. Gingival disease with no bone loss can be easily reversed. Clinical assessment of bone loss can be useful but radiographs are essential.

The ideal tooth in size and shape with the best surrounding bone is usually the canine tooth. There is usually little to chose in these parameters between the upper or lower canine. Other single-rooted teeth can be used in the absence of a canine. The assessment of suitability of the tooth depends on clinical examination but mainly on radiological assessment. The mainstay views are orthopantomograms (OPT) and intra-oral periapical radiographs (IOPAs). These views are essential. They give enough information in the majority of cases. CT scans can be useful to get more detail and are advocated by some operators.

All other things being equal, the choice of upper or lower canine depends on the proximity of the maxillary sinus in the upper and, although rarely a problem, the proximity of the mental foramen in the lower. The lower canine harvesting is straightforward but the buccal plate is occasionally a little thin and the lingual muco-periosteum is more difficult to preserve. The upper canine occasionally gives too much bone palatally and there is the risk of violation of the antrum; however, technically, the harvesting is easier.

The patient must be given full information at this stage to give adequate consent. Complications will be dealt with later but side effects of the dental part of the procedure, such as the inevitable gap left in the dentition and the possible methods of management, should be mentioned at this stage.

The patient's regular dental practitioner should be informed at this stage so that preparation to replace the missing tooth may be made, also the oral hygiene and periodontal condition can be optimized preoperatively.

Occasionally, there is no tooth suitable due to deficient surrounding tissues and in this circumstance an allogaft may be considered.

PSYCHOLOGICAL ASSESSMENT PRIOR TO OOKP SURGERY

Before undertaking such major surgery, it is important to explore several issues: is further surgery really wanted and if so who is it that actually wants the surgery? Is it the patient, his relatives, his spouse or indeed the doctor?

The assessment of a patient referred for consideration of OOKP surgery warrants special attention, because of the nature of the treatment and the nature of the population group for whom it is considered. Almost without exception, patients being considered for OOKP surgery will have had years of poor sight and so are at an increased risk of psychopathology.[7] In fact, most have also undergone multiple procedures, disappointments and years of emotional stresses but, nevertheless, may have become well adjusted to their predicament. As is the case for any surgical procedure, the potential patient must appreciate the risks involved and have a realistic appreciation of the potential benefits. However, candidates for OOKP surgery must also understand that the formation of an osteo-odonto-keratoprosthesis involves multiple operations, usually over a period of months and sometimes years. During that time there will be multiple hospital admissions and follow-up visits and there are likely to be setbacks along the way, which may or may not be readily rectifiable. The patient must also appreciate the significant financial, time and emotional stresses that they, and those close to them, will encounter.

Surgical results demonstrate that modern OOKP surgery has the potential to restore people registered as blind to a level of vision with which they can return to reading, recognizing faces and navigating around familiar and unfamiliar environments. This optimal outcome of the surgery does, however, often differ from patient's expectations having heard they can have "their eyesight restored." The field of vision is limited and will not satisfy the legal requirements for driving in the UK and some other countries. The eye in which the prosthesis has been implanted will not look like a normal eye and will still impact on their social interactions, particularly with strangers. The prosthesis needs careful attention and follow-up and its vulnerability will preclude them from activities with a high risk of contact or contamination.

It is undoubtedly a challenge to explain the risks involved in the procedure to the patient. The worst optical outcome is no perception of light. To lose perception of light, even if the best vision beforehand was hand movements only, is a devastating step emotionally and may impair the body's circadian rhythms and mood. Also, patients have to be informed that there is a significant risk of complications and the possibility of blindness exists, even in eyes that have had a period of good vision. The patients have to be able to commit to lifelong follow-up. This can be difficult when patients are referred from far away, though shared care with the referring or local ophthalmologist may be possible. Even when the patient does not pay for the surgery there

is a cost and time implication in attending follow-up regularly from a distant region.

As well as the risks to visual function, the patient must also be informed of the risks to their general health by prolonged anaesthesia, of multiple operations and systemic immunosuppression in case of an allograft situation.

We are conscious that acceptance of blindness as a permanent reality is an important step in adjustment to poor sight, and is a key for rehabilitation. Thus providing patients with hope of restoring sight should not be taken lightly as it can have detrimental effects on their adjustment in terms of social interaction and physical functioning.[8]

SURGICAL TECHNIQUE

Stage I

OOKP surgery is usually carried out in two stages. In the first stage, a monoradicular tooth is harvested to prepare an osteo-odonto-lamina. The root and surrounding jaw bone is sliced sagittally and then removed by cutting across the bridging bone. Whilst the crown is grasped with extraction forceps the tooth and the bone are pared down on either the mesial or outer surface with a diamond dusted flywheel, to expose pulp that is removed. A hole is drilled through dentine through which the anterior part of a PMMA optical cylinder is cemented in place. The crown is removed prior to drying with filtered oxygen and cementing of the optical cylinder. The saw, flywheel, and drill and bur tips are constantly irrigated with balanced salt solution to provide cooling. Where periosteum has been detached, it is glued back with fibrin glue. The KPro is then implanted into a submuscular pouch (often the lower eye lid of the fellow eye) for a period of 2–4 months.

A buccal mucous membrane graft is used to cover the ocular surface. It is more physiological than other coverings, i.e. fascia lata, donor sclera, etc. There are stem cells present, it has proliferating capability and is adapted to high bacterial load. It will be vascularized by the time of Stage 2 surgery and will subsequently provide the blood supply to the bone part of the OOKP lamina. Once harvested, the fat from the buccal mucous membrane graft is removed with curved scissors and the graft soaked in an antibiotic solution until required. The eye is prepared by isolating the recti with stay sutures, a 360 degree peritomy performed and the conjunctiva and tenons separated from underlying sclera. Corneal epithelium and Bowman's membrane are removed. The buccal mucosa is then trimmed to obtain an oval piece of adequate size to fit snugly on the front of the eye. The mucous membrane graft is sutured onto the side of the insertion of the four recti muscles and to the sclera in four quadrants with interrupted 6-0 vicryl. If possible, the cut edge of the graft should also be sutured to the conjunctiva.

