Preventing secondary cataract and anterior capsule contraction by modification of intraocular lenses

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Advances in intraocular lens (IOL) design have led to the use of lenses with improved performance including tinting, asphericity, multifocality and accommodation. To maximize the visual performance of these IOLs, postoperative complications such as secondary cataracts and anterior capsule contraction must be prevented. Various types of secondary cataracts may occur, each associated with complex biological reactions. Different design configurations, including square-edge IOLs, have been used to prevent secondary cataracts and anterior capsule contraction, but these have not been successful in sufficiently eliminating these complications. We have found that surface modification of IOL surfaces chemically improves surface quality and is also useful in preventing secondary cataracts and anterior capsule contraction. The UV/ozone treatment that we used as a surface modification method is a simple and highly effective method with no safety issues regarding materials following treatment. The combination of square-edge design and surface modification may be able to completely eliminate these postoperative complications.

KEYWORDS: anterior capsular contraction • cell adhesion • drug delivery • intraocular lens • postcataract surgery complications • secondary cataract • square edge • surface modification • UV/ozone

Biological reactions after cataract surgery

There are several types of secondary cataracts and anterior capsule contraction, each with a different mechanism and time of onset (Figure 1) [2,3]. Early after surgery with continuous curvilinear capsulorhexis (CCC), lens epithelial cells (LECs) are in contact with the aqueous humor, leading to a wound healing reaction with the IOL (implanted artificial material). The residual LECs begin to migrate and proliferate, causing a foreign body reaction with production of macrophages and various cytokines [4,5]. During the first few months after surgery, early secondary cataracts can develop due to fibroblast opacification from collagen and fibronectin derived from residual LECs near the anterior capsulorhexis. This fibrous opacification is due to fibroblast-like transformation of LECs and is called epithelial–mesenchymal transition (EMT) [6]. TGFβ/Smad signals play a role in EMT. The...
fibrous opacification changes lead to contraction and narrowing of the anterior capsule opening, which causes IOL displacement and deterioration in visual performance. The fibrous opacification can also extend to the posterior capsule, leading to early development of a postoperative secondary cataract and poor visual acuity. Approximately 1 month after surgery, the lens capsule contracts to the configuration of the IOL, the lens capsule and IOL adhere, capsular bending occurs, and the wound healing reaction subsides. At a later stage after surgery, proliferated lens epithelial cells migrate and differentiate. A donut-shaped remnant of cells may form (Soemmering’s ring), and granular opacification due to so-called Elschnig pearls may occur. Another late postoperative complication is capsular block syndrome, which occurs due to accumulation of a white milky substance between the posterior capsule and IOL.

IOL: Intraocular lens.
IOL characteristics, anterior capsule contraction & secondary cataracts

Secondary cataracts are the most common postcataract surgery complication, with a 5-year rate ranging between 18.4 and 38.4% [8]. What types of IOLs tend to be associated with a higher incidence of secondary cataracts? An important issue is the type of IOL material. Along with technical advances in cataract surgery, there have been advances in different types of materials used for IOLs. From polymethyl methacrylate (PMMA), the original material, to more current softer materials like silicone, hydrophobic acrylic and hydrophilic acrylic, each material has certain characteristics and is associated with various biological reactions [9]. PMMA is the oldest material used and is known for long-term stability. It is relatively inexpensive, but the incidence of secondary cataracts tends to be high. Hydrophobic acrylic (acrylic foldable lens) is increasingly being used as an IOL material and, as will be discussed later, the square-edge optic design and material characteristics are associated with a low incidence of secondary cataracts. However, disadvantages include the high frequency of small bright spots, so-called ‘glistening’, in the IOLs [10] and increasing of light scattering on surface of the IOLs [11]. Silicone is also frequently used as an IOL material due to the relative ease of lens processing and high stability. But a drawback is the relatively high incidence of anterior capsule contraction [12]. In addition, silicone tends to adhere to liquid silicone and is thus not suitable for vitreo-retinal surgery. The incidence of secondary cataracts with silicone is reported to be low in some studies [13], but higher (26.6%) than with hydrophobic acrylic (6.5%) in other studies [14]. The main component used in hydrophilic
acrylic for soft contact lenses is 2-hydroxyethyl methacrylate (HEMA). Although this is thought to have a high biocompatibility because it is a gel material, it is associated with marked LEC proliferation and a high incidence of secondary cataracts. In addition, calcium deposition also presents a major problem.

