Title: Corneal Sensitivity after Ocular Surgery

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Abstract

The cornea is densely innervated with free nerve endings to provide a high level of sensitivity to foreign bodies or noxious substances. They also provide trophic support to the tissues of the cornea and facilitate their repair and replacement. Any reduction in the function of the nerve endings through disease, contact lens wear or surgery may lead to corneal disease, damage or reduced healing. Assessment of the corneal nerve function can be made by the use of specialised instruments (aesthesiometers) that stimulate the corneal nerves using different modalities – mechanical, chemical, thermal. Each modality assesses the function of a different cohort of corneal nerve type. Ocular surgery, particularly corneal surgery, can produce significant damage to the corneal innervation. However, for the majority of surgical procedures, corneal sensation eventually returns to pre-operative levels given enough time. The principal exceptions to this are penetrating keratoplasty, epikeratophakia and cryo-keratomileusis, where sensation rarely returns to normal. For all types of surgery, the pattern of corneal sensation loss and recovery depends on the type, depth and extent of incision since these influence the number of nerve fibres severed, and on the healing response of the patient.

Introduction

The human cornea is a densely-innervated tissue that provides a high level of sensitivity for ocular protection through the detection of foreign objects or noxious substances. Corneal innervation also plays an important role in the trophic maintenance and repair of the cornea. Any alterations to normal innervation of the cornea will not only lessen the ability to detect objects or substances that could damage the eye, but also reduce its wound-healing ability.

Reduction in corneal sensitivity may occur from the desensitisation of nerve fibres, such as during contact lens wear, or from nerve damage during the progression of specific corneal and ocular diseases. The treatment can potentially cause further compromise of the existing corneal innervation. In most cases, however, there are complex processes of re-innervation during the recovery stage following treatment, which may be partial or complete, but which commonly occurs over a prolonged period.

Recent times have seen a proliferation in the variety of procedures for the treatment of ocular disease, conditions and refractive error. Current surgical techniques, however, still impact on corneal sensitivity, having different effects on corneal sensation which depend upon the location, size, depth, and orientation of surgical incisions to the ocular surface.

Corneal Innervation and Measurement of Sensitivity

The cornea is a highly specialised tissue that performs four roles in the eye: 1) transparency, allowing light to enter the eye; 2) refraction, focussing the light entering the eye; 3) containment of intraocular structures; and 4) protection of the eye against trauma. The protection of this essential organ is achieved in a gross manner by the eyebrows, eyelids and eyelashes, and avoidance responses to objects seen to approach the eye. Also of importance is the extremely sensitive network of fine nerve endings within the corneal epithelium. These nerve endings detect any potential noxious agent present on the corneal surface, stimulating lid closure and tear production.

The quality of the epithelial nerve sensitivity can be assessed by measuring how well the nerves respond to various stimuli, such as mechanical probing, in the form of a nylon thread,[1,2] a thermally-cooling air-pulse,[3] or to mechanical, thermal (warming) or chemical stimuli presented pneumatically.[4,5] The ability to assess corneal sensitivity has allowed the investigation of various different physiological, pathological and surgical factors on corneal nerve function.[6-9]

During surgery, damage to nerve function can be minimised by using short, shallow, linear incisions that avoid cutting across the radially oriented corneal nerves. Shorter incisions reduce both the damage caused and the extent of healing required in the cornea post-operatively. However, most incisions are circumferential, which can sever many nerve fibre bundles. Excimer laser refractive surgery (PRK, LASIK, LASEK) affects the cornea and its sensory nerve network in a very different way. The reshaping of the anterior corneal surface involves the removal of a large volume of corneal tissue, over a wide surface area.[10,11] As a consequence, the epithelial sensory nerves are significantly affected within the treatment zone.

Innervation of the Cornea

The corneal epithelium has the highest nerve density of free nerve endings of any tissue in the body: 300-600 times that of the skin, and 20-40 times that of dental pulp.[12] This extensive network of fine nerve endings produces an exquisitely sensitive response to any mechanical, thermal or chemical stimulus.[12] The nerves also play a role in the maintenance and health of the corneal epithelium. A reduction in corneal nerve supply will result in impaired wound healing, decreased epithelial metabolism and reduced epithelial cell adhesion (e.g. neurotrophic keratopathy).[13,14] In addition, impairment of the corneal nerves disrupts the feedback loop for basal tear production, leading to diminished lacrimal secretion and blink reflex, with subsequent drying of the ocular surface.[15-18]

Derivation of the Corneal Nerve Supply

The corneal nerves are derived from the nasociliary nerve, which is a branch of the ophthalmic nerve, derived from the first division of the Vth cranial nerve (Trigeminal). The nerves supplying the cornea pass along the long ciliary nerve, which is a branch of the nasociliary nerve. They penetrate the posterior sclera, then pass between the sclera and choroid, coursing anteriorly to provide the sensory supply for the cornea, iris, ciliary body, trabecular meshwork and sclera.

Upon reaching the corneal limbus, the nerves produce an annular limbal plexus then join one of two nerve systems. Approximately 50-90 deeper nerve trunks enter the mid-stroma radially, at an average depth of 293 ± 106μm, from various sites around the corneal circumference. More superficial nerves enter the posterior epithelium as finer nerves that contribute to the peripheral subbasal nerve plexus.[19] Each mid-stromal trunk contains 900 to 1200 myelinated and unmyelinated axons of diameter 0.5-5μm, which travel centripetally, mainly in the superficial 150μm of the anterior stroma.[20] The posterior stroma contains only small-to-medium diameter nerve bundles and scattered individual axons.[21] However, this lower nerve density is still sufficient to provide axons from which new nerves can re-innervate the remaining cornea after anterior stromal surgery.