Fine Details of Harvesting Buccal Mucous Membrane Graft

The buccal graft must be full thickness mucosa and of an area large enough to extend from medial to lateral canthi and from upper to lower lid fornices. This usually means harvesting a graft of 3 centimeters in diameter. The mouth is opened with a speculum, the parotid duct is identified, and local anaesthetic with adrenaline is injected. A compression type retractor with the inner holder having a minimum internal diameter of 3 centimeters can be used. The outline of the graft is marked taking into account the parotid duct; this can usually be accommodated by going below the duct opening.

The mucosa is incised along its circumference and scissors are introduced under the mucosa to free the graft from the underlying tissue. The graft can then be delivered. Haemostasis is achieved. There is usually no need for any sutures, although in Japan surgeons have been using artificial mucous membrane to cover the harvest site.

Fine Details of Harvesting Tooth, Root and Surrounding Jaw Bone

The harvest of the alveolar/dental complex involves the sectioning of bone on either sides and apical to the chosen tooth and removing the tooth and its surrounding alveolar bone, together with the associated mucoperiosteum. An incision is made to the bone and mucoperioteum elevated from adjacent teeth. The bone cuts are made between the teeth and below the chosen tooth with a fine saw, under constant irrigation to minimize any thermal injury to the lamina. The complex is then removed from the mouth in readiness to prepare the lamina. The resulting alveolar defect is covered as best as possible with adjacent mucosa but the exposed bone epithelializes very rapidly. In Japan, surgeons have been covering the defect with artificial mucous membrane grafting to accelerate wound healing. The patient is advised regarding oral hygiene and diet; hard food

should be avoided for some time. Antibiotics and analgesics are prescribed.

When Not to Do Ocular Surface Reconstruction and Tooth Harvesting Together

If the eye is very dry or there is a risk of the mucous membrane graft not taking, it may be better to perform Stage I surgery in two steps. The mucous membrane graft to the eye is done first (stage IA), and it is only when the graft has been shown to be well established before the patient is readmitted for tooth harvesting and preparing an OOKP lamina (stage IB). Otherwise if there is a significant delay in mucous membrane healing, or if further partial or full repeat mucosal grafting proves necessary, the lamina may be resorbed whilst buried in the lid for an excessively long time.

Stage II

Stage II surgery is carried out two to four months after Stage I in order for soft tissue to invest into the bone pores of the lamina. The interval also allows the lamina to recover from thermal damage, and any infection introduced from the oral cavity can be treated whilst the lamina is submuscular rather than on the eye. If the lamina is implanted submuscularly for a longer period of time, there may be significant resorption of the lamina. The first step in Stage II surgery is to retrieve the buried lamina for inspection. It is only if this is of adequate size that the surgeon proceeds to preparing the eye for receiving the device. After the OOKP lamina is retrieved from its submuscular pocket, soft tissue is excised from the posterior surface and trimmed from the anterior. A template is made of the lamina in order to plan placement of a Flieringa ring, and pre-placed sutures for securing the lamina. The lamina is temporarily returned to its submuscular pocket until the cornea is about to be trephined.

Traction sutures are applied to the lids for access to the eye. A superior rectus stay suture is placed and a buccal graft flap is fashioned by making an arcuate incision from 3 o'clock to 9 o'clock under constant irrigation with BSS and adrenaline. The flap is reflected and the cornea exposed. The buccal mucous flap is then reflected and a Flieringa ring sutured in place with sutures left long at 3 and 9 o'clock for traction. The center of the cornea is marked and the template placed on the cornea and cardinal sutures are pre-placed. Intravenous mannitol has by then been administered to reduce the intraocular pressure before trephination. The cornea is partially trephined, the size depending on the diameter of the posterior part of the optical cylinder. This is completed with scissors or a blade. The iris is then completely removed using forceps. If the patient is phakic, the lens is removed by ECCE (Falcinelli advocates an ICCE). A posterior capsulotomy is made and an anterior vitrectomy performed with a vitrector, with adequate traction provided by the surgical assistant on the two Flieringa ring sutures. The lamina is then sutured to the cornea with the posterior part of the optical cylinder traversing the corneal opening. Sterile air is then injected to reinflate the eye and indirect fundoscopy performed to ascertain adequate centration, to take note of the appearance of the posterior pole of the eye, and any presence of blood in the vitreous. Further interrupted sutures are applied to secure the lamina onto the sclera. The Flieringa ring is then removed, the buccal mucous membrane is repositioned and sutured in place, with a hole cut through the membrane to allow the anterior part of the optical cylinder to protrude (Figures 1 and 2).

Anaesthesia for OOKP

The technique of general anaesthetic for OOKP surgery, both stage one and stage two is similar. The preoperative visit is conduct in the usual manner as with any lengthy surgery but concentrating on any systemic disease associated with the corneal opacity. For instance the opacity may be due to Stevens Johnson syndrome, which may be due to a drug allergy. Also other mucous membranes may be involved compromising the airway or making urinary catheter placement difficult. Other causes of airway problems encountered in patients needing this surgery may be caustic or acid

