Biomaterials and advanced polymers change the face of anterior segment surgery

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Recent advances in fields such as tissue engineering, advanced biomaterials and injectable polymers promise to alter the face of anterior segment surgery radically in coming years, according to an international panel of vision scientists.

A clinical research symposium devoted to the theme of “New biomaterials and drug delivery in anterior segment surgery” enabled delegates attending the XXIII Congress of the ESCRS to catch up on the technological advances in biomaterials and drug delivery systems that promise a paradigm shift in treatment modalities in the near future.

Opening the session with a look at the role of biodegradable biomaterials in ophthalmology and ocular drug delivery, Hannu Uusitalo MD, professor and chairman, Department of Ophthalmology, University of Kuopio, Finland, reminded delegates that biomaterials, whether non-degradable such as intraocular lenses, or biodegradable such as viscoelastics, are already widely used by ophthalmologists.

Focusing on the applications of biodegradable biomaterials, Dr Uusitalo said that these offered several clear advantages to clinicians.

“There are several reasons why these biodegradable biomaterials are beneficial – they can be used, for example, in certain uses as surgical implants, for drug delivery, gene therapy, tissue repair and tissue engineering. Also in practical terms, synthetic biodegradable copolymers are relatively straightforward and inexpensive to produce,” he said.

Dr Uusitalo presented data on three different biodegradable copolymers (Bio-1, Bio-2 and Bio-3) degradation time varying from 2-3 months to 2 years. All three materials have shown that they interact well within ocular tissues and can also be used for cell and tissue repair at least for corneal, conjunctival and retinal pigment epithelial cells.

A straightforward application of new biomaterials will be in glaucoma surgery, Dr Uusitalo said.

“The reason we opted for deep sclerectomy is that we already use a biomaterial for such procedures that is made of collagen and is better known as AquaFlow (Staar Surgical). The basic idea is to replace this expensive manufactured biomaterial with a more simplified synthetic biomaterial,” he said. In the study, the copolymers were well tolerated and showed promising rates of biodegradation.

“It is clear after just a few weeks there is some activation of extracellular matrix suggesting that there is a minor wound-healing process going on around the implant,” said Dr Uusitalo.

He added that drug delivery is one of the more promising potential applications of such biomaterials.

“For many reasons, in ophthalmic surgery it is beneficial to have certain drugs around the operation area and it could be very beneficial if we could combine drugs to the implant to better control wound healing and inflammation. The drug release from the implant can be controlled by modifying the biomaterial or the structure of the implant,” he said.

Dr Uusitalo said that other potential applications for the next generation of copolymers include gene therapy and tissue engineering.

“These biomaterials can be adapted to help cultured tissues bind to the ocular tissues and then the biomaterials will degrade naturally over time,” he concluded.

Onlays for refractive correction

Implanting synthetic onlays onto the surface of the cornea to correct refractive errors could become a viable alternative to spectacles and contact lenses in the near future, according to Viviana Fernandez MD, Bascom Palmer Eye Institute, University of Miami School of Medicine, USA and Vision CRC, Sydney, Australia.

Dr Fernandez noted that a successful corneal onlay depends on the development of a biocompatible polymer material that will maintain a healthy cornea after implantation and will promote growth of corneal epithelial cells over the onlay, as well as devising a technique to attach the onlay with minimal surgical invasiveness.

“There are several advantages to using an onlay. The procedure is reversible with no removal of stromal tissue, it provides fast visual rehabilitation, it is predictable and easy to suture, and it can be performed in the clinic,” she said.

Focusing on the essential prerequisites for a successful implantable contact lens, Dr Fernandez said that there were several important criteria that should be respected.

First, the polymer used should have a high nutrient porosity, with a biologically active surface able to support epithelial migration, persistent adhesions and stratification. The material should also be transparent, biocompatible and remain stable over time. Ideally, it should also feature non-invasive hydrophobic strategies for attachment to the cornea and be easily manipulated by surgeons, she said.