Another factor related to secondary cataract formation is configuration of the IOL optic. As reported by Nagata et al. and Nishi et al., it is well known that design of an IOL optic with a sharp edge can reduce the incidence of secondary cataracts [15,16]. With a sharp IOL optic edge, the lens capsule contracts during the process of postoperative wound healing, forming a strong boundary (capsular bend) between the lens capsule and IOL edge. Thus, even if residual LECs proliferate and migrate, this is prevented by the IOL edge (contact inhibition), which makes it difficult for LECs to extend to the posterior capsule. This results in a lower incidence of secondary cataracts. It is well-known that sharp-edge configuration of a hydrophobic acrylic IOL inhibits the development of secondary cataracts, but with different materials such as silicone [17] and PMMA [18] as well, sharp optic edges also reduce the incidence of secondary cataracts. The time for completion of capsular bending is also related to the development of secondary cataracts and IOL materials affect the rate of capsular bending. Capsular bend formation occurs more rapidly with hydrophobic acrylic and silicone, but is slower with PMMA and hydrophilic acrylic IOLs [19]. There is a corresponding effect on the clinical incidence of secondary cataracts.

Figure 3. Effect of surface modification on adhesion. There is some LECs adhesion on the untreated plate, but absolutely no cell adhesion on the 2-methacryloyloxyethyl phosphorylcholine coated plate. However, on the UV/ozone treated plate, there is greater LECs adhesion than on the untreated plate. LEC: Lens epithelial cell.

Figure 4. Effect of surface modification on preventing secondary cataracts (central tissue of posterior capsule). The effect of surface modification on inhibition of secondary cataracts was evaluated in an experimental model using white rabbits. At 2 weeks after surgery, tissue under the IOL at the center of posterior capsule was examined histologically. In the control and 2-methacryloyloxyethyl phosphorylcholine groups, multiple layers of LECs are present, with progression to secondary cataract formation. However, in the UV/ozone treated group, only a thin layer of LECs is present, with minimal secondary cataract formation. LEC: Lens epithelial cells; MPC: 2-methacryloyloxyethyl phosphorylcholine.
IOL configuration also has other effects on the development of secondary cataracts. The greater the IOL is pushed towards the posterior capsule, in other words, the greater the angle formed between the optic and haptics, the stronger the compression is against the posterior capsule. This seems to reduce the incidence of secondary cataracts, but there are no clear-cut data regarding this relationship [20]. When total IOL length is longer, the pressure of the IOL against the posterior capsule is also greater, which would also be expected to prevent the development of secondary cataracts. But if the IOL is too large, wrinkles of the posterior capsule may allow migration of LECs into the posterior capsule, thus causing secondary cataracts [21]. A lower incidence of secondary cataracts with IOLs less than 13.5 mm in total length has also been reported [22]. The relationship between optic size and secondary cataracts has also been investigated. A comparison between 5.5 and 6.0 mm hydrophobic acrylic IOLs showed a lower incidence of secondary cataracts with the 6.0 mm optic [23]. In a rabbit study, secondary cataracts were less likely to develop with a 5.5 mm IOL compared with a 7.0 mm IOL [24]. This demonstrates the effects of optic size on development of secondary cataracts.

Other studies have not demonstrated a relationship between IOL optic edge configuration and anterior capsule contraction, but smaller CCC size may increase anterior capsule contraction [25]. In addition, residual LECs also play a role in anterior capsule contraction and the effects of removing LECs on inhibition of anterior capsule contraction have been investigated [26]. However, like secondary cataracts, postoperative complications of anterior capsule contraction are still a problem that has not yet been adequately eliminated.