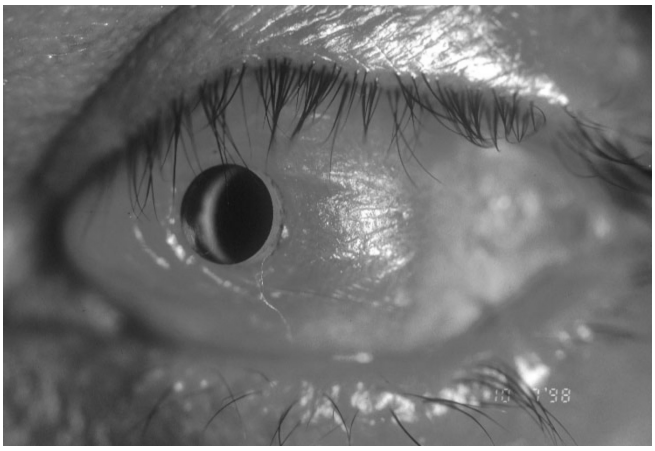

FIGURE 1 **Slit lamp photograph of an OOKP eye.**

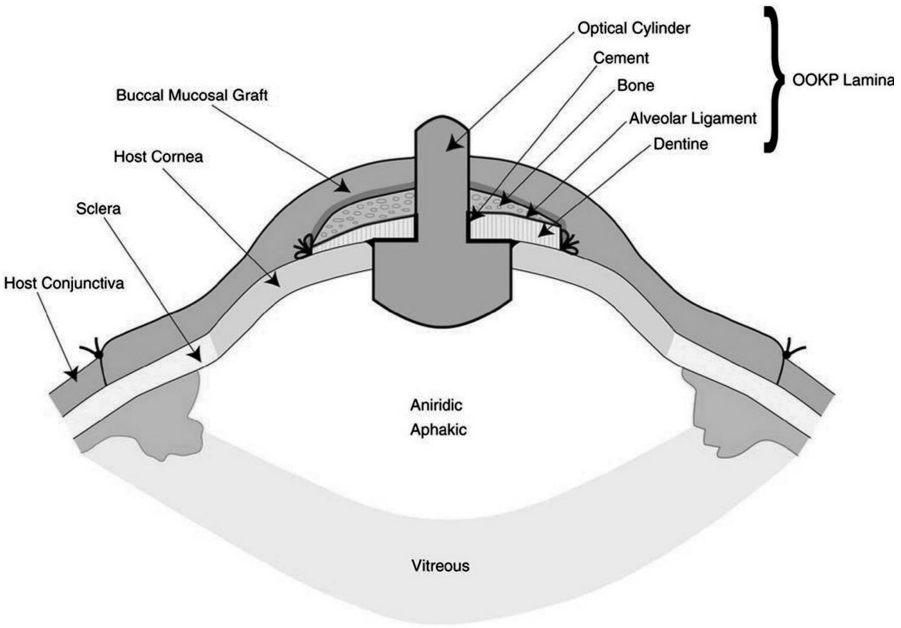

FIGURE 2 **Schematic diagram of cross section anatomy of an OOKP eye.**

scarring around the face. All such problems need to be identified and a management plan formulated prior to induction of anaesthesia. Patients attending for a second stage procedure may exhibit airway problems as a result of the first stage surgery the most common being scarring around the site used for harvesting the buccal mucous membrane. Scarring at this site can severely limit mouth opening.

Both stages require the administration of antibiotics at induction of the anaesthesia. The antibiotics for each stage in penicillin tolerant patients are 3.2 g of Timentin and 500 mgs of Metronidazole. In the case of patients allergic to penicillin, the Timentin is substituted with Ceftazidime 1 g. During the first stage the oral surgeon will require access to the mouth and so a nasotrachael tube is used, for the second stage a RAE or similar orotracheal tube can be used. After placement of an 18-gauge intravenous cannula, anaesthesia is induced; we prefer Propofol Fentanyl Ondansetron and Atracurium. IPPV followed by nitrous oxide, oxygen and Isoflurane (this is the same for both Stages I and II).

For Stage II where the eye is opened, mannitol is administered and therefore a urinary catheter must be placed at induction of anaesthesia.

The conduct of the anaesthetic is aimed at obtaining good operating conditions for the surgeon; to this end a little "head up" position for the operating table and the maintenance of a hypotensive technique is employed.

Postoperative Care

The immediate post-operative period requires pain relief, prednisolone 20 mg and lansoprazole 30 mg for five days, and oral antibiotics for a week. After Stage I, a conformer is often in place over the buccal mucous membrane and daily glass rodding is carried out to the fornices to keep them open. The patient uses chlorhexidine and nystatin mouth washes. Post Stage II, Diamox, steroids and antibiotics are continued. The optic is cleaned and the health of the buccal mucous membrane monitored. The skin sutures are removed after 5 days and the patient is admitted for 1 week for each stage.

Follow-Up Visits

The follow-up is life-long and at weekly intervals for one month, then monthly for three months, then every two months for six months, then every four months. If stable, then follow-up can be at longer intervals, possibly shared with the referring ophthalmologist. At the follow-up visits the vision is checked, unaided and with correction and pinhole, and a refraction performed. The intraocular pressure is checked digitally, the lids examined, the buccal mucous membrane assessed, including color, dryness and presence of any areas of thinning or ulceration. The optical cylinder is examined specifically looking at the cement, seeing

if there is tilting or lengthening and the presence of a retroprosthetic membrane. The stability of the optical cylinder is also tested by prodding with a cotton-tipped stick. Fundoscopy is carried out to check the optic disc and macula, B-scan to detect early peripheral detachments and visual field assessments are made 6 monthly for diagnosis and monitoring glaucoma. Resorption of the bone may be assessed clinically by palpating the mass and dimensions of the lamina, and radiologically using spiral CT, MRI or electron beam tomography.

If the patient has had an allograft, they will be using ciclosporin. An empirical serum level of between 100 and 200 ng/ml is aimed for and after base line investigations the urea and electrolytes, creatinine and ciclosporin levels are monitored at 3 days, 7 days, fortnightly for 2 months, every month for 4 months, then 2 monthly if stable.

GENERAL RESULTS OF OOKP

OOKP is based on the principle of using the patient's own tooth to form a biological frame to support an acrylic optic to restore sight in patients with end-stage ocular surface disease where conventional grafts fail because of vascularization, rejection or dessication. In diseases with severe ocular surface inflammation and dry eyes this technique has been found to be more successful[9–18] than other purely synthetic prostheses.[19–30]

A non-comparative case series was recently presented based on the retrospective analysis of hospital records and independent review (RT) of 29 patients who underwent surgery in Brighton from January 1996 to January 2003. The surgical technique was the Falcinelli-modified OOKP and has been described in detail in previous publications.[13–16] Additional modifications followed by the Brighton surgical team include performing ECCE instead of ICCE in phakic patients and use of second and third generation optical cylinders in patients operated after June 1999. All patients have had technically successful operations and the procedure has shown good results[17] in term of visual gain, long-term retention and low rate of sight-threatening complications in patients with end-stage corneal disease and the results appear better than those reported for other KPro devices in patients with similar aetiology. Difficulty in assessing the posterior segment before surgery to rule out optic atrophy or macular degeneration can affect statistical results for visual improvement.