Recent research indicates that collagen I coated polymer materials that mimic the basement membrane of the corneal epithelium promote the most favourable growth of epithelial cells in vivo in comparison to wholly biological or synthetic materials.

In a separate presentation, Dr Fernandez reported on the results of an in vivo pilot trial of poly(styrene-b-isobutylene-b-styrene) (SIBS, InnFocus LLC – University of Miami) a novel biocompatible polymer that has enjoyed unprecedented success as a drug eluting vehicle in coronary stenting. This material is ideally suited for applications with and without drugs for ocular implants, she said.

Dr Fernandez explained that polymers developed prior to SIBS tended to provoke a foreign body reaction which, in the conjunctival-Tenon space, was usually followed by encapsulation and thus could not be used for controlled drug release systems.

Initial results in experimental animal trials, however, found that SIBS has shown very promising results, with very good biocompatibility and no evidence of inflammation, encapsulation, extrusions, or other foreign body reactions, concluded Dr Fernandez.

Tissue engineering for ocular surface reconstruction

The field of tissue engineering for ocular surface reconstruction has witnessed impressive progress in recent years but the best is yet to come, according to Shigeru Kinoshita MD PhD, Department of Ophthalmology, Kyoto Prefectural University of Medicine, Japan.

Dr Kinoshita said that since Dr Grazzella Pellegrini’s groundbreaking report on cultivated corneal epithelium in 1997, many researchers have used different techniques to improve the quality of cultivated corneal epithelial cell sheets.

“Various approaches have been tried to find the ideal epithelial carrier including contact lens, fibrin, amniotic membrane and so forth, with mixed results,” said Dr Kinoshita.

He added that the consensus now seems to be that amniotic membrane offers the most promising role as epithelial carrier.

Explaining the technique, Dr Kinoshita said that the first step is to collect limbal epithelial cells, including basal cells, from the donor cornea. These cell suspensions are seeded onto the amniotic membrane and cultured for two weeks. The epithelial sheet is then transplanted onto the ocular surface.

He noted that it is important for the corneal epithelial sheet to have two important characteristics for successful transplantation: first, to display a reasonable level of activity in terms of the proliferation of the basal cells, and second, to demonstrate tight adhesion of the most superficial cell layer.

“We would like to use this technique at the acute phase of ocular surface disorders such as the acute phase of ocular thermal injury, chemical injury or Stevens-Johnson syndrome. At this point most doctors think that radical surgery at the acute phase is a kind of contraindication, so if we could use this kind of cultivated epithelial sheet perhaps we could foster a sort of paradigm shift in treating these difficult cases. It could certainly minimize the damage to the underlying stroma,” said Dr Kinoshita.

Principal complications associated with the procedure include immunological rejection or
Viviana Fernandez

Dr. Kinoshita cited the case of one such patient in the acute phase of Stevens-Johnson syndrome who received allogeneic cultivated corneal epithelial sheet and encountered three rejections.

Dr. Kinoshita said that a promising solution to such problems lies in moving the strategy of regenerative medicine from allografts to autografts, by selecting oral mucosal epithelial cells as a substitute for corneal epithelial cells.

Indications for cultivated mucosal epithelial transplantation tend to vary on a case-by-case basis, he explained.

“For unilateral cases, we use autologous corneal epithelial stem cell transplantation. For bilaterally affected cases, especially young patients, we would probably use cultivated oral epithelial transplantation. For bilaterally affected elder patients, or acute phase cases, we normally use allogeneic corneal epithelial stem cell transplantation.”

Dr. Kinoshita said early results with such methods had proved extremely promising and he predicted even better results in the future.

“It’s an exciting field at the moment. Many researchers will make marked progress in regenerative medicine and tissue engineering in the future, and I believe that we will establish sophisticated surgical modalities in the next ten years,” he said.

