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.

Material 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 poloxomer 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 (P. t. t. 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 shows air Vinyl filled with poloxamer hydrogel.

Figure 1 Air Vinyl was used as an in vitro lens model. The photograph shows air Vinyl filled with poloxamer hydrogel.
(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 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>
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<tr>
<th>Complications</th>
<th>No of eyes (%)</th>
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<tbody>
<tr>
<td>Posterior capsular rupture</td>
<td>1 (5)</td>
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<tr>
<td>Extension of CCC opening</td>
<td>4 (20)</td>
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<tr>
<td>Leakage of poloxamer</td>
<td>1 (5)</td>
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<tr>
<td>Incomplete lens filling</td>
<td>2 (10)</td>
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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.

Two different methods have been used to refill the lens capsule after endcapsular phacoemulsification. One involves the implantation of the refilled endcapsular balloon, and the other direct lens filling. However, currently, the balloon implantation seems to be no longer a topic of study. 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.

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. Silicone polymer has been widely used as a refilling material 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. 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. Furthermore, the use of silicone has been associated with severe PCO, 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. 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. For this reason Nishi et al. 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. 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. As a result of this thermal gelation and extremely low toxicity, the poloxamer hydrogel is currently used as a carrier for pharmaceuticals and as an agent for the animal study of hyperlipidaemia. This material has also shown an ability to inhibit platelet aggregation and to reduce postoperative adhesion.

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 5 Rabbit lens filled with poloxamer hydrogel immediately after operation.

Figure 6 (A) Slit lamp photograph of the rabbit eye at postoperative week 1 shows clear 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.
REFERENCES

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