The overall results with OOKP are good compared with those reported in literature for other available methods in patients with end stage ocular surface disease due to severe inflammatory syndromes like Stevens Johnson syndrome, ocular cicatricial pemphigoid, graft-versus-host disease, etc. Any differences in results of OOKP from other centers must be analyzed carefully, giving due consideration to whether the results are really different, i.e. are they statistically significant? If so, could this be due to the case mix depending on aetiology, severity, visual potential, etc; or could it be due to the surgeon's learning curve? Finally, is there a real difference in techniques such as OOKP versus fully non-biological devices, variations in the same technique, i.e. OOKP with ECCE versus ICCE, use of different cylinder designs, etc., and has the patients' full visual potential been attained? Hence, the Brighton team supports a continued sharing of information between centers, involvement of more ophthalmologists to help with shared care and the establishment of a multicenter database with standardized data entry, pooling of data and independent analysis of results.

COMPLICATIONS

Complications of OOKP surgery may include oral, ocular and systemic complications if the patient is on immunosuppresion. During Stage I surgery there may be risk of globe perforation, post-operatively there may risk of lamina and mucous membrane infection, and lamina resorption. During Stage II surgery there may be risk of vitreous haemorrhage, choroidal and retinal detachment. Post-operatively vision may be limited by a pre-existing condition such as glaucoma or macular disease. There can be resorption of the lamina, fistula formation and extrusion of the optical cylinder. Reducing the incidence of complications requires accurate surgery and meticulous follow-up. There may be trophic changes of the buccal membrane after either Stage I or II leading to erosions and this can be related to a bony spur on the optical lamina. In these cases the treatment is that the flap is lifted and any eroded bone removed with smoothing. Covering the mucous membrane with other tissue such as sclera or skin is not recommended. Retroprosthetic membrane formation is rare with OOKP surgery unlike other keratoprosthesis because of the removal of the iris and lens and through

anterior vitrectomy. If the membrane does develop and is visually significant it may be removed by YAG laser capsulotomy, or via a pars plana approach.

Oral Complications

Buccal Mucosa Harvest Site

The graft harvest bed is left to granulate. This usually takes place rapidly and is complete at two to four weeks. Occasionally there is an excess of scarring, resulting in limitation of mouth opening requiring mouth opening exercises and massage of the scar, otherwise this can easily be dealt with by incision of the scar bands.

Alveolar Graft Harvest Site

The complications are due to poor healing at the site resulting in exposure of roots of adjacent teeth, and damage to adjacent anatomy. The areas most at risk are the roots of adjacent teeth and maxillary sinus. The dental damage can be avoided by using very fine blades and careful technique. The damage to the maxillary sinus can be avoided by not making the apical cut too high but if the root of the donor tooth is very close to the maxillary sinus this complication is unavoidable.

Should dental damage occur, the patient must be informed and careful watch kept on the tooth to treat any problems that arise as soon as possible.

Breach of the maxillary sinus can be closed by advancement of surrounding mucosa. Should the oroantral fistula remain patent, an obturator will be needed to prevent nasal reflux until formal closure can be carried out.

Oculoplastics in OOKP Patients

Oculoplastic complications associated with OOKP surgery include forniceal and tarsal conjunctival cicatrization, associated with ocular surface inflammation and primary disease process. As a result, patients may have shallow fornices, upper or lower lid cicatricial entropion and wide palpebral apertures. Shallow fornices can be treated by use of a mucous membrane graft and/or fornix deepening sutures. A cicatricial entropion can be corrected by lamellar division, through a grey line incision. Permanent lateral tarsorrhaphy, medial canthoplasty, lateral canthal sling, and upper lid retractor recession using an anterior or posterior approach are procedures that can be used to reduce a wide palpebral aperture.

In cases of buccal mucous membrane thinning, ulceration, and/or necrosis, one should exclude and treat any underlying infection. Therefore taking swabs from the graft should be performed on a routine basis. Following successful treatment of an underlying infection a mucosoplasty should be performed. This involves mobilization of thick buccal mucosal tissue from the periphery to the center of the graft by using bipedicle or transposition flaps followed by regrafting of the peripheral donor site with fresh tissue. Failing that, a new buccal mucous membrane graft can be used. Finally, if none of the above methods is successful, the anterior lamella of the upper lid can be undermined and pulled down over the optical cylinder on to de-epithelialized buccal mucous membrane graft, allowing the posterior lamella to fall back. An opening can then be made in the anterior lamella for the optical cylinder to protrude.

Consideration should be given on the cosmesis of these patients. A cosmetic shell with a custom-made hole to fit onto the optical cylinder can be considered. If the patient is happy with the prosthesis, then he can lighten the tint of his dark glasses, allowing more light to get through the optical cylinder, thus using his limited vision more effectively. We are, however, limited by the length of the modified optical cylinder peg to support a cosmetic shell and we are concerned about pressure necrosis of the buccal mucous membrane graft. On the other hand, others believe that some pressure on the lamina is essential to avoid bone loss.

Glaucoma

Glaucoma is a major problem in keratoprostheses and there has been an incidence of up to 75%. This is complicated by the fact that there is no reliable measurement of intraocular pressure and the optics of a KPro may not allow detection of early visual field defects due to decentration and design of the optics. Diagnosis of glaucoma will rely on digital palpation, optic nerve head appearance and visual field defects. Other methods to detect glaucoma include electrodiagnostics with VEPs significantly reduced in OOKP patients with glaucoma compared to controls (79%).[31] Glaucoma may be pre-existing or secondary to KPro surgery. Management of glaucoma in keratoprosthesis involves systemic medication (acetazolamide) or surgery. We have used topical medication but we are uncertain how much drug penetration there is in this circumstance, though there may be the possibility of

some effect from systemic absorption. Several surgical methods are available from cyclodiastasis to endolaser cyclophotocoaguation, to aqueous shunts with or without valves, to the retro-equatorial drainage "thin silicone tube." From reports of surgery with Ahmed valve and OOKP, it is suggested that this is not performed simultaneously with OOKP surgery to reduce the risk of hypotony. A Baerveldt implant may have some advantages if simultaneous surgery is being considered as temporary occlusion of the tube with an absorbable suture is possible. Glaucoma following KPro surgery is a serious issue and vigorous management is essential for long-term retention of a patient's sight in the presence of a technically successful device.

