Injectable accommodative lenses, a preclinical study
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 4

Effect of infusion bottle height on lens power after lens refilling with and without a plug.

Published as: Steven A.Koopmans, MD, Thom Terwee, MSc, Henk J Haitjema, PhD, Jan Barkhof MSc, Aart C.Kooijman, PhD. Effect of infusion bottle height on lens power after lens refilling with and without a plug. Journal of Cataract and Refractive Surgery 2003;29:1989-1995.
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Abstract

Purpose: To evaluate the influence of the intraoperative infusion bottle height on the power of refilled pig lenses.

Setting: Research laboratory, Pharmacia Intraocular Lens Manufacturing Plant, Groningen, the Netherlands.

Methods: This study comprised 2 groups of pig eyes. In 1 group, the lens was refilled with silicone oil using a plug to close the capsulorhexis; in the other group no plug was used. The anterior chamber depth, lens thickness, and vitreous chamber depth were measured by A-scan ultrasound. The total refraction of the eye was measured with a Hartinger refractometer. Measurements were performed with the infusion bottle at 0 cm, 25 cm, 50 cm, 75 cm and 100 cm above eye level. Calculations using a model eye were performed to evaluate the change in lens power based on the empirical data.

Results: The mean change in the power of refilled lenses caused by the varying height of the infusion bottle was 1.8 diopters. Lenses refilled with a plug had a thickness similar to that of natural lenses. Lenses refilled without a plug were significantly thinner (p<0.05). The power of lenses refilled with a plug was significantly higher than that of lenses refilled without using a plug (p<.05).

Conclusions: During lens refilling, infusion bottle height influenced the resulting lens power. Using a plug to close the capsulorhexis resulted in refilled lens dimensions similar to those of the natural lens.
Introduction
Replacing the contents of the capsular bag of the crystalline lens by injecting a flexible polymer into the bag might restore accommodation after the onset of presbyopia. First described by Kessler\(^1\) this procedure includes lens nucleus and cortex removal through a small capsulorhexis and refilling the capsular bag by injecting a polymer. Leakage of the polymer from the capsular bag can be prevented by using a plug\(^2\), although this type of surgery has also been performed without a plug\(^3\).

In-vitro studies of refilled human eyes\(^4\) and in-vivo studies of non-human primate eyes\(^5\) found accommodative changes in refilled lenses, indicating the potential of this procedure. The technique is under development, and several problems must be solved before its in-vivo use in human eyes. One problem is the surgeons’ ability to control the optical power of the refilled lens. In conventional cataract surgery, the surgeon can determine postoperative refraction by preoperatively calculating the intraocular lens (IOL) power based on axial length measurements and keratometry. Intraocular lenses with a wide range of powers are available and are produced in advance under strict quality control. In contrast, during in vivo lens refilling, the surgeon must determine the postoperative lens power intraoperatively. Several factors can influence the power of the refilled lens.

One way to control the power of a refilled lens is by selecting a refill polymer with an appropriate refractive index. Ho et al.\(^6\) evaluated the accommodative amplitude and ametropia correction achievable by varying the refractive index of the polymer used to refill lenses in model eyes. They concluded that increasing the refractive index is useful for correcting hypermetropia but that decreasing it for myopia would result in a limited amplitude of accommodation. Their calculations were based on the assumption that the curvature of the natural lens is exactly reproduced after lens refilling.

Another way to control the power of a refilled lens is to add more or less material to the capsular bag during surgery\(^7\). The capsular bag of the natural lens limits the size of the refilled lens. However, we do not know to what extent the original surface shape is reproduced. In a previous study\(^4\), we found that the mean lens power in a group of refilled human lenses was significantly higher than in a group of natural lenses, although the lens diameter and the lens thickness were not significantly different between groups and the refractive index of the polymer...
used to refill the lenses was the same as that of natural lenses (1.428). This suggests that the curvature of refilled lenses differs from that of natural lenses.