The myelinated nerves lose their myelin sheath soon after entering the stroma.[22] As these axons pass towards the epithelium, they ramify and divide to form a poorly characterised sub-epithelial plexus in the superficial stroma.[12,19,23] Anteriorly-directed nerves emerge from the sub-epithelial plexus, at an average of 204±58 sites, to enter the basal epithelial cell layer.[19,24] As they do so, the nerve bundles lose their remaining Schwann cell coverings. These nerves then combine in bundles with peripheral nerves from the limbal plexus, which enter the basal epithelium from the limbus, to form the sub-basal nerve plexus.[25] The sub-basal nerve plexus lies between the epithelial basal cells and Bowman's layer, and typically runs parallel to the corneal surface in a whorl-like pattern.[26] In some cases, the path of the nerve fibres deforms the lateral or basal borders of the basal cells, such that the fibres appear to be fully enclosed. Each nerve fibre contains from 1-40 axons.[24,25] The fibres are of four different types – mechano-sensory, polymodal, mechano-heat and 'cold' neurones - and are arranged within the corneal epithelium according to their type.[27,28,29] For the measurement of corneal sensitivity, there are two principal nerve types that mediate the corneal nerve response: A∂ fibres that remain in the sub-basal nerve plexus, and C fibres that turn upwards from this plexus towards the surface.[30] A∂ fibres are large diameter (8–10µm), straight nerves that respond primarily to mechanical stimuli, while C fibres are small diameter (5–8µm), beaded nerves that respond to thermal and chemical stimuli (Figure 1).[5,27,31,32,33]

Within the epithelium the anteriorly-oriented fibres in the basal epithelial layer pass through the wing-cell layer towards the superficial cells, where they end in fine, unspecialised, nerve endings. These free terminals are usually swollen and can be found throughout the depth of the epithelium. Some of the nerve endings in the superficial layer can extend up to the last desmosomal junction between two superficial cells and are separated from the external environment only by this junction.[12,23,34]

Corneal Nerve Repair Mechanisms

The repair of the corneal nerve supply generally occurs in two phases, although the pattern and timing of the process varies with the type and extent of initial tissue damage.[35,36,37] The first phase involves nerves from the undamaged epithelium surrounding the wound, and the second phase originates in the undamaged stroma deep to the wound. During each phase, re-innervation occurs by an initial degeneration of the original fibres within or close to the wound, followed by the regeneration of new terminals and axons into the healing tissue.[7]

With a purely epithelial wound, degeneration of damaged nerves occurs rapidly, and any nerves within the wound area will have degenerated by 24 hours after the trauma. By 48 hours, further degeneration of the nerves in the undamaged stromal plexus occurs, up to approximately 0.5mm from the wound margin.[35,38] Simultaneously, at around 16 hours, the first collateral nerve sprouts start growing from the intra-epithelial axons in the undamaged cornea adjacent to the wound. By 24 hours, a dense hyperplasia of these neurites can be seen. The nerve sprouts completely surround the wound and orientate themselves perpendicularly to the edge. Terminals from these sprouts then grow horizontally to enter the basal cell layer of the newly repaired epithelium within the wound area. The purpose of these temporary neurites is not known, but they may result from the increased release of epithelial neurotrophic factor.[36,39]

The second phase of the re-innervation process begins around 7 days after the injury and can extend for 14-21 days depending on the extent of the original injury. New nerve growth develops in the stromal plexus of the surrounding undamaged cornea. New terminals grow obliquely into the newly-formed, reorganised epithelium from the damaged stumps of the original axons that had innervated the area. At the same time as these new nerve endings are developing, the nerve sprouts formed in the first phase begin to degenerate and have disappeared entirely by 3 weeks. The second phase re-innervation re-establishes a normal pattern of corneal epithelial innervation within about 4 weeks, although tactile sensitivity will still be below normal levels for some time.[36,40]

Peri-limbal and deeper stromal wounds that damage the main ciliary nerve bundles at the limbus (e.g. cataract surgery) or portions of the stromal nerve supply (e.g. penetrating keratoplasty) will inevitably produce longer lasting damage to the epithelial nerve supply. All those nerves distal to the incision will degenerate producing an immediate loss of corneal sensitivity. Collateral growth of new nerve sprouts from undamaged axons occurs, but is much reduced and nearly all of the new nerve growth develops from the stromal nerve stumps that pass through the wound scar. The re-modelling takes at least 60 days to occur, and the resulting innervation density will be lower than normal. The whole nerve supply architecture will remain distorted even after 30 months.[35,40] The recovery of sensitivity will be slow, and may never return to previous levels, depending on the type and extent of the damage.[41]

Measurement of Corneal Sensitivity

The Cochet-Bonnet Aesthesiometer (CBA) is the most common method for assessing corneal sensitivity.[2] Introduced in 1960, the instrument uses a thin nylon thread (diameter 0.12mm) to apply a direct mechanical stimulus to the corneal nerves. The technique relies on the resistance of the thread to bending. As the thread is gently pressed against the corneal surface, the force required to bend the thread is transferred to the cornea. A variation in the intensity of this stimulus is achieved by varying the length of the nylon thread, which in turn alters the force that must be applied to produce a bend in the thread – the shorter the thread, the greater the force required.