Retinal Detachment

Early detection and treatment of a retinal detachment is essential. Patients may have symptoms such as a sudden onset of floaters, flashing lights or a shadow across the vision. Detachments may be detected by fundoscopy or with B-scan ultrasonography. Surgical techniques may involve using a BIOM system or temporarily replacing the OOKP lamina using an Eckardt keratoprosthesis. Endoscopic surgery may have several advantages, such as not needing to view through the optical cylinder and not needing to detach the membrane or lamina. Disadvantages of this technique are a learning curve, it can be difficult to orientate oneself, and the equipment is expensive.

Resorption and Extrusion of OOKP Lamina

Results of the Strampelli's OOKP-technique, modified by Falcinelli, showed good long-term results with 2% loss of prosthesis over 27 years. Some cases of decentration of an initially well aligned cylinder are due to bone resorption of the osteo-odonto-lamina. Causes of resorption and extrusion may be due to inflammation, ulceration and infection of the mucous membrane or skin. Diagnosis of resorption of the lamina at an early stage may be difficult due to the presence of the mucous membrane graft. An evaluation of the OOKP lamina status can be made by biomicroscopy, Seidel-test, ocular hypotension, CT (conventional or spiral CT), or EBT. In one series[33] slow resorption of the lamina was seen mainly of the inferior half. There was found to be extremely fast resorption in children.

Clinical warning symptoms and signs of resorption may be a change in refraction, elongation or tilting of the optical cylinder, loss of the lamina dimensions or an aqueous leak.

Imaging of the OOKP Lamina

The critical feature for the long-term stability of the OOKP appears to be in the maintenance of the osteo-odonto-lamina. Reduction in the dimensions of the laminae can result in aqueous leakage, inflammation, extrusion of the optical cylinder and endophthalmitis. As such, it is important to detect such cases of laminar resorption so that prophylactic measures can be taken to prevent such complications from occurring. Imaging techniques such as electron beam tomography (EBT) and multi-detector computed tomography (MDCT) are valuable in detecting such cases. Other methods of imaging like B-scan echography are limited because the laminae causes sound attenuation and shadowing while magnetic resonance imaging (MRI) is subject to movement artefact with poor spatial resolution. Image acquisition with MRI is also considerably longer than with CT. Conventional CT only allows 2-dimensional reconstruction.[32]

Electron Beam Tomography

EBT (GE Imatron, GE Medical Systems, USA) is a modified form of computed tomography and utilizes electron beams that are focused onto tungsten target rings positioned beneath the patient. This is then passed to an array of detectors that generates cross-sectional images. EBT is rapid (50–100 ms per scan) and is widely used for evaluating cardiac function, coronary artery calcium content and blood flow analysis.

In our unit, EBT has been successfully performed on 10 eyes that have undergone OOKP surgery using the following parameters: axial plane scan with an acquisition time of 100 ms, a slice thickness of 1.5 mm, table feed = 1 mm and pitch = 0.66. Three-dimensional volumetric reconstruction of the OOKP was then performed utilizing an Aquarius Terarecon Workstation. Maximum Intensity Projections (MIP) and Shaded Surface Display (SSD) techniques were then used to calculate the dimensions of the OOKP laminae. Calculation of the windowing, that is, calculation of the range of densities of tissues to be displayed in Hounsfield Units (HU), is crucial in SSD techniques. This ensures the correct volume of bony tissue is displayed. Problems arise

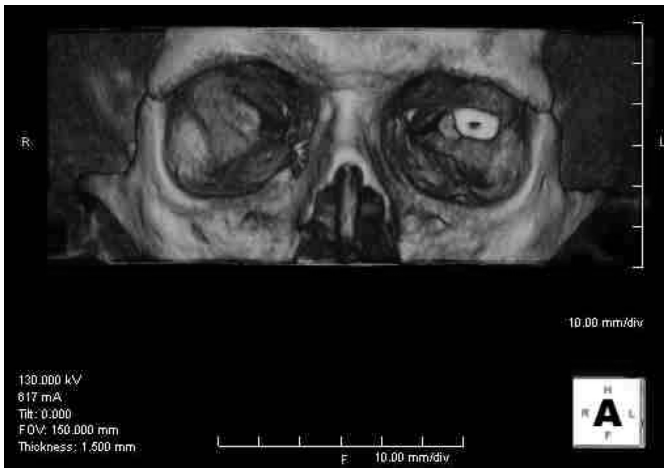

FIGURE 3a **Electron beam tomography (EBM) of mid-face showing a well defined OOKP lamina in front of the left orbit. The lamina has an intact rim around the optic.**

in assessing bone of this size due to beam hardening and volume averaging. These measurements were measured and compared to those obtained at the time of surgery and a morphological assessment done. The mean age of the patients was 52 years (range 32 to 79 years) and the mean time from surgery to EBT was 38 months (range 12 to 62 months). Minor reductions in the laminae were found in all patients with significant reductions in 2 patients.

Figure 3a shows the 3D reconstructed image of a well-sited OOKP with a good rim of laminae around the optic. Figures 3b and c are of another patient where significant thinning of the inferior rim of the lamina was seen (33 years old, Stevens-Johnson Syndrome, autograft, lamina covered with buccal mucosa, OOKP surgery 52 months ago). This patient has since undergone removal of the OOKP and preparation of a new OOKP to prevent potential complications of endophthalmitis. The resorption of the laminae was confirmed at the time of the OOKP removal.

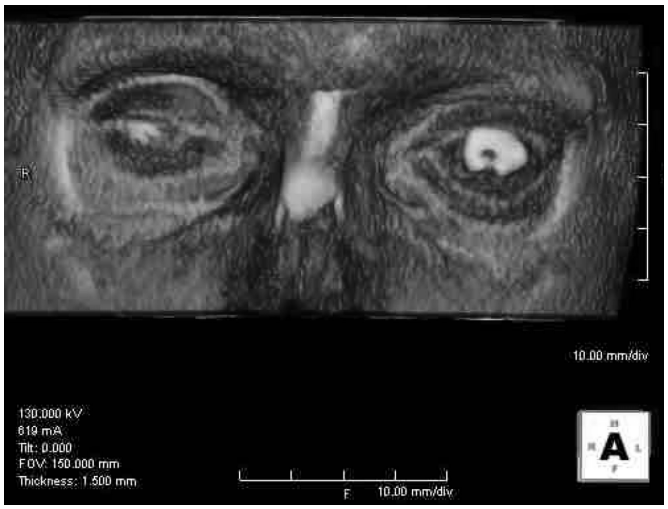

FIGURE 3b **EBT of left eye OOKP showing significant thinning of the inferior rim of the lamina.**