**A new era of ultra-small implants**

Advances in injectable polymers and new lens designs and materials are helping to pave the way towards a new generation of ultra-small incision implants, according to Suresh K. Pandey MD, Intraocular Implant Unit, Sydney Eye Hospital, Australia.

“As we all know, cataract surgery has undergone incredible transformations since the first implant by Sir Harold Ridley. With microincision cataract surgery (MICS) we now have the interest in developing ultra-small incision intraocular lenses,” said Dr. Pandey.

Focusing on the early laboratory performance of three such IOLs – ThinOptX Ultrachoice (ThinOptx), AcInTec Smart IOL (AcriTec) and SmartIOL (Medenium Inc.) – Dr. Pandey said these lenses were designed for use in bimanual microphacoemulsification. For micro coaxial phaco, another approach pioneered by Dr Takayuki Akihoshi using specially adapted instruments allows for the insertion of an AcrySof foldable IOL (Alcon Inc) through a sub 2.0 mm incision, said Dr Pandey.

In the experimental study with ultra-small IOLs, Dr. Pandey, together with Dr. Nick Mamalis and Dr. Liliana Werner (from John A. Moran Eye Center, Salt Lake City, Utah) studied capsular bag geometry after implantation in post-mortem human eyes using the Miyake-Apple technique (continuous curvilinear capsulorhexis (CCC) of 4.5 mm, hydrodissection, aspiration of lens substance, capsular bag cleaning and IOL insertion).

The IOLs showed well-controlled unrolling/unfolding within the capsular bag after injection of warm BSS and the Miyake-Apple technique demonstrated “optimum fit” of the IOL in the capsular bag, reported Dr. Pandey. Furthermore, there were no issues with CCC ovaling, capsular bag distortion, zonular stress, or posterior capsular striae, and it was also easy to remove the viscoelastic from the capsular bag.

Dr. Pandey reported that all three IOLs showed encouraging results in these experimental studies but stressed that further large scale clinical studies were needed to confirm these initial impressions.

Turning to injectable polymers, Dr. Pandey noted that the first attempt to refill the lens capsule to restore accommodation was performed by Dr. Kessler in 1964. The surgical procedure for lens refilling involves the endocapsular removal of lens substance through a mini-CCC of 0.8-1.2 mm diameter, followed by refilling of the capsular bag with injectable material such as silicone, collagen, HEMA/acrylic copolymer, poloxamer (thermosensitive polymer hydrogel) or polystyrene-polysobutylene-polystyrene, said Dr. Pandey.

He said that there were still challenges to be overcome in the development of the “ideal polymer”, including prevention of leakage during injection, in-the-bag removal of hard cataract through mini-CCC, maintenance of capsular bag transparency, and management of refractive surprises.

Dr. Pandey said that the ideal refilling material should meet a number of important criteria: it should be biocompatible, optimally flexible, transparent, and homogeneous, with a refractive index greater than that of the crystalline lens. It should have a specific gravity heavier than that of water, and should be easy to prepare and inject with no leakage from the capsular opening. It should also permit rapid solidification to the required state and quick and correct determination of the endpoint of injection for desired lens power, while allowing for the adjustment of refractive surprise in the postoperative period. Finally, it should also inhibit the proliferation of lens epithelial cells to ensure capsular bag transparency, he concluded.

**Perfect Capsule for paediatric patients**

Sealed capsular irrigation using the Perfect Capsule (Milvella) device developed by Dr Anthony Maloof may help tackle some of the complications associated with cataract surgery in paediatric patients, according to Charlotte Zetterstrom, MD, St. Erik’s Eye Hospital, Stockholm, Sweden.

“It is well known that after-cataract is a real problem in children. In adults we have a range of good lenses available and it is not such a major problem as in paediatric patients. So we decided to test this Perfect Capsule device to see how well it might work in children or small eyes,” she said.