Although this instrument has become the standard method for assessing corneal sensitivity, there are major deficiencies in its design and this has led to the development of newer instruments.[42,43,44] The Draeger Electronic-Optic Aesthesiometer used a fine metal wire attached to a solenoid motor to apply varying stimulus intensities to the cornea.[45] It produced a stimulus similar to the CBA, but was less affected by ambient, environmental influences. The Belmonte Aesthesiometer uses pressurised air mixes, released at the cornea through an air-jet, to stimulate the corneal nerves.[46] In a series of experiments, this instrument has been used to show that the corneal nerve fibres respond to different stimulus modalities.[32,47,48] The Non-Contact Corneal Aesthesiometer (NCCA) uses a controlled air-pulse, of pre-determined pressure and duration, aimed at the anterior ocular surface to produce a localised cooling of the tear-film.[3,49] This cooling is transferred to the corneal epithelium where it is detected by the nerves. Mechanical techniques, such as the Cochet-Bonnet and Draeger Aesthesiometers, stimulate the A∂ fibres, whereas the NCCA, which produces cooling, predominantly stimulates the C fibres of the corneal innervation.

Corneal sensitivity can be assessed at various locations on the corneal surface, depending on the area of interest. For example, in LASIK a comparison is often made between the centre of the flap and the paracentral area of the flap adjacent to the hinge. However, for the majority of assessments, only the central cornea is measured.

Effects of Ocular Surgery on Corneal Sensation

All types of corneal surgery inevitably alter corneal sensitivity, since the corneal nerve supply will be damaged. The pattern of loss and recovery produced will depend on the type (linear incision, laser excision, thermal laser), depth, location and extent of wound made, since these influence the number of nerve fibres damaged or severed, and on the healing response of the patient. Other types of ocular surgery, such as retinal detachment repair or squint surgery, can also affect the corneal nerve supply.[6,9]

Cataract Surgery

In cataract surgery the cloudy lens is removed and a new intraocular lens is inserted through an incision at, or just anterior or posterior to the limbus. As the technique has evolved it has been possible for the length of the incision to be reduced.

Large Incision Cataract Surgery

In large-incision extracapsular cataract surgery the nucleus is removed intact, requiring a full-thickness incision 12-13mm long to be made circumferential to the limbus. Corneal sensitivity is severely reduced within the sector of the cornea central to the arc of incision.[50,51,52,53] The incision cuts through both the limbal nerve plexus and the large centripetal nerve fibres. As a result, the corneal epithelium and stroma supplied by these nerves becomes denervated. After such a major insult, the recovery of sensation is slow. Little improvement occurs by 1 year post-operatively, and even at 2 years, sensitivity is below normal in the majority of cases.[54,55,56,57,58]

Manual Small Incision Cataract Surgery

Manual small incision cataract surgery is a technique mainly used in the developing world. It also delivers the nucleus whole, as in extracapsular surgery, but through a smaller, more posterior incision in the sclera. Scleral incisions generally produce less effect on the corneal sensation than corneal incisions.[59] A straight or curved incision, 6-8mm long, is made 3-4mm behind the limbus, and a tunnel is fashioned to enter the anterior chamber at the level of Schwalbe's line. No significant reduction in corneal sensitivity occurs in the central or 4 mid-peripheral quadrants in the first 2 weeks postoperatively.[60]

Rarely, patients undergoing cataract extraction cannot be given an intraocular lens, in which case they may be fitted with a contact lens. Both rigid gas permeable lenses and soft lenses reduce corneal sensation,[6,61] so it is important to monitor corneal health in these patients as for any other contact lens wearer.

With the advent of phacoemulsification and foldable intraocular lenses, cataract surgery can be performed through a small 2-3mm tunnel incision. This still reduces corneal sensitivity, but over a much smaller area and is possibly followed by a quicker recovery.[62] This pattern is also evident in patients who undergo a surgical iridectomy, or a trabeculectomy which is performed in the anterior sclera. The smaller incision arc causes less nerve damage, and the sensitivity loss is generally limited to corneal locations at the central and peripheral cornea adjacent to the incision site.[63] Recovery to pre-operative normal levels usually occurs between 3 to 9 months.[56,64,65] This is delayed by the presence of dry eye disease prior to surgery[66] and accelerated with the topical applications of cyclosporine-A post-operatively to treat dry eye.[67] Recovery does not appear to be influenced by the mechanism of phacoemulsification occurring at the tip, as shown in a recent study that compared torsional technology to conventional longitudinal movement of the tip.[68]

Small Corneal Tunnel Incision for Phacoemulsification Surgery

Small incision cataract surgery is sometimes combined with limbal relaxing incisions (LRIs) to address pre-existing corneal astigmatism. These arcuate incisions at 90% depth can also produce a sector of reduced corneal sensation, in a similar way to more central arcuate keratotomies (see below).

Corneal Transplantation

The reduction in sensitivity following corneal transplantation depends upon the depth and thickness of the tissue removed and replaced. There is a spectrum of procedures ranging from full thickness penetrating keratoplasty (PK), through lamellar procedures in which the anterior or posterior layers are replaced, to overlays (tectonic grafts or epikeratophakia) with minimal removal of tissue. In all these procedures, the donor cornea inevitably has no innervation immediately after surgery.