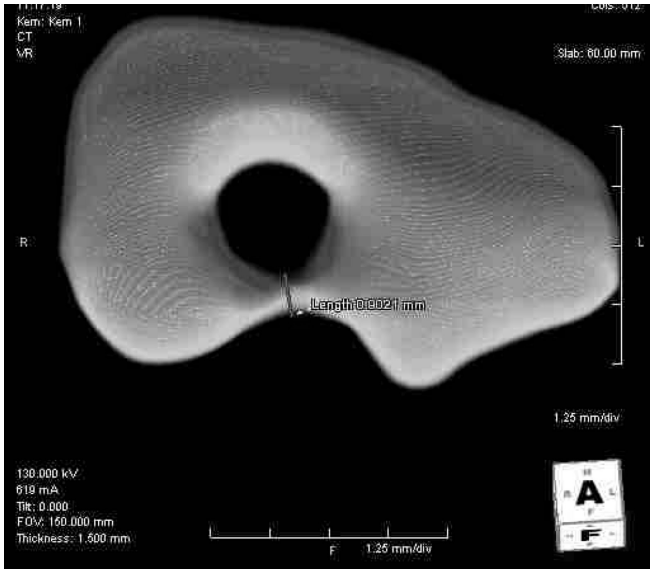

FIGURE 3c **Detailed Shaded Surface Display reconstruction of the OOKP lamina from Figure 3b, showing the inferior rim measuring only 0.9 mm.**

Multi-Detector Computed Tomography[33]

In nine patients, Stoiber et al. successfully performed spiral CT scans (Toshiba X-press/SX, Toshiba Corporation, Japan), 3-dimensional datasets created by using a shaded surface display technique. The dimensions of the OOKP were measured and compared with the measurements taken at the time of surgery. The mean age of the patients was 48.4 years (range 32 to 75 years) and the mean time from surgery to MDCT was 4 years (range 1 to 6 years).

A minor reduction in laminar dimensions, mainly in the anterior and inferior part, could be found in all the patients. In one patient, there was complete resorption of the inferior half of the laminae (79 years old, ocular pemphigoid, autograft, laminae covered with lower lid skin, OOKP surgery 24 months ago). No correlation between the degree of reduction in the dimensions and patient age, diagnosis or length of follow-up could be found. The degree of resolution on spiral CT was impressive as even Baerveldt glaucoma implants were visible on the scans.

The OOKP as described by Strampelli and modified by Falcinelli does show good long-term results but we must always be aware of the eventual signs of resorption of the osteodental laminae. Up to recently, there was

no reliable method of imaging the laminae precisely in vivo. It is now possible to image the laminae with modalities like EBT or MDCT and significant thinning of the laminae has been found using both modalities. This allows closer follow-up of this group of patients to look out for signs of aqueous leakage, optic extrusion or inflammation. In the case of some patients with significant laminae thinning, prophylactic measures like removing the OOKP and preparing a new OOKP may be considered to preserve the function of the eye.

EBT has two advantages over MDCT in that lower doses of radiation are involved (1/3 that of MDCT) and image acquisition by EBT is much more rapid, thus reducing the potential problem of movement artefact. Problems in defining the actual dimensions of the OOKP relate to the fact that the alveolar and denticular bone have a wide range of densities and the target of the scan is small and close to the spatial limits of resolution of either modality. MDCT will deliver higher quality images with greater signal to noise in the data sets obtained but at greater exposure to radiation dose. Both EBT and MDCT are practical and accurate diagnostic tools in imaging the OOKP.

We would recommend a baseline morphological assessment of the OOKP initially by either EBT or MDCT after the OOKP has been implanted to define the dimensions radiologically. We would then regularly monitor the dimensions of the OOKP with clinical assessment to identify cases at risk of optic extrusion and consequent endophthalmitis.

Allografts

The absence of teeth has been considered a contraindication for the procedure in the past. The idea of using a tooth donated from a blood relative was proposed by Falcinelli and some results have been reported since.[16]

There is, however, still a paucity of literature available on the outcome of OOKP surgery performed using tooth allografts in edentulous patients who are suffering from these disorders and the exact long-term outcome in terms of visual stability and complications of immunosuppressive treatment are not clearly defined.

Further experience with performing allografts (CL and JH) in edentulous patients with blindness from Stevens-Johnson Syndrome, ocular cicatricial pemphigoid and ectodermal dysplasia has been recently reported.[34]

OOKP allografts are fashioned from a canine tooth donated by an HLA-matched living relative. Tooth donations are usually sought from offspring, siblings or parents. HLA matching is done and the donor with the best possible match is chosen out of the selected potential donors. In the case of an allograft where a tooth is donated, the donor has to be counselled and microbiological screening tests including syphilis, HBV, HCV and HIV are performed. The patient is made aware that in these circumstances there is a higher risk of resorption of the lamina, and that they need to be on lifelong immunosuppression even if the donor is HLA matched, to prevent graft rejection and prolong the life of the grafted OOKP lamina. Some surgeons who have experience in performing allografts advocate immunosuppression for a duration of 6–12 months only (Falcinelli: personal communication). Since the OOKP osseous tissue is encapsulated by highly vascular tissue, the chances of immunologically mediated chronic inflammation is high, hence the Brighton Group advocates lifelong immunosuppression.

The immunosuppressive agent of choice is systemic ciclosporin A, which is one of the most widely used agents in transplant patients. This drug has the benefit of having a selective inhibitory action on the cells that mediate transplant rejection, particularly the T helper cells, and hence is relatively free from causing profound generalized cytotoxicity. Ciclosporin A is derived from the fungus Tolypocladium inflatumgans. It acts mainly on T cells by binding to ciclophillin, which is an intracellular peptide. The binding action results in inhibition of protein synthesis required for T-cell activation. Ciclosporin has other additional effects, such as inhibiting the expression of IL-2 receptors and blocking the production of interferon-gamma.[35]

Ciclosporin therapy is started a day before Stage 1 when the tooth lamina is prepared and implanted. Baseline investigations should be done such as recording the blood pressure and blood tests, which include a full blood count, renal and liver function tests. The initial dose is 2.5 mg/kg/day divided in two doses 12 hours apart, which are rounded off to the nearest 25 mg. Patients are advised to swallow the capsules whole with half a glass of water and to avoid taking grapefruit or grapefruit juice within one hour of ciclosporin.