Based on experiments with pig lenses, Nishi et al\textsuperscript{7} suggest that refilling 60\% of the capsular bag maximizes the accommodative amplitude. It is not certain that the same rule applies to human lenses. Assuming that Nishi et al’s results apply to the human eye and that the amount of filling determines the accommodative amplitude and lens power, the ability to select the amount of material to inject may be limited.

Postoperative changes in lens position and capsular bag size from shrinkage and the effect of intraocular pressure (IOP) differences during and after surgery on the curvature of the intraocular structures might contribute to changes in lens power postoperatively.

Another factor might be the height of the infusion bottle that provides intraocular pressure during surgery. This can be adjusted intraoperatively to control lens power during refilling, as suggested by Hettlich et al.\textsuperscript{8} However, their study lacked quantitative data.

Thus, we assessed the influence of infusion bottle height on the refractive state of refilled pig lenses. Because refilling techniques using a capsular plug or not using one have been described, we evaluated the effect of infusion height with both techniques.

**Materials and methods.**

Eyes of 6-month-old pigs were obtained from the local slaughter house. The eyes were kept in a saline solution consisting of 8 g/L sodium chloride, 0.4 g/L potassium chloride, 1 g/L glucose, 2.38 g/L N-2-hydroxyethylpiperazine-N’-2-ethane sulfonic acid, and 0.1 g/L anhydrous dibasic sodium phosphate and stored in a refrigerator at 5\textdegree C until use. All experiments started within 8 hours after enucleation. Extraocular muscles and conjunctiva were removed with scissors.

Eyes were assigned to 1 of 2 groups. In 1 group (n=9), a plug was used to prevent polymer leakage from the capsular bag. In the other group (n=10) no plug was used. A 4-0 nylon suture was attached to the optic nerve. The eye was then placed on a stand consisting of a solid, upright cylinder, with an excavation at the end. Two holes were drilled through the bottom of the excavation through which the sutures were passed and tied to attach the eye to the stand.
The anterior chamber depth (ACD), lens thickness, axial length (AL), refraction, and the radii of curvature of the cornea and the anterior and posterior lens surfaces were measured. Measurements were first performed on the unpressurized, untouched eyes. They were repeated after an anterior chamber maintainer (ACM) connected to an infusion bottle was inserted. The fluid surface of the bottle was positioned 0 cm, 50 cm, and 100 cm above the eye. The contents of the capsular bag were removed, the lens capsule was filled with silicone oil, and the measurements were repeated with the fluid surface of the infusion 100 cm, 75 cm, 50 cm, 25 cm and 0 cm above eye level.

Anterior chamber depth, Lens Thickness and AL

For axial dimension measurements, the eye, attached to the stand, was placed in a glass beaker filled with the saline solution. The suture from the posterior pole, fixing the eye on the stand, prevented the eye from floating in the saline. An A-scan probe (Sonomed A-5500, Lake Success, New York) was fixed to a second stand and the tip of the probe was positioned in the saline solution in the beaker above the eye. The probe was aligned visually with the optical axis of the eye, and small adjustments were made in order to obtain the highest echo signal peaks from the lens and retina. Then the ACD, lens thickness and total AL were measured using the electronic gates in the A-scan instrument (Figure 1). The infusion bottle was subsequently adjusted to the proper height, with care taken not to change the position of the eye and the A-scan probe; the measurements were repeated. A sound velocity of 1640 m/s was used for the natural pig lenses and 1066 m/s for lenses refilled with silicone oil. The sound velocity of the silicone oil was determined by performing A-scan measurements of a 10.0 mm cylinder filled with silicone oil at room temperature.
Refraction