Penetrating and Deep Anterior Lamellar Keratoplasty

In PK, removal of the central corneal button from the host will damage the remnant nerves in the adjacent host corneal tissue. Although the host corneal epithelium and the sub-epithelial nerve plexus quickly recover, re-innervation of the stroma takes longer.[69,70] In nerve regeneration following simple corneal incisions, new nerves grow towards the central cornea along the channels that the degenerated nerves had used. This speeds the regenerative process, and ensures that the new nerve ends don't have to burrow through the densely-packed, stromal collagen lamellae to establish a new path. However when the tissue is replaced, as in transplantation, the nerves that are present in the peripheral host cornea do not align with the channels in the graft. Re-innervation is severely restricted and any recovery of sensation occurs slowly, being initiated at the periphery, with a gradual progression towards the centre of the graft.[70,71,72,73,74,75] This pattern emphasises the importance of a fully-functional stromal nerve supply, in addition to the sub-epithelial plexus, in the recovery of a normal corneal sensitivity.

Although some re-innervation of the corneal epithelium over the graft must occur from the un-damaged peripheral corneal epithelium, this is insufficient to provide a full level of sensation. The earliest that central corneal sensitivity is detectable within the graft is 18 months post-operatively. In a study by Macalister et al,[76] 66% of subjects had no central sensitivity and only 9% had normal sensitivity at 4 years post-operatively. By 7 years, 39% were still without any measurable sensitivity. Rao et al.[72] found that the graft can remain completely anaesthetic, or hypoaesthetic, even 32 years after transplantation.

Two studies have shown that there is no difference in the rate of recovery of sensation between PK and deep anterior lamellar keratoplasty (replacement of 90-96% of corneal thickness). In both procedures, Lin et al[77] found that sensitivity was reduced 12 months post-operatively, and Ceccuzzi et al[78] reported a 91% recovery to pre-surgery levels after 2 years post-operatively. Darwish et al,[79] however, measured sensitivity changes using the NCCA (which stimulates C fibres rather than A∂ fibres) and found levels not significantly different to pre-surgery baseline at 12 months. This suggests that recovery rates differ between the different nerve fiber types. Al-Aqaba et al[80] performed a histochemical analysis on 12 failed full-thickness corneal grafts of mean survival duration of 6.4 years. The study found evidence of abnormal architecture and orientation of corneal nerves that persisted 14 years after surgery. It also showed that regenerated stromal nerves remained in the stroma, and did not contribute to epithelial innervation. Long-term alterations in corneal nerve morphology were confirmed in studies using *in vivo* confocal microscopy.[81,82] One study found that the sub-basal nerve density was still reduced 40 years post-surgery.[81] It seems that patients can expect some neural recovery, but that the majority will be left with a sub-normal level of sensitivity.[83,76]

Posterior lamellar keratoplasty

A posterior lamellar or endothelial keratoplasty is used in conditions where there is purely an insufficiency of the endothelium, such as Fuchs corneal dystrophy. The host Desçemet's membrane and endothelium are replaced by those from a donor, thereby retaining the neural structure of the anterior host cornea following surgery. Only two studies have investigated the effect of this procedure on corneal sensitivity. Kumar et al.[84] demonstrated relative preservation of corneal sensitivity after Descemet stripping automated endothelial keratoplasty (DSAEK) technique. However, Ahuja et al.[85] found sensitivity was reduced compared to pre-operative levels using a similar surgical technique (Descemet stripping endothelial keratoplasty, DSEK). The same study found that, although sensitivity recovered to pre-surgery levels within 3 years, it did not improve to levels similar to normal corneas.[85] This suggests that nerve loss in the host periphery prior to surgery due to persistent oedema or scarring was long-lasting.

Patients awaiting corneal transplant and suffering from symptomatic bullous keratopathy may have recurrent corneal erosions treated with anterior stromal puncture. This promotes new adhesion complexes between the epithelium and underlying stroma from the secretion of extracellular matrix proteins.[86] In these cases, there is relief of symptoms, particularly pain, presumably from fewer bullae ruptures. Interestingly, corneal sensitivity improves following the procedure,[87] suggesting recovery in nerve morphology with the improved corneal surface.

Arcuate Keratotomy

An arcuate keratotomy incision is a short (3-7mm) circumferential corneal incision addressing astigmatism, for example following corneal transplantation. It is made at a diameter of 6-7mm and to only 90-95% depth. There is a sectoral loss and recovery of sensitivity confined to the portion of the cornea central to the incisions, as in cataract surgery. Shivitz and Arrowsmith[88] found that, with an incision of less than 80% corneal thickness, 72.8% of patients had a normal sensitivity after 1 year, whereas with 90% corneal thickness incisions, no recovery of sensation was measured after the same time period. Increasing the number of incisions also slows the recovery. However, in general, corneal sensitivity returns to normal levels by 1 year post-operatively.[38,88,83,89] Studies involving animals have shown the faster recovery of experimentally damaged nerves with the topical application of therapeutic agents, such as semaphoring 3A inhibitor,[90] pituitary adenylate cyclase-activating polypeptide,[91] macrophage migration inhibitory factor,[92] nerve growth factor,[93] drug FK962,[94] and pigment epithelial-derived factor plus docosahexaenoic acid.[95]