Drug delivery & surface modification

The physical methods such as the square-edge IOL have limitations and have not completely inhibited secondary cataract. On the other hand, many studies have demonstrated the inhibitory effects of chemical methods on secondary cataract. These methods include instillation of eyedrops [27,28] and perfusion of the lens capsule with a drug [29], but they are experimental and have not been put to practical use. Drug release from the IOL has also been studied as a chemical method of inhibiting secondary cataract, and processing of the IOL with a ring or stick made of materials allowing sustained drug release has been performed [30–32]. There are some chemical methods of inhibiting secondary cataract that have not yet been clinically used.

Figure 5. Effect of surface modification on preventing secondary cataracts (peripheral tissue of the lens capsule). This shows the peripheral tissue 2 weeks after surgery. In the control and MPC groups, marked proliferation of residual lens epithelial cells is observed, but with UV/ozone treatment, cell proliferation is inhibited.
Recently, a 2-methacryloyloxyethyl phosphorylcholine (MPC) coating was produced, which decreased adhesion of platelet, macrophage, lens epithelial cells and bacteria [36,37].

The AcrySof IOL® (Alcon) has a lower incidence of secondary cataracts [39]. The thickness of Lens epithelial cells proliferation was measured in the center of the posterior capsule. Thickness was 61.9 ± 35.2 µm in the untreated, 78.6 ± 19.6 µm in the MPC, but only 16.7 ± 9.1µm in the UV/ozone group. Multiple comparison analysis showed statistically significant inhibition of secondary cataract formation in the UV/ozone treated group.

* p < 0.05 (multiple comparison analysis).

** Figure 6. Quantification of secondary cataract formation (center of posterior capsule). The thickness of Lens epithelial cell proliferation was measured in the center of the posterior capsule. Thickness was 61.9 ± 35.2 µm in the untreated, 78.6 ± 19.6 µm in the MPC, but only 16.7 ± 9.1µm in the UV/ozone group. Multiple comparison analysis showed statistically significant inhibition of secondary cataract formation in the UV/ozone treated group.

MPC: 2-methacryloyloxyethyl phosphorylcholine.

Surface modification is another chemical method for changing characteristics of the surface of IOls. Heparin surface modification (HSM) decreases adhesion of cells and inflammations after cataract surgery. However, a recent study shows the ratio of posterior capsular opacification is high using HSM. Recently, a 2-methacryloyloxyethyl phosphorylcholine (MPC) coating was produced, which decreased adhesion of platelet, macrophage, lens epithelial cells and bacteria [36,37]. The AcrySof IOL® (Alcon) has a lower incidence of secondary cataract formation [19], thus suggesting that a role is played by plasma treatment that increased adhesion force on the surface of the IOL [38,39]. However, relations between surface modifications and preventions of secondary cataract have not been well clarified.

Linnola et al. have proposed a ‘sandwich theory’ on the inhibition of secondary cataract formation after cataract surgery [40]. They have shown that if the IOL posterior surface is adherent to the posterior capsule early after surgery through LECs, adhesive proteins such as fibronectin, hydronectin and laminin, as well as extracellular matrix such as collagen IV, then LECs proliferation can be inhibited and secondary cataracts can be prevented. Based on this hypothesis, we have attempted to prevent secondary cataract formation by increasing adhesion between the IOL and posterior capsule. This involves IOL surface chemical modification to increase adhesion of the IOL surface, thus producing stronger adhesion between the IOL and posterior capsule. We actually attempted to inhibit the proliferation and migration of LECs and prevent the development of secondary cataracts [39]. The material selected for these experiments was hydrophobic acrylic, which is increasingly being used as a soft IOL material. Hydrophobic acrylic has a glass transition temperature (Tg) of approximately 15°C and extensive cross-linking occurs. Therefore, unlike silicone, which has less cross-linking, where the effects of surface modification can be lost, the effects of surface modification of hydrophobic acrylic are more likely to be maintained over a long period [41]. Our method of choice for surface modification was UV/ozone treatment (Figure 2). UV/ozone treatment consists of the use of UV and sterilizing light energy to produce active oxygen.