The eye resting on the cylindrical stand was placed under a Hartinger refractometer (Carl Zeiss) with the measuring axis oriented vertically (Figure 2). The light emitted by the refractometer was centered inside the pupil by visual adjustment. The cornea was wet, and the refraction was obtained. To do this, the operator aligned three vertical bars inside the refractometer and then read the refraction value on a diopter (D) scale. Because the visibility of the vertical bars depends on the optical quality of the eye’s media, visibility of the 3 bars was rated as low, medium or high. Readings were obtained at different infusion bottle heights. While the infusion bottle was being adjusted to the proper height, care was taken not to change the eye’s position.
Two fiber-optic light guides (Schott KL1500) were attached next to the lens of the surgical microscope as a light source for Purkinje images. Purkinje images are seen when reflection of light occurs at the various curved surfaces of the eye’s anterior segment. The local radius of curvature of these surfaces can be calculated from the size of the Purkinje image. A charge-coupled device (CCD) camera (Hitachi HV C20) was attached to the microscope, and the output of the camera was fed to a frame grabber board (Matrox Meteor) installed on a personal computer. Images were obtained through the surgical microscope for Purkinje images I,III and IV, which were reflected by the eye under the microscope. Image magnification (pixels per mm) was calibrated by placing a ruler with a millimeter scale adjacent to the cornea. From the Purkinje image heights the radii of the cornea and the anterior and the posterior lens surfaces were calculated. Readings were taken at different infusion heights. The cornea was wet with the saline solution before the images were obtained.

Figure 2. Setup for measurement of refraction using a Hartinger refractometer. A similar setup was used to photograph the Purkinje images through the surgical microscope.

Radius
**Lens refilling surgery**

After a paracentesis of the anterior chamber was created, an ACM was inserted and connected to a bottle of saline solution positioned 50 cm above the eye. A 3.2 mm corneo-scleral tunnel incision was made and the anterior lens capsule was punctured with a 27-gauge needle. A 1.0 to 1.5 mm minicircular capsulorhexis was created in the periphery of the lens with a forceps. The lens matter was manually aspirated with a blunt 18-gauge cannula connected with an extension tube to a 10 cc syringe.

In the group in which a plug was not used, a 21-gauge was inserted in the capsular bag and silicone oil injected until the bag was full. The cannula was then retracted and silicone material leaking from the capsular bag was flushed out of the anterior chamber, aided by the infusion fluid entering the eye through the ACM. The precise amount of silicone oil injected in the capsular bag was not recorded; however, in an experiment in 50 pig eyes using a similar technique, a mean of 0.26 mL ±0.1 (SD) was injected (unpublished data). The corneal incision was closed with a 10-0 nylon suture, and the eye remained pressurized by the infusion.

In the group in which a plug was used, the procedure was the same until after the capsular bag was emptied, at which time the ACM was removed and sodium hyaluronate 1% (Healon®) injected into the anterior chamber. Next, a plug was introduced into the capsular bag, which was refilled through the capsulorhexis by injecting silicone oil through a a 25-gauge cannula until the bag was full. In an experiment in 10 pig eyes using a plug, a mean of 0.35 mL ±0.1 (SD) of silicone oil could be injected (unpublished data). The cannula was then retracted and the plug was manipulated into position to close the capsulorhexis. The ACM was reinserted and the Healon flushed out of the anterior chamber through the corneal incision. The incision was closed with a 10-0 nylon suture, and the eye remained pressurized by the infusion.

**Silicone oil**

The silicone oil used was part A of a 2-component silicone polymer (Pharmacia), previously described\(^4\). The oil has a refractive index of 1.428 and a viscosity of 1750 cP at 25 °C. As only part A was used, the material did not polymerize.
Data Analysis

Two effects - crystalline lens position and the radii of curvature of the lens surfaces - may change the refractive state of the pig eye depending on the height of the infusion bottle above eye level. The anterior and the posterior radius of lens curvature could not be measured because of poor visibility of the Purkinje images. Therefore, a model eye was used to evaluate the influence of infusion bottle height on lens power.