Tectonic Overlay Grafts and Epikeratophakia

A tectonic corneal graft is performed when a patch of donor tissue is transplanted onto the surface of a host cornea which has an actual or threatened perforation. This typically occurs as a result of severe corneal inflammation or previous infection, and the aim is to restore the integrity of the globe. There are no studies of corneal sensitivity after such procedures, but we can extrapolate from studies on epikeratophakia and cryo-keratomileusis. Epikeratophakia is a refractive surgery technique that involves the grafting of a lenticule of donor tissue to the anterior surface of the cornea, but is rarely performed these days. Cryo-keratomileusis is similar, but involves the removal, freezing, re-shaping and re-attachment of a portion of the host cornea. Following epikeratophakia, the new anterior surface has no nerve supply and a new innervation must develop in much the same way as that after penetrating keratoplasty. As a result, the pattern of sensitivity recovery measured is much the same.[96,97,98,99] With cryo-keratomileusis, the re-shaped corneal button has undergone freezing in addition to removal from the donor, both of which will have destroyed the corneal nerves. Re-innervation of the corneal button and sensation recovery will also be limited, in a similar manner to keratoplasty.[99,100,101,102,103] For example, at 5 years post-epikeratoplasty, only minimal corneal sensitivity was measured in the central zone, but by 10 years post-operatively it had significantly returned. However, only 17.7% of eyes at 10 years had a normal central corneal sensitivity.[104] Epikeratoplasty may also include a centrally-placed keratectomy, but no difference in loss and recovery has been found between those patients with a keratectomy and those without.

Radial Keratotomy

In radial keratotomy, typically 4-8 radial incisions are made in the cornea to flatten its centre to treat myopia. The degree of flattening depends on the type, depth and number of incisions made, and these factors also define the extent of sensitivity loss.[38,41,105] The normal radial incisions are parallel to the axis of the radiating stromal nerve fibres and so produce minimal damage.

Intra Corneal Ring Segments

This surgical technique offers a reversible method for the correction of low myopic refractive errors, but is now more commonly used to stabilise the corneal profile in cases of progressive keratoconus. Small PMMA rings are inserted into a channel at two-thirds depth in the mid-peripheral stroma to produce an alteration to the shape of the anterior corneal surface. The epithelial nerves are not affected, and the stromal nerves are untouched superficial and deep to the ring segments. A small 2-3mm radial incision in the cornea allows insertion, but this produces no long-term reduction in corneal sensation, and sensitivity returns to pre-operative levels after 1 year.[106]

Excimer Laser Surface Procedures

The excimer laser can remove tissue from a large area of the superficial cornea with extreme precision, and with minimal damage to adjacent tissue. It therefore affects the corneal nerve supply in a very different way to a scalpel incision.[11,107,108,109] It has a role in refractive surgery, and is used to treat certain corneal surface diseases.

Photo-refractive Keratectomy

Photo-refractive keratectomy (PRK) uses excimer laser technology to directly alter the corneal refractive power over a large surface area. Myopic PRK procedures remove central corneal tissue over a typical treatment zone of 8-8.5mm diameter to produce a saucer-shaped excision that is deeper centrally than peripherally. Hyperopic PRK has a wider 'ring-donut' shaped treatment zone approximately 9mm in diameter. The majority of tissue is removed in the mid-peripheral zone, with peripheral blending. In both procedures, the corneal epithelium is manually debrided in the treatment zone, and this removes all of the sensitive epithelial nerve supply. The excimer laser then ablates the exposed stroma to a depth (10-150μm) dependent on the dioptric correction required and the diameter of the ablation zone.[110] This procedure removes a significant proportion of the anterior stromal nerve supply. As a result, when the corneal epithelium has grown back over the exposed stroma, any re-innervation that takes place can only do so from the peripheral un-touched epithelial supply and the remnant stromal supply deep to the excision.

The majority of research into the pattern of corneal sensitivity loss and recovery after photo-refractive keratectomy has been performed using the CBA or another similar mechanical stimulus, and have therefore considered the surgical effect on the A∂ fibres. There have only been a limited number of studies that have assessed the effect on the C fibres using a thermally-cooling stimulus. The vast majority of studies have also only considered myopic PRK rather than hyperopic PRK.

Myopic PRK

The majority of studies on myopic PRK used mechanical stimuli and found a short-term reduction in sensitivity.[83,111,112,113,114,115] Sensitivity returned to pre-operative levels by 6 months or even earlier, unless the ablation depth was very deep (approximately 100μm, or corrections greater than -6.00D). For the majority of refractive errors corrected, where the ablation depth was less than 100μm, there was no relationship between the pattern of corneal sensation loss and recovery and ablation depth. In contrast, a study that assessed corneal sensitivity to a thermally-cooling stimulus, found that sensitivity did not recover until 1 year after surgery.[116] This difference may be related to the different neural architecture of the two nerve types that mediate the two stimuli, and how this architecture is changed after PRK. An early histological study in rabbit eyes[117] and *in vivo* confocal microscopy studies on human eyes[118-120] have shown the recovery of corneal innervation after PRK to be disorganised. The crude lattice of nerves that re-innervates the corneal epithelium may provide a network more readily able to detect the mechanical surface deformation stimulus of the CBA. In contrast, the cooling stimulus of the NCCA may require a more complete re-organisation of the corneal nerves, with a network of fine C fibre nerve endings arranged close to the epithelial surface. By necessity this takes longer, and so recovery of the C fibre sensation would take longer too.