Using these active species such as ozone, surface characteristics are improved, including the generation of OH and COOH substituents, which increases wettability and adhesion [42]. To confirm improvement of the IOL surface, we performed surface analysis (ESCA analysis) [43]. This showed generation of new OH substituents, COOH substituents and nitrogen-containing substituents on the IOL surface, thus confirming chemical changes of the material in the uppermost layer of IOL. To examine the effects on adhesion produced by surface modification, we also used MPC as an opposite treatment to decrease surface adhesion. This MPC polymer has a cell membrane-like structure that is known to inhibit cell and protein adhesion. After these two different types of surface modification of the hydrophobic acrylic material, we compared wettability using a contact angle test (sessile drop method) [44]. The contact angle was approximately 90° for the untreated sample, approximately 65° for the UV/ozone-treated sample, and approximately 105° for the MPC-coated sample. This demonstrated differences in wettability. To compare cell adhesion of materials with each type of surface modification, we isolated and cultured LECs from white rabbits and mixed the LECs with minimum essential medium (MEM). Then we dripped the mixture of LECs and MEM that was created in advance on to acrylic plates that were either untreated or treated by the two different surface modification procedures. These were cultured for 6 h, washed, fixed in formalin, stained with hematoxylin and eosin to visualize the cells, then LECs adhesion was examined. As shown in Figure 3, there was some LECs adhesion on the untreated plate, but absolutely no LECs adhesion to the MPC-coated plate. However, on the UV/ozone treated plate, there was clearly greater LECs adhesion than on the untreated plate. Our experimental findings suggested that UV/ozone treatment would be useful in increasing adhesion between an IOL and the posterior capsule.

Surface modification & prevention of secondary cataracts

To evaluate these effects on prevention of secondary cataracts, IOls (VA-60BB, Hoya) currently used in clinical practice were treated as stated above with UV/ozone to increase adhesion and MPC to decrease adhesion. Phacoemulsification was performed in white rabbits (aged 8 weeks, with a weight of approximately 2 kg), and the IOls were implanted. At 2 weeks after surgery, histologic examination of LECs proliferation
Surface modification of IOLs

Review

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Surface modification and prevention of anterior capsule contraction

In addition to inhibitory effects on secondary cataract formation, the effects of surface modification on anterior capsule contraction were also evaluated. As described previously, phacoemulsification was performed in white rabbits (aged 8 weeks, weighing approximately 2 kg). At 1 and 2 weeks after surgery, slitlamp examination of the anterior segment was performed, photographs were taken with an

**Figure 7. Effect of surface modification on anterior capsule contraction.** Postoperative anterior capsule contraction was evaluated using a Nidek EAS-1000. In the untreated and UV/ozone groups, a large anterior capsule opening was maintained, but in the MPC groups, anterior capsule contraction was already present after 1 week, with contraction of the anterior capsule opening.

MPC: 2-methacryloyloxyethyl phosphorylcholine.

(hematoxylin and eosin staining) at the center of the posterior capsule was performed (Figure 4). In the untreated and MPC coated groups, multiple layers of LECs were present on the posterior capsule, with progression to secondary cataract formation. However, in the UV/ozone treated group, only a thin layer of LECs was present on the posterior capsule, with minimal secondary cataract formation. Marked cellular proliferation in the tissue surrounding the posterior capsule was also observed in the untreated and MPC coated groups, but cellular proliferation was inhibited in the UV/ozone treated group (Figure 5). Thickness of LECs proliferation was measured in the center of the posterior capsule (Figure 6). The thickness was 61.9 ± 35.2 µm in the untreated, 78.6 ± 19.6 µm in the MPC and 16.7 ± 9.1µm in the UV/ozone group. Kruscal Wallis test and multiple comparison analysis (Fisher’s protected least significant difference) showed statistically significant inhibition of secondary cataract formation with UV/ozone treatment.