Based on paraxial optics, a model eye with 4 surfaces was programmed using Excel-97 software (Microsoft). The model was fed with the measured axial dimensions (ACD, lens thickness, and vitreous chamber depth) and the refraction values for each eye at different infusion bottle heights (table 1). For the corneal anterior radius of curvature a fixed value of 8.45 mm was used. This was obtained by averaging the values of all anterior corneal radii calculated from the first Purkinje image for 16 refilled eyes with an infusion bottle height of 50 cm. The mean anterior corneal radius was between 8.31 and 8.51 mm, while the infusion bottle height varied between 25 and 100 cm above eye level. Other parameters used in the model were taken from the literature as follows: posterior radius of curvature of the cornea = anterior radius of curvature - 0.06 mm; corneal thickness; and all refractive indices of the media except the refractive index of the silicone oil (ie 1.428).

A value for the posterior lens curvature was obtained with data from another experiment. The capsular bag was refilled with silicone that polymerized into a rigid, hard lens in 45 minutes at 21°C. This polymer included part B, a cross linking substance, as well as part A. The lenses were removed from the eye after polymerization and their contours were photographed with a CCD camera from a distance of 25 cm. The images were calibrated by taking a photograph of a steel ball of known dimensions before each session. The anterior and the posterior curvatures of the lenses were determined by fitting a sphere to the contours. The posterior lens curvature was independent of the infusion bottle height during polymerization in the interval between 20 cm and 100 cm (Figure 3). This justified the use of a fixed value (-5.26 mm) for the posterior lens curvature in the model. Based on this model, the anterior lens curvature with the best fit for the empirical data was calculated using the Excel solve function; the resulting lens power was calculated using the thick lens formula.
SPSS 10 software (SPSS Inc) was used for repeated-measurements analysis of variance (ANOVA).

Table 1.

<table>
<thead>
<tr>
<th>Parameters used in the model eye.</th>
<th>Fixed Value</th>
<th>Variable Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean anterior corneal radius of curvature (mm)</td>
<td>8.45 mm*</td>
<td>--</td>
</tr>
<tr>
<td>Posterior corneal radius of curvature (mm)</td>
<td>8.39 mm**</td>
<td>--</td>
</tr>
<tr>
<td>Anterior lens radius of curvature (mm)</td>
<td>--</td>
<td>Solved by the model</td>
</tr>
<tr>
<td>Posterior lens radius of curvature (mm)</td>
<td>-5.26 mm***</td>
<td>--</td>
</tr>
<tr>
<td>Corneal thickness (mm)</td>
<td>0.8 mm⁹</td>
<td>--</td>
</tr>
<tr>
<td>Anterior chamber depth (mm)</td>
<td>--</td>
<td>Measured by A-scan</td>
</tr>
<tr>
<td>Lens thickness (mm)</td>
<td>--</td>
<td>Measured by A-scan</td>
</tr>
<tr>
<td>Vitreous chamber depth (mm)</td>
<td>--</td>
<td>Measured by A-scan</td>
</tr>
<tr>
<td>Refractive index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>air</td>
<td>1.00</td>
<td>--</td>
</tr>
<tr>
<td>cornea</td>
<td>1.373⁹</td>
<td>--</td>
</tr>
<tr>
<td>lens</td>
<td>1.508⁹/1.428****</td>
<td>--</td>
</tr>
<tr>
<td>aqueous</td>
<td>1.3339⁹</td>
<td>--</td>
</tr>
<tr>
<td>vitreous</td>
<td>1.3339⁹</td>
<td>--</td>
</tr>
<tr>
<td>Total eye refraction (D)</td>
<td>---</td>
<td>Measured with Hartinger refractometer</td>
</tr>
</tbody>
</table>

*Mean of 16 pig eyes with refilled lenses with infusion bottle height 50 cm above the eye. SD = 0.57 (range 7.70-9.76)