Hyper-sensitivity after PRK surgery has been reported in rabbits, which persisted for up to 10 weeks after surgery.[121] No similar findings have been reported for studies on humans. However, hyper-sensitivity of regenerating corneal nerve C fibres has been reported,[122] and a study by Gallar et al[123] found hyper-sensitivity following LASIK. This latter finding has been attributed to the greater stimulus resolution possible with the Belmonte aesthesiometer. It is therefore possible, that there could be some short-term (1-2 weeks) hyper-sensitivity following PRK if measurements were made using a sufficiently sensitive device.

Hyperopic PRK

Only one published paper has considered the effect of low-powered hyperopic PRK correction on corneal sensation.[124] This study used the cooling stimulus of the NCCA to assess the loss and recovery of C fibre mediated sensitivity. Although a similar result might be expected, to that found with myopic PRK, sensitivity was found to not change significantly after surgery. This unusual result can be explained by again considering the effect of surgery on the corneal architecture. Unlike myopic PRK where a large, deep central ablation occurs, in hyperopic PRK the central corneal stroma is preserved and a peripheral ring is ablated. Since the ablations attempted in the study where not deep (2-4 Dioptres), the deeper stromal nerve supply to the central cornea was most-likely preserved. Even with the debridement or ablation of the central epithelial nerve supply, the virtually un-touched stromal nerve supply is sufficient to maintain corneal sensation. However, for this to be confirmed, measurements of corneal sensation at both the central cornea and at the area of cornea where maximum ablation depth occurred would need to be taken. The authors also suggested that the short-term hyper-sensitivity of regenerating C fibres may have masked some of the initial sensitivity loss following corneal epithelium removal.

Photo-therapeutic Keratectomy

One other important use of excimer laser ablation is for photo-therapeutic keratectomy (PTK). This procedure produces a broad excision of uniform depth, or masking fluid can be used during the removal of proud irregularities. It is used to treat superficial corneal pathological conditions and has a wide variety of indications including removal of band keratopathy or superficial scars and improving epithelial adhesion in recurrent erosion. No attempt is made to alter the patient's refraction. Removal of abnormal tissue can lead to an improvement in corneal sensation after PTK, both in terms of increased sensitivity and a reduction in discomfort. Creation of a smoother corneal surface may also improve tear film quality and conjunctival squamous metaplasia.[125] Patients with herpetic corneal scarring commonly have reduced corneal sensitivity before the procedure, and therefore unsurprisingly, corneal sensitivity measurements are slightly lower at 6 months compared with other patients.

Excimer Laser Flap Procedures

In refractive procedures under a flap, a layer of epithelium or epithelium plus stroma is raised before the excimer laser refractive correction is applied to the stromal bed, and then the flap is replaced. In contrast to surface treatments, this provides the opportunity for some innervation of the surface layers to remain intact.

Laser in-situ Keratomileusis

Laser *in-situ* keratomileusis (LASIK) is a development of PRK, in which a corneal flap is produced that includes superficial stroma as well as epithelium. A micro-keratome is used to cut through the superficial stroma, creating a thin (160-180μm thick) flap. This is then peeled back, exposing the underlying stroma for ablation in a similar way to PRK. The flap is then carefully replaced over the treatment zone. An alternative method for the flap creation is the use of a femtosecond laser, creating a thinner (90-100 μm thick) flap. Further details discussed below.

From the point of view of corneal innervation, the micro-keratome cuts through the epithelial nerve supply in the periphery of the flap, and the deep nerve supply across the base of the flap. The only exception to this is in the 45°-60° sector central to the hinge, where the epithelial supply is preserved. This is in contrast to the formally-used procedures of epikeratophakia and cryokeratomileusis, where the flap was totally removed without a hinge and no nerve supply to the flap was retained. In LASIK, the laser ablation will remove the central portion of the stromal nerve supply to an even greater depth.

This more complex surgical procedure has produced a mixed set of results. The majority of published studies have found less reduction in sensitivity following LASIK than with PRK.[126,127,128,129,130,131,132,133] However, this reduction in sensitivity has a longer duration, up to about 6 months.[114,115,129,134,135,136] Several studies found a greater initial loss of sensitivity with deeper ablations, but after 6 months this difference no longer persisted.[137,138,139] Topical application of cyclosporine[140] and protein-free calf blood extract[141] have been shown to speed the recovery of corneal sensitivity following LASIK.