Dr Zetterstrom described the PerfectCapsule as a foldable silicone device with a 5.0 mm inner diameter, a thickness of 0.7 mm and a total diameter of 7.0 mm. Because it is foldable, the device can be inserted through a 2.8 mm incision.

The Perfect Capsule is designed to temporarily seal a capsulorhexis of less than 5 mm, noted Dr. Zetterstrom. The device uses a vacuum ring similar to that used to fixate the globe during LASIK that attaches onto the outer surface of the anterior lens capsule and seals around the rhexis. There is a channel through which an irrigating solution can be passed into the capsular bag, and there is also a channel through the same area for the outflow of the fluid.

“The capsular bag is emptied and then you apply this ring on the anterior capsule so you have a sealed and closed system. To achieve this you have to put on some vacuum and then you have two tubing structures: one for irrigation and one which evacuates the substance you are using,” said Dr Zetterstrom.

In a study of the Perfect Capsule in newborn rabbit eyes, Dr Zetterstrom tested the device using either regular balanced salt solution, de-ionised water, or the anti-fibrotic agent 5-fluorouracil (5-FU) for irrigation, in order to assess which combination proved most effective at preventing after-cataract.

The study showed significantly less PCO in Group 3, which used 5-FU, noted Dr Zetterstrom, with no statistical difference in PCO rates between Group 1 (Perfect Capsule and water) and Group 2 (Perfect Capsule and BS).

Dr Zetterstrom concluded that...
Perfect Capsule appears to be effective in preventing PCO and after-cataract, especially when used in conjunction with 5-FU. She added that further investigations with longer follow-up were needed to assess its safety and effectiveness in paediatric patients.

A new twist on OVDs

A new ophthalmic viscosurgical device (OVD) that combines sodium hyaluronate with lidocaine showed no toxic or cataractogenic effects in rabbit eyes, according to a study conducted at the Moran Eye Center at the University of Utah, Salt Lake City, United States. Liliana Werner MD PhD presented the results of an in vivo study that evaluated the toxicity of a new visco-anaesthetic ophthalmic viscosurgical device (VisThesia and VisThesia Light, Carl Zeiss Meditec group).

There are several benefits in mixing a viscoelastic solution with an anaesthetic solution, noted Dr Werner. Such an approach combines the advantages of visco-surgery in terms of maintenance of the anterior chamber depth, capsular bag expansion, and protection of corneal endothelium, while also ensuring a prolonged anaesthesia. There are also no extra surgical steps necessary for intracameral injection of lidocaine.

In the first part of the study, the effects of the solutions on the corneal endothelium were evaluated in vitro using rabbit corneas. Another part of the study looked at 29 rabbits that underwent bilateral phacoemulsification and were injected with 0.2 ml of the solution in the capsular bag. After clinical follow-up of 15, 60, or 90 days, the rabbits were sacrificed and their eyes were removed and processed for evaluation.

Dr Werner and colleagues also injected the anterior chambers of 40 phakic rabbit eyes with 0.1 ml of the OVD solution. This study has recently been published in the J Cataract Refract Surg (Werner L, Pandey SK, Izak AM, Hickman MS, LeBoyer RM, Mamalis N. Evaluation of the cataractogenic effect of viscoanaesthetic solutions to the rabbit crystalline lens. J Cataract Refract Surg 2005; 31:1414-1420).

Dr Werner reported that the enucleated eyes showed no signs of toxicity to the corneal endothelium, ciliary body, or the retina. She also said there were no signs of cell necrosis, cell degeneration, or fibrous metaplasia. She concluded that the study showed that VisThesia could prolong the anaesthetic effect of the lidocaine during either cataract surgery or phakic IOL implantation.

Water ➔ Cell lysis

• Deionized distilled water ➔ osmotic lysis because of hypotonia (Crowston et al JCRS 2004)

Difference between eyes

• At all controls significant difference between the eyes in the 5-FU-group but not in the other groups