** Anterior corneal curvature – 0.06; see text.

*** see text

**** Refractive index of the natural pig lens/silicone-oil refilled lens.
Results

Missing values

First Purkinje image measurements were obtained in most eyes; however, measurements of the third and fourth Purkinje image were difficult, because they were difficult to visualize. Therefore, the latter 2 measurements were not used to assess the anterior and posterior lens curvatures. Visibility of the measurement bars in the Hartinger refractometer was average or even high in all eyes. When the infusion bottle was lowered from 25 cm to 0 cm in eyes refilled without a plug, the silicone oil escaped from the capsular bag and filled the anterior chamber. In eyes in which a plug was used, the silicone oil did not escape into the anterior chamber when the infusion bottle was lowered to 0 cm; however, the cornea was wrinkled in some cases, precluding reliable refraction measurements. Because measurements at 0 cm infusion height were incomplete in both groups, only measurements with the infusion bottle 25 cm or higher above eye level were used. In the group of eyes with plugged lenses, 1 eye had a missing lens power value at 50 cm infusion height. The mean lens power in the group at 50 cm was used in this case.

Figure 3. Posterior radius of curvature versus infusion bottle height in lenses refilled with a material that polymerises, making the lens hard.
Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Natural Lenses</th>
<th>Refill Lenses with Plug</th>
<th>Refill Lenses without Plug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean corneal curvature (mm)</td>
<td>8.3 ± 0.5</td>
<td>8.3 ± 0.6</td>
<td>8.0 ± 0.9</td>
</tr>
<tr>
<td>Mean ACD (mm)*</td>
<td>3.4 ± 0.8</td>
<td>3.5 ± 0.9</td>
<td>4.8 ± 0.7**</td>
</tr>
<tr>
<td>Mean lens thickness (mm)</td>
<td>6.4 ± 0.2</td>
<td>6.5 ± 0.8</td>
<td>4.8 ± 0.6**</td>
</tr>
<tr>
<td>Mean AL (mm)</td>
<td>21.2 ± 0.7</td>
<td>21.4 ± 0.7</td>
<td>21.4 ± 0.3</td>
</tr>
<tr>
<td>Mean vitreous chamber depth (mm)</td>
<td>10.6 ± 1.0</td>
<td>10.6 ± 0.9</td>
<td>11.1 ± 0.8</td>
</tr>
<tr>
<td>Mean refraction (D)</td>
<td>+2.7 ± 4.4</td>
<td>+11.4 ± 3.7**</td>
<td>+13.5 ± 3.4**</td>
</tr>
</tbody>
</table>

Means ± SD
ACD = anterior chamber depth; AL = axial length
* Measured by ultrasound, corneal thickness (0.6mm)
**P<.05, 2-tailed Student t test

Differences between groups

Table 2 shows the empirically obtained mean values for ocular parameters before and after lens refilling surgery at an infusion bottle height of 50 cm. Lens refilling in the presence of a capsular plug resulted in a lens thickness closely approaching that of natural lenses. The mean refraction of the refilled eyes in both groups was more hyperopic than that of the natural lens.

Ocular refraction

Ocular refraction depended on infusion bottle height (Figure 4). Refraction became more hyperopic with increasing bottle height. The mean increase in hyperopia when the bottle was moved from 25 cm to 100 cm above eye level was 1.6 ± 0.6D. This increase was not significantly different between the no-plug group and the plug group.
Lens power

Figure 5 shows the relationship between infusion bottle height and the power of the refilled lens obtained by model calculations. The mean decrease in power when the bottle was moved from 25 cm to 100 cm above eye level was $1.8 \pm 1.8\text{D}$. The difference between groups was not statistically significant.

The optical power of lenses refilled without a plug was less than that of lenses refilled with a plug ($P=.03$). A repeated-measures ANOVA with Greenhouse-Geisser
(GG) correction yielded a significant correlation between the infusion height and the resulting lens power ($p=.028$; GG epsilon=0.56). Using the same statistics, a linear correlation between the infusion height and the lens power ($P=.006$) was detected. Figure 5 shows the lens power as a function of infusion bottle height in all eyes before lens refilling surgery. Between 0 and 100 cm, the mean lens power variation was 4.7 D and between 50 and 100 cm, 0.7 D. The power of the refilled lenses was less than that of natural lenses.