The dose is then increased to 4 mg/kg/day and then 5 mg/kg/day to attain a target serum trough level of 100–200 ng/ml. Higher target level of 150–200 ng/ml is set as ciclosporin is being used as a single agent in

Brighton.[17] In other solid organ transplants and in limbal stem cell allografts, combination therapy with multiple drugs such as prednisolone, cyclophosphamide, tacrolimus (FK-506) and mycophenollate mofetil are used along with ciclosporin and target levels of the latter are then set lower at 100–150 ng/ml. There is no literature available of any other immunosuppressive drug regimes in OOKP.

The blood sample should be taken approximately 12 hours (±1 hour) after the last dose and before the next dose to correctly monitor drug therapy. After any change in dose, a repeat ciclosporin level, urea and electrolytes should be checked 4–10 days later and the dose further adjusted if required. The appearance of side effects is monitored by checking the blood pressure and general health of the patient and repeating the blood tests. Estimation of ciclosporin level, urea and electrolytes is advocated every 2 weeks for the first 2 months, every month for the next 4 months, every 2 months up to a year after treatment was started and then 6 monthly thereafter. In case the ciclosporin levels are more than the target range, or creatinine level rises more than 30% from baseline, then the dose should be reduced by 25% and the levels rechecked after 4–7 days.

A large number of drugs interact with ciclosporin and compatibility of any concomitant medication should be checked by consulting a drug interaction manual or a qualified pharmacologist. Generally, drugs that affect the cytochrome P450 system are likely to affect the levels of ciclosporin by altering its metabolism in the liver.[36] Alcohol, aciclovir, acetazolamide, amphotericin B, aminoglycosides, atorvastatin, carbamazepine, clarithromycin, erythromycin, fluconazole, ketoconazole, verapamil are among some of the common drugs that can increase the ciclosporin levels and precipitate its toxic effects. Nephrotoxicity is most common, occurring in 25 to 75% of cases. The effect is dose related and reversible if detected early and the dose reduced accordingly. Hyperlipidaemia, glucose intolerance, thrombocytopenia, neurological toxicity with headache, tremors and pseudotumour cerebri are other effects. Patients should also be made aware of the possibility of developing hirsutism and gingival hyperplasia.

Optical Cylinder

The single piece optical cylinder, which currently replaces all the optical elements of the eye, has a vital role to play in the visual rehabilitation of OOKP patients. However, it is a small part of a highly complex operation and therefore must have minimal impact on the potential medical success of the procedure. Present designs for use in OOKP surgery involve a single piece of CQ (clinical quality) PMMA manufactured by lathe cutting and tumble polishing. PMMA has been used for the optical cylinders since the outset of OOKP surgery. It is long established as an intraocular material and shows minimal signs of wear or scratching even in Italian patients whose follow up is 20–30 years.

The ideal optical cylinder would produce the same imaging performance as the optics it replaces. This is a very tall order, since we would require an approximate 160° horizontal visual field and visual acuity of 6/5. Reported results[6] for the original Italian designs did indeed achieve a good visual acuity and the reported visual field was 40°, although the figure does vary with ametropia and physiological factors. There is good reason for the relatively narrow visual field; the cylinder by necessity is long and narrow and the field of view is akin to looking through a tube (Figure 4a). The length of the anterior portion of the cylinder is determined by the fact that it must extend through the osteo-odonto-lamina, the mucous membrane and possibly provide a spigot on which to attach a cosmetic shell. This dimension is 5.75 mm for current UK designs (Figure 4b). A diameter of 3.5 to 4 mm is chosen for the anterior section of the cylinder. This dimension should be within the dentine of the osteo-odonto-lamina and also avoids too much glare by providing a moderate pupil size. The posterior section of the cylinder extends into the eye from the supporting lamina. Its length is determined by the steep curvature of the posterior surface and the desire to avoid retro-prosthetic membrane growth. Currently this section measures 3 mm, giving an overall length of 8.75 mm (Figure 4b).

Recent attempts have been made to improve the visual field, since it is an important aspect of vision; it is of limited value to achieve a visual acuity of 6/5 if the visual field is very narrow. An increase in the visual field has been achieved by slightly expanding the diameter of the posterior section of the cylinder and optimizing the design for image quality across the field.[37] All new designs still have to achieve a potential visual acuity of 6/5 or better as calculated by our design programs, assuming a normal retinal-neural contrast threshold function. Initial results were encouraging and the cylinders currently in use in the UK are the second generation to be designed by us. Although it is possible to have

