The influence of viscoelastic substances on the corneal endothelial cell population during cataract surgery: a prospective study of cohesive and dispersive viscoelastics

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ABSTRACT.

Purpose: To compare the ability of cohesive and dispersive ophthalmic viscoelastic devices (OVDs) to protect the corneal endothelium following in-the-bag phacoemulsification with implantation of a foldable posterior chamber intraocular lens (IOL).

Methods: In a prospective single-masked randomized study, 60 eyes of 60 cataract patients were assigned to three groups of 20 patients each, according to which OVD was used: Celoftal®, Vitrax® or Healon®. The corneal response to surgery was evaluated by measuