EXTENDED REPORT

In vitro and in vivo study of lens refilling with poloxamer hydrogel

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Aim: To evaluate the compatibility of poloxamer hydrogel as a material for an injectable intraocular lens, in vivo and in vitro.

Methods: The appropriate concentration of poloxamer hydrogel was determined for injection by examining the transparency and gelling temperature of this material, assessing the lens capsule refilling technique, and studying the postoperative findings in a rabbit model.

Results: Poloxamer hydrogel showed excellent transparency and 25% was identified as an appropriate concentration for the lens refilling material. The authors developed a technique for injecting the material in vivo and obtained excellent short term results.

Conclusions: Poloxamer hydrogel was identified as an appropriate material for direct lens refilling, and the developed injection technique produced excellent short term results.

In spite of advances in intraocular lens material development and design, the loss of accommodation remains a significant limitation of current cataract surgery. Posterior capsular opacification (PCO) is the most common complication and its prevention is an important issue for improving the quality of surgery. To overcome these problems, injectable intraocular lenses are under study. Two different methods exist for making the lens. One involves the implantation of the refilled endocapsular balloon, and the other is the direct lens filling technique. However, these days balloon implantation is rarely used in studies, and in the case of the direct lens refilling technique, silicone has been mainly used as a lens refilling material. However, silicone has an inherent disadvantage; specifically, its low specific gravity and PCO has been reported to be a complication. In this study, we used a thermosensitive poloxamer hydrogel as a lens refilling material in an effort to overcome the problems associated with silicone.

MATERIALS AND METHODS

Preparation of intraocular lens material

We used air Vinyl, which is similar to a normal crystalline lens in size, volume, and thickness (10 mm in diameter, 5 mm in height, 0.2 ml in volume, 15–20 µm in thickness), as an in vitro lens model (Fig 1). To confirm the transparency of the poloxamer hydrogel, we injected it into the air Vinyl and placed it in a 36.5°C water bath for 24 hours, and then compared it with the air Vinyl filled with balanced salt solution (BSS). The gelling temperature of the poloxamer hydrogel was assessed against concentration, and we determined the appropriate concentration of the hydrogel as a lens filling material in terms of the injection operation and its refractive index.

Lens refilling procedure

Twenty male New Zealand white rabbits (*Pasteurella* free) weighing 2.5–3.0 kg were used. The animals were housed and treated in accordance with the Association for Research in Vision and Ophthalmology statements for the use of animals in ophthalmic and vision research. After the pupil was maximally dilated with 2.5% phenylephrine HCl, each rabbit was anaesthetised with topical oxybuprocaine

(proparacaine) and intramuscular ketamine hydrochloride 40 mg/kg and xylazine hydrochloride 5 mg/kg. A 2.5 mm clear corneal incision was made at the 12 o'clock position for phacoemulsification surgery. A larger side port than usual was made at the 3 o'clock position for BSS injection during surgery. After 1% sodium hyaluronate had been injected into the anterior chamber, a small (1.5–2 mm in diameter) continuous curvilinear capsulorhexis (CCC) was created using a 26 gauge needle and a capsulorhexis forceps at the 12 o'clock site of the peripheral anterior lens capsule. The technique was almost the same as previously described by Tahi *et al.*¹ Once irregular portions were found within the CCC margin, the portions were trimmed with a diathermy in order to avoid extension of the capsulotomy opening (Fig 2A). After hydrodissection and hydrodelineation, phacoemulsification was performed (Fig 2B). To avoid damaging the small capsulotomy margin, the sleeve was removed from the phaco tip, and to maintain the depth of the anterior chamber, BSS was injected through the 3 o'clock incision site separated from a phaco tip. Cortical remnants were removed by irrigation and aspiration. After confirming that there was no extension of the capsulorhexis even after the endocapsular phacoemulsification, 0.3 ml of poloxamer hydrogel, which had been allowed to harden at room temperature (20°C), was injected into the capsular bag using a 18 gauge cannula

Figure 1 Air Vinyl was used as an in vitro lens model. The photograph shows air Vinyl filled with poloxamer hydrogel.

Figure 2 (A) A small continuous circular capsulorhexis, 2 mm in diameter. (B) Endocapsular phacoemulsification and aspiration. (C) Injection of poloxamer hydrogel using an 18 gauge cannula.

(Fig 2C). To ensure it remained as one mass, we injected it slowly and carefully. After injecting the poloxamer hydrogel, remaining hyaluronate sodium was removed from anterior chamber by irrigation and aspiration.

Intraoperative complications and surgical success rate were assessed. One rabbit was killed immediately after surgery by injecting succinylcholine after anaesthesia and the refilled lens was obtained. Slit lamp examinations were performed on the animals over a period of 3 months.

RESULTS

In vitro study

By making preliminary injections into air Vinyl, it was found that the poloxamer hydrogel exposed to low temperature was easy to inject, and when exposed to a higher temperature showed no leaking after injection. We confirmed the transparency of the poloxamer hydrogel and determined the optimum concentration required for this experiment. Figure 3 shows that air Vinyl filled with the poloxamer hydrogel was as transparent as that filled with BSS. We could see underlying letters clearly through the air Vinyl in both cases. Figure 4 shows the gelling temperature of the poloxamer hydrogel versus concentration. As expected the higher the concentration of the poloxamer hydrogel, the

Figure 3 Underlying letters could be seen through air Vinyl filled with poloxamer hydrogel (left) as well as that filled with BSS (right).

Figure 4 Gelling temperature of poloxamer hydrogel.

lower was the gelling temperature. A 25% poloxamer hydrogel appeared appropriate for the direct lens filling method. The refractive index of the poloxamer hydrogel was 1.36.