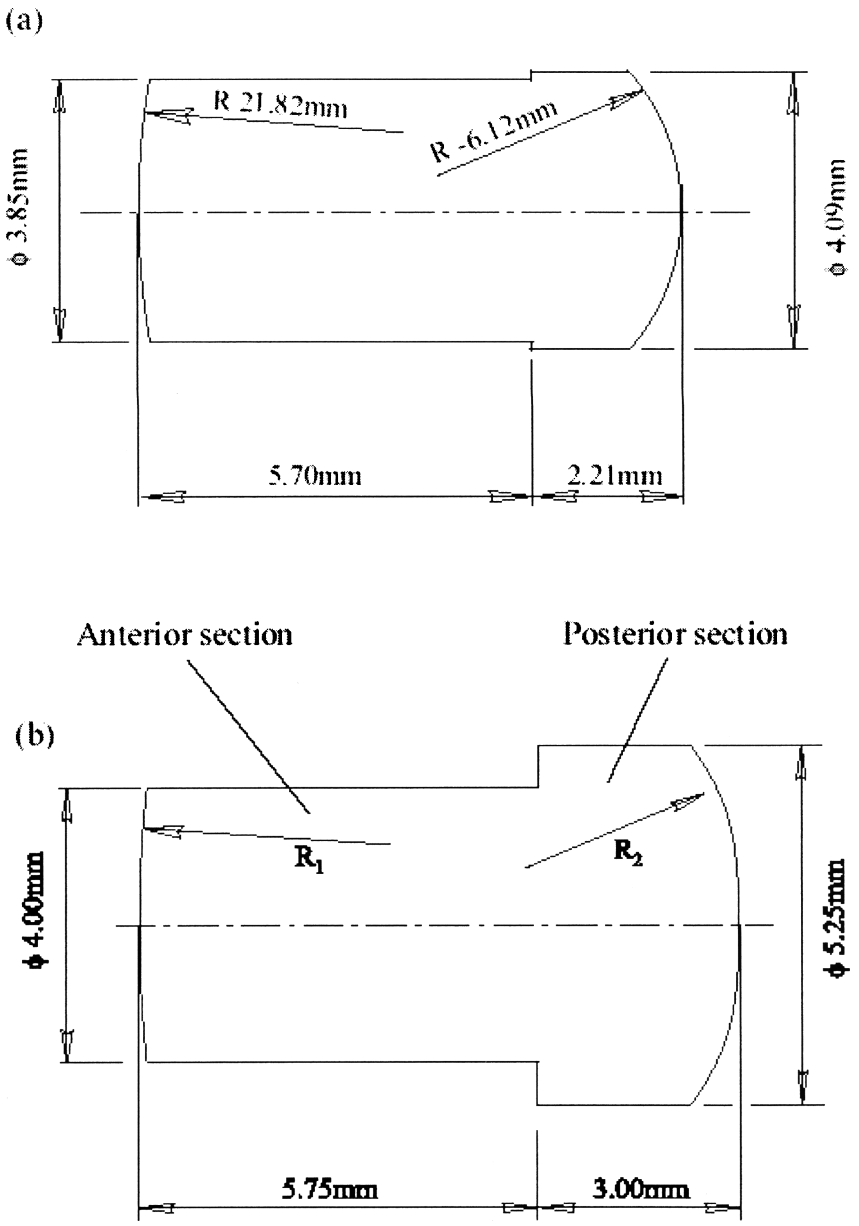

FIGURE 4 **Dimensions of a 28.5 mm "Biom[etry]" Italian cylinder measured in our laboratory and (b) the wider diameter version of our current UK design. Note that the choice of radii of curvature controls the image quality as well as the back vertex power of the cylinder.**

more complex (2 component) designs that improve the visual field, these would add an additional layer of technical complexity to an already difficult procedure. The interested reader is referred to one of our publications for further details.[38] An alternative approach, described by Hille, is to leave the patient significantly myopic.[39] The negative spectacle lens correction acts as an inverse telephoto wide-angle lens to increase the visual field. This has again proved successful, although we caution against *electing* to leave a patient significantly visually impaired without correction. Synthetic OOKPs (see below) offer another alternative to improve the visual rehabilitation of these patients, since the design of the optical cylinder is not constrained by the anatomy of the tooth root.

TOWARDS A SYNTHETIC OOKP: THE RATIONAL SELECTION OF DENTAL LAMINATE SUBSTITUTES

The key feature of the OOKP that might explain its success is the fact that inter-connected pore spaces of the bone provides fixation of supporting tissue. A "synthetic" analogue of this structure would make the OOKP easier to use and more widespread, whilst allowing more freedom in design of both optic and support

TABLE 2 **Basic Requirements for a Synthetic Structure to Mimic the OOKP Support Frame**

OOKP lamina property	Indicated requirements
Porosity (Tissue integration)	*Graded interconnected porosity in these dimensions *Microporosity: 15–40 micrometers *Macroporosity: 50–150 micrometers
Mineral constitution (Biological tolerance and stability)	*High crystallinity *Moderate ionicity *Calcium phosphate/carbonate *Ca/P ratio of 1.5–1.67 *Non-stoichiometric hydroxyapatite

frame. Table 2 provides a summary of the key features of the OOKP support frame and the consequent requirements of a synthetic analogue.

Whereas it is important to pursue the development of polymer-based porous support frames for keratoprostheses that can support cellular integration, a more obvious and pragmatic approach to a synthetic OOKP is to seek alternative porous inorganic analogues of the dental lamina. There are a variety of methodologies for making porous ceramic solids and a large number of natural inorganic sources that match dental alveolar bone in both the size of pores and their arrangement. Both coral skeletons and sea urchin spines, for example, possess a pore geometry (the specific arrangement of cells) very similar to common types of bone, with either open or closed cells. The clinical literature describing the results of coral skeletons implanted into the human body is very positive.[40] Both hard tissues and soft connective tissue penetrate the pores and channels rapidly and remain healthy therein. Inflammation is uncommon because of the healthy state of tissue and this also inhibits bacterial contamination. The pore structure of different coral skeletons, such as *Porites* and *Seriatopora*, match up with different varieties of bone and make obvious candidate materials. It is clear from detailed studies of the potential of this approach,[41–43] and from initial clinical exploration[38] that marine-derived porous inorganic materials offer a convenient and potentially effective route to a synthetic OOKP.

SETTING UP AN OOKP SURGICAL CENTER

Those interested in learning OOKP surgery should contact a member of the OOKP teaching group (Falcinelli, Rome, Italy; Liu, Brighton, England; Grabner, Salzburg, Austria; Hille, Holmberg, Germany). As the process of patient selection, counselling, pre-operative work up, surgical program and post-operative care, including recognition and management of complications, is complex, it is important not to attempt to offer OOKP surgery without formal training. Such training should include attending an OOKP course, spending time in the operating theater, seeing patients in clinic and studying patients' medical records at the host institution, and then the teacher should supervise the first few cases at the trainee's institution. The use of technology allows case conference on the internet as well as telemedicine. The supervision of Stage II surgery of the first case of OOKP surgery in Japan was done through telemedicine due to the SARS epidemic. Whilst expensive and requiring a lot of effort to set up, it nevertheless allowed remote supervision from England.

The trainer and trainee should have a clear agreement at the outset regarding the level and length of support, publishing rights, visiting academic position, medical indemnity and any honorarium to avoid misunderstanding. The trainee should ideally be a corneal surgeon who has had broad training in ophthalmology, who has support of his corneal colleagues nationally, and who works in a center of excellence with excellent oro-surgical, anaesthetic, oculoplastic, vitreoretinal, glaucoma, radiological, and microbiological support.

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