**Figure 5.** Infusion bottle height versus lens power found by model eye calculations. The calculations used data obtained with the A-scan and Hartinger refractometer at different infusion bottle heights.
Discussion

We found that the refraction in pig eyes with refilled lenses was influenced by infusion bottle height. Moving the infusion bottle from 25 to 100 cm above the eye changed the refractive power of the entire eye by approximately 1.6 D. Moving the infusion bottle from 25 to 100 cm above the eye level changed the lens power by approximately 1.8 D, based on the model calculations. If the change in lens power cannot be increased in the human eye, adjusting the infusion bottle height has no practical value since the lens power cannot be adjusted enough to attain emmetropia. When implanted during cataract surgery in normal eyes, IOLs with a power from 0 to 30 D are needed to achieve emmetropia in most patients. Our technique might be useful for fine-tuning the IOL power.

We used silicone oil to refill the lenses to study their dimensions at different infusion heights above the same eye while eliminating the influence of polymerization. During lens refilling, the material can polymerize and form a lens with a certain shape memory. This polymerization is necessary to prevent leakage from the capsular bag and guarantee long-term stability. However, even natural lenses that have an inherent shape memory are influenced by infusion bottle height. Because refilled lenses are designed to have elastic and viscous properties comparable to those of a natural lens, it is likely that secondary lens power change will occur when the infusion bottle is removed after surgery. If this is true, adjusting the infusion bottle height cannot be used to preset the lens power.

To predict the refraction after surgery, based on intraoperative refraction measurements, this study suggests that the IOP- as determined by infusion - should be in the same physiological range as the pressure in the closed eye. This was confirmed by O'Donnell and coauthors. An infusion bottle height of 25 to 100 cm corresponds to 18 to 76 mm Hg; thus, the infusion bottle should be approximately 25 cm above eye level in order to approach physiological postoperative pressure levels.

We used fresh pig eyes because they were readily available and the clarity of the media was excellent. The natural pig lens is more spherical and thicker than the human lens. The actual influence of infusion bottle height on the power of refilled human lenses remains to be elucidated.

Our study also found that the posterior radius of curvature of the refilled pig lenses was not influenced by the infusion bottle height. The literature cites a value of
–5.23 mm for the posterior radius of curvature in natural pig lenses. We found a mean value in refilled pig lenses of approximately –5.26 mm at different infusion heights. This value may have been stable over the range of heights because the vitreous body shapes the posterior face of the lens. It is well known that the vitreous body adheres tightly to the posterior face of the lens in young eyes. Studies of the role of the vitreous body in determining the shape of the refilled lens (eg, by experimental vitrectomy) might help clarify these results.

The thickness of lenses refilled using a plug was more similar to that of natural lenses than the thickness of refilled lenses without a plug. Also, the power of lenses refilled using a plug was higher than that of those refilled without using a plug. Thus, lens refilling using a plug is more suitable for reproducing the original lens dimensions. The refilled lenses in our study had a power between 25.0 and 30.0 D, while natural pig lenses have a power of approximately 50 D. This is a result of the difference in equivalent refractive indices of the natural pig lens and the refractive index of silicone oil (1.508 versus 1.428). The silicone oil was made to resemble the equivalent refractive index of a human lens, not to a pig lens. When we replaced the refractive index value 1.428 by 1.508 in our calculations, the mean power of the lenses refilled using a plug was 48.6 D. This value is similar to the mean value of the power of the natural lenses (47.8 D) at an infusion bottle height of 50 cm.

In conclusion, the power of natural or refilled pig lenses, with or without use of a plug, was affected by infusion bottle height. The thickness of lenses refilled using a plug was more similar to that of natural pig lenses than that of lenses refilled without a plug. In addition, pig eyes refilled in the presence of a plug had a higher lens power.
References