Surface modification and prevention of anterior capsule contraction

In addition to inhibitory effects on secondary cataract formation, the effects of surface modification on anterior capsule contraction were also evaluated. As described previously, phacoemulsification was performed in white rabbits (aged 8 weeks, weighing approximately 2 kg). At 1 and 2 weeks after surgery, slitlamp examination of the anterior segment was performed, photographs were taken with an
In addition, stronger adhesion between the capsule and IOL LECs, which in turn prevented secondary cataract formation. Conversely, MPC treatment decreased adhesion of the IOL surface. UV/ozone treatment increased adhesion of the IOL surface. This inhibited the proliferation and migration of LECs, with development of secondary cataracts and anterior capsule contraction. In a previous study [45], we found that even with a round-edged rigid PMMA IOL, UV/ozone treatment was effective in increasing cell adhesion, with prevention of secondary cataracts. There are several types of surface treatment to increase cell adhesion, one example being argon plasma treatment. However, in this study we found UV/ozone to be more effective than argon plasma treatment [39]. In addition, from the standpoint of safety, argon plasma is associated with an etching effect that may promote surface deterioration, whereas UV/ozone treatment causes minimal damage to lenses [46]. The data we have obtained to date indicate that lenses subject to UV/ozone treatment have a markedly high biological safety with favorable results on cytotoxicity, genotoxicity and implantation tests and, thus, may have valuable clinical applications in the future.

**IOL surface modification, secondary cataracts & anterior capsule contraction**

Our findings demonstrate that even with the same IOL material, surface modification can alter IOL surface characteristics. UV/ozone treatment increased adhesion of the IOL surface. Conversely, MPC treatment decreased adhesion of the IOL surface. In this study, increased adhesion of the IOL surface led to early postoperative adhesion between the IOL and lens capsule. This inhibited the proliferation and migration of LECs, which in turn prevented secondary cataract formation. In addition, stronger adhesion between the capsule and IOL prevented anterior capsule contraction (Figure 12). However, decreased adhesion of the IOL surface led to weaker adhesion between the IOL and lens capsule. The result is earlier proliferation and migration of LECs, with development of secondary cataracts and anterior capsule contraction. In a previous study [45], we found that even with a round-edged rigid PMMA IOL, UV/ozone treatment was effective in increasing cell adhesion, with prevention of secondary cataracts.

**Expert commentary & five-year view**

Future development of novel IOLs should include not only square-edge design, but also surface modification to completely prevent secondary cataracts and anterior capsule contraction. The complete prevention of secondary cataracts can enhance IOL performance, including tinting, asphericity, multifocality and accommodation. Partial surface modification of the IOL front, back and edge is also possible. A
Prevention of post-cataract surgery complications such as secondary cataracts and anterior capsule contraction is necessary to maximize intraocular lens (IOL) optical performance. Various types of secondary cataracts and anterior capsule contraction related to wound healing reactions may occur after cataract surgery. Square-edge design of IOL optics may reduce the incidence of secondary cataracts but cannot completely prevent this complication. There are some chemical methods of inhibiting secondary cataract that have not been clinically used yet. UV/ozone treatment of hydrophobic acrylic increases surface adhesion of cells and proteins. In this experimental study, UV/ozone treatment statistically significantly prevented secondary cataracts and anterior capsule contraction. Improvement in surface modification techniques may be able to completely prevent secondary cataracts and anterior capsule contraction.

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Surface modification of IOLs

Report describing the prevention of secondary cataract using different surface modification on intraocular lenses (IOLs).

Report demonstrates that IOL posterior surface is adherent to the posterior capsule through lens epithelial cells (sandwich theory).

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