This outcome following LASIK can be attributed to the greater preservation of the corneal epithelial and anterior stromal innervation via the hinge of the corneal flap. The sector central to the hinge has some reduction in corneal sensation, but this loss is not as severe, and recovery occurs more quickly, than the centre of the flap and those portions of the flap furthest from the hinge.[128,142,143] There is some disagreement on the influence of hinge position on corneal sensitivity, with studies showing either less reduction,[142,143] no difference,[144,145,146] or greater reduction[134] in nasal or temporal-hinged eyes compared to superior-hinged eyes. In addition, Donnenfeld et al[142] showed greater loss with a narrower hinge, while Mian et al[145] noted hinge angle and thickness has no effect on sensitivity loss. Nevertheless, it is likely that the prolonged depression in sensitivity reflects the need of the regenerating neurones to re-populate the stromal flap rather than just the new epithelium. As such, it reflects the problems of re-innervation encountered with corneal transplantation. In general, corneal nerve regeneration after LASIK follows a slower pattern than that found after PRK, with a greater delay in the development of new nerve fibres. However, as the nerve fibres become better organised, sensitivity returns to normal levels.[150,128,147]

In recent years, alternative methods to conventional LASIK have developed with the advent of the femtosecond laser for refractive surgery. When used in place of the micro-keratome for flap creation (i.e. FS-LASIK), femtosecond laser cuts have been shown to produce better uniformity and predictability of the flap thickness than conventional LASIK,[148] which results in less damage to the corneal nerves.[149,150] In the femtosecond lenticule extraction (FLEx) technique, the femtosecond laser is used to create a lenticule within the stroma that is removed with forceps after the flap is lifted. In small incision lenticule extraction (SMILE), the lenticule is removed through a 3-4mm opening in the peripheral cornea, rather than a full flap. This has been shown to produce less sub-basal nerve density loss, with faster recovery of corneal sensitivity,[151] when compared to FS-LASIK[152,153,154] and FLEx-treated eyes.[155,156,157] Less reduction in corneal sensitivity and faster recovery is found when the standard 70-degree angled laser side cut flap is replaced with an inverted 130-degree cut,[158] presumably because of improved wound healing and apposition of severed nerves from a more stable flap post-surgery.[159]

Laser Sub-epithelial Keratomileusis

Laser sub-epithelial keratomileusis (LASEK) was developed for patients considering refractive surgery who have low myopia, thin corneas, or a pre-disposition to flap trauma. LASEK combines elements of both PRK and LASIK techniques. The hinged flap that is made and restored following ablation is only a thin epithelial sheet. It is separated from the cornea, using either the application of an alcohol solution,[160] or an epikeratome.[161] The excimer laser ablation is then applied to the stromal surface in a similar way to PRK. The deeper stromal nerves are thus spared during the ablation process. Disruption to nerve fibres in the sub-basal, sub-epithelial and anterior stromal layers still occurs following surgery, with the reduction in corneal sensitivity correlating with ablation depth.[162,163,164] Two studies showed the initial reduction in corneal sensitivity was less and recovery faster after LASEK than conventional LASIK.[165,166] Another study involving LASEK showed corneal sensitivity recovered faster when the flap was created with an epikeratome compared to using alcohol solution.[150] Darwish et al,[167] however, found no such difference between LASIK and LASEK when sensitivity was measured using the NCCA. In addition, Patel et al[168] found no difference in sensitivity changes between flaps created with the femtosecond laser and the microkeratome using the Belmonte aesthesiometer. Therefore, it appears that LASIK has a greater impact than LASEK on the damage and regeneration of A∂ fibres, whereas there is no difference between the two techniques on recovery of C fibers.

Dry eye is a common complaint following all types of photorefractive surgery. Several studies have speculated that post-operative reduction in corneal sensitivity disrupts the feedback loop for basal tear production, leading to diminished lacrimal secretion and poor tear film, which produces dry eye symptoms.[169,170,171,172,173]

Collagen Cross-Linking

Cross-linking is a relatively new procedure that can delay or prevent the progression of keratoconus. Debridement of the central cornea epithelium is followed by topical application of riboflavin solution and irradiation of the exposed corneal stroma with Ultraviolet A radiation.[174] This results in chemical bonding between adjacent collagen lamellae to prevent slippage leading to ectasia. Many studies show a significant loss of corneal sensitivity immediately after surgery, followed by a gradual recovery towards pre-operative levels over the ensuing 6 to 12 months.[175,176,177,178,179,180] Nerve morphology is affected over a similar time course. One study showed that sub-basal nerve density recovers to pre-operative levels after 7 to 12 months. However, normal levels were still not reached by 5 years post-operatively.[181] Less reduction and more rapid recovery in corneal sensitivity is achieved when the epithelium is not removed, which is the recommended procedure for patients with less than 400 μm corneal thickness.[182]

Cyclophotocoagulation

This procedure is used to selectively damage the ciliary body to decrease production of aqueous humour, as a treatment for glaucoma. It is accomplished by directing the beam from a neodymium:yttrium-aluminium-garnet (Nd:YAG) laser perpendicular to the sclera at a point 1-2mm posterior to the limbus. The beam passes through the sclera and is absorbed by melanin in the pigmented tissue.

Pre-existing corneal conditions (e.g. long-term use of topical beta-blockers, corneal surgery with large incision, some corneal dystrophies, high myopia, anterior uveitis or diabetes mellitus)[183] may pre-dispose the patient to neurotrophic cornea defects. In severe conditions, this can lead to corneal perforation.[184] However, changes in corneal innervation or sensation can be reduced by good patient selection and avoidance of the 3 and 9 o'clock limbal regions.[185] Subjects in this study were pre-selected to exclude corneas with previous complications, diabetes, rheumatoid arthritis, amyloidosis, or herpetic eye disease, and this may have removed those 'at-risk' groups that developed neurotrophic defects observed in other studies. Not exceeding the recommended laser power level of 2500mW for 2.5 secs has also been suggested to prevent neurotrophic keratopathy development as a result of nerve damage.[183]

In contrast, a study in dogs found a 27.4% overall reduction in corneal sensitivity in all areas of the cornea, from pre-op levels after 2 weeks.[186] No measurement was made of recovery time.