In vivo study

Only 12 rabbits were operated upon successfully, injection failed in the other eight rabbits because of intraoperative complications (Table 1). Figure 5 shows the enucleated rabbit lens tightly filled with poloxamer hydrogel immediately after the operation. No active inflammation was observed in the ocular tissue at a postoperative week and the bright red reflex, indicative of the excellent transparency of the refilled lens was observed (Fig 6A). We could also see the retinal vessels of the rabbit eye through the poloxamer in the capsular bag by indirect ophthalmoscopic examination (Fig 6B). At the 3 month examination, melting of the poloxamer hydrogel was noted from the region of the capsular opening where aqueous humour was in contact with the poloxamer, but still no ocular inflammation or posterior capsular opacification was apparent.

DISCUSSION

Advances in IOL and cataract removal technologies allow surgeons today to complete cataract surgery through incisions as small as 1.5 mm. Although foldable lenses have been

Table 1 Intraoperative complications of lens refilling with poloxamer hydrogel in 20 rabbit eyes

Complications	No of eyes (%)
Posterior capsular rupture	1 (5)
Extension of CCC opening	4 (20)
Leakage of poloxamer	1 (5)
Incomplete lens filling	2 (10)

Figure 5 Rabbit lens filled with poloxamer hydrogel immediately after operation.

a great improvement, there is still a need for lenses that can be positioned through an even smaller incision. By injecting lens material into the capsular bag as a liquid, and its transformation to a solid, a full size lens can be created in situ in the eye. An additional advantage of this technique is that, owing to the formation of a full size lens, it might overcome some of the complications of conventional IOL implantation—namely, decentration and posterior capsular opacification.²

Two different methods have been used to refill the lens capsule after endocapsular phacoemulsification. One involves the implantation of the refilled endocapsular balloon,^{3–8} and the other direct lens filling.^{9–14} However, currently, the balloon implantation seems to be no longer a topic of study.⁹ The reason is because the technique is limited in terms of the discrepancy between the shape of the individual lens capsule and that of the preformed balloon, wrinkling of the anterior and posterior capsule-balloon surfaces, and the technical complexity of the surgery.^{3,9}

In terms of the direct lens filling technique, the identification of the most appropriate material is currently the major problem. The viscosity of the material should be low enough to enable its injection through a small gauge needle but high enough to displace viscoelastic material and balanced salt solution as well as aqueous humour in the capsular bag.⁴ Silicone polymer has been widely used as a refilling material,^{9–13} but silicone has a number of disadvantages. Because silicone has a lower specific gravity than water and is not cohesive enough to replace fluid in the capsular bag, it is technically extremely difficult to fill the bag.⁵ Also, it is difficult to prepare a precured silicone gel with viscosity that is both low enough to allow injection and high enough to prevent leakage.⁵ Furthermore, the use of silicone has been associated with severe PCO,² the prevention of which is

essential for making an injectable intraocular lens, because the use of Nd:YAG laser capsulotomy may annul the accommodation attained.⁹ Another one of the serious problems of silicone is its long setting time. Up to 12 hours may be needed, which increases the risk of material leakage out of the capsular bag through the surgical incision.² For this reason Nishi *et al*^{10,11} tried to prevent silicone leakage by sealing the capsule with a plug. However, they reported that they found it difficult to insert a plug into the capsular bag.

Poloxamer hydrogel is a non-toxic poly(ethylene oxide/propylene oxide/ethylene oxide) (PEO/PPO/PEO) tri-block copolymer with a weight average molecular weight of 12 500, which contains 70% hydrophilic ethylene oxide units and 30% hydrophobic propylene oxide units.¹⁵ A solution of this material is a clear liquid at room temperature, and on warming to body temperature it forms a stiff and clear gel by undergoing a sol-gel transition.¹⁵ As a result of this thermal gelation and extremely low toxicity, the poloxamer hydrogel is currently used as a carrier for pharmaceuticals¹⁶ and as an agent for the animal study of hyperlipidaemia.¹⁷ This material has also shown an ability to inhibit platelet aggregation¹⁸ and to reduce postoperative adhesion.¹⁹

In this study, it was found possible to make the poloxamer hydrogel suitable for injection and to fill the lens capsule with material that rapidly forms a gel at body temperature. Remarkably, no PCO was observed even at a postoperative 3 months, but it is not clear whether this was due to a PCO preventative effect of the poloxamer hydrogel, to the barrier created by space occupied by the poloxamer hydrogel or to an antiadhesive effect of this material. This study shows that the poloxamer hydrogel can overcome the problems of silicone.

However, the poloxamer hydrogel has a lower refractive index (1.36) than the natural lens (1.42), and we did not measure the refraction and the accommodation amplitude after lens refilling with poloxamer hydrogel. Accordingly, more studies are required on the method of filling for emmetropia and on the possibility of accommodation.

Regardless of the problems that remain to be resolved, poloxamer hydrogel demonstrates the feasibility of the development of an injectable intraocular lens for the following reasons. Firstly, poloxamer is inert and transparent. Secondly, it is an excellent material for injecting because its solidity can be controlled by temperature, we were easily able to inject it into the capsular bag and prevent leakage after injection. Thirdly, it could prevent capsular opacification.

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Figure 6 (A) Slit lamp photograph of the rabbit eye at postoperative week 1 shows stable poloxamer in the capsular bag with good red reflex. (B) Retinal vessels of the rabbit eye could be seen through the poloxamer in the capsular bag at postoperative week 1.

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