Immuno-histochemical analysis of the nerve fibres reported a loss of the major nerve bundles, suggesting that the nerves in the area of laser application are destroyed.

Retinal Detachment Surgery

The impact of retinal detachment surgery, which commonly involves pars plana vitrectomy, is not immediately apparent. However, a significant decrease in sensitivity has been found in eyes treated with an encircling band. No significant decrease was found in eyes treated with localised radial or circumferential silicone or sponge explants alone. The mechanism is unclear, but may be due to surgically induced inflammation of the ciliary nerves as they course between the sclera and choroid, or to damage produced by compression of the nerves from the scleral buckle or by surgical perforation. There may be a contribution from post-operative inflammation and surface irregularity as an encircling band requires a full peritomy, whereas local explants require only sectoral incisions of the conjunctiva at the limbus. It is also not clear whether the effect on sensitivity is long-term, as the pattern of recovery does not correlate with time post-operatively. However there may be a lot of variations in the damage to extraocular tissue during similar operations. Most studies find that sensation eventually returns to normal levels.[187,188,189,190] In eyes treated with circumferential laser photocoagulation, corneal sensitivity may be reduced for 6 months after surgery.[191] Damage is thought to occur to ciliary nerves in the supra-choroidal space.[192,193] One paper has raised the possibility of whether the fine nerves in the sub-basal nerve plexus could be damaged as the laser passes through the cornea, but there is no pigment in the cornea to absorb the energy, and the rays are not focussed there.[191]

Strabismus Surgery

Ocular discomfort and dryness is a commonly-reported symptom after strabismus surgery. In the first study to explore the relationship between ocular sensitivity and symptoms,[194] no change in central corneal sensation was observed. However, conjunctival sensation was reduced after surgery, which persisted during the 3 months duration of the study. This effect was suggested to be due to electro-cauterisation of the circum-limbal blood vessels damaging the peri-limbal nerve fibres. A later study found goblet cell density was reduced up to 2 months after surgery, resulting in instability of the ocular tear film and hence another possible cause of ocular irritation symptoms.[195] A more recent study found more dry eye symptoms and tear film instability with a limbal incision technique than fornix incisions.[196] Central corneal sensitivity was also reduced following limbal incisions, whereas it was unchanged with fornix incisions, which suggests limbal incisions cause partial denervation of the cornea. Despite the detected adverse effects, all studies found most ocular signs and symptoms recovered to baseline levels within 2-4 months post-surgery.

Conclusions

Transient reductions in corneal sensitivity have been recorded after most types of corneal surgery. Incisions into the ocular surface damage the complex network of superficial nerve fibres and terminals, with greater reductions in sensitivity seen with a greater arc length and depth into the mid-stroma, and if incisions are circumferential rather than radial. Incisions or debridement of the corneal epithelium will result in temporary loss of corneal sensitivity from the damage or removal of the sub-basal and sub-epithelial nerve plexi. Recovery of corneal sensitivity from such procedures to pre-operative levels is generally expected within 6 months for mechanical stimuli, or up to 1 year for thermal or chemical stimuli. Circumferential stromal and limbal incisions, however, cut through deeper trunks of the neural supply to the corneal surface. Although sensitivity loss is confined to the sector of the cornea central to the arc of incision, recovery is generally slower than epithelial procedures. Procedures involving the transplantation of corneal tissue show the slowest recovery due to a lack of alignment of nerve channels between host and donor tissue. A sub-normal level of sensitivity is commonly observed after many years post-operatively. Other types of surgery, such as for squint or retinal detachment, can alter corneal sensitivity by affecting the nerves as they travel towards the cornea. In such cases, the severity and recovery time are generally less in comparison to procedures that involve incisions to the ocular surface.

To summarise, all types of ocular surgery can affect corneal innervation. However, for the majority of patients, corneal sensitivity can be expected to return to normal levels with time, and only when the most severe damage to the corneal innervation occurs will there be a permanent reduction or absence in corneal sensitivity. Nevertheless, a quick recovery of the corneal nerve function to normal levels is important in the continuing maintenance of a healthy cornea, as several cases of surgically induced neurotrophic epitheliopathy have been recorded,[18,187] as well as secondary effects on the tear film and contact lens tolerance. It is therefore important that clinicians are aware of this to provide appropriate management, especially in the presence of pre-existing disease that might delay or influence recovery of corneal sensation.

Method of Literature Search

A systematic search was completed using several scientific publication databases. Articles were selected for inclusion that evaluated any aspect of corneal sensation change, as a result of ocular surgery, and each article was critically assessed for the contribution it gave to the understanding of this area. For articles published between 2000 to 2017, articles relevant to corneal sensitivity, ocular surgery interventions, and measurement techniques were found using the search terms outlined in the PubMed search strategy (available on request), which provides the detailed search strategy in PubMed and Ovid Embase. The languages of focus were: English, French, German, Polish, Japanese, Danish, and Russian, however, the database searches were not limited to these, and other languages were considered. Articles prior to 2000 were searched through Medline, ISI Web of Science, and other databases.

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Figure Legends

Figure 1: Schematic diagram of corneal innervation showing a cross-sectional and layered views from the limbus to the central cornea and arrangement of the A delta and C fibres within the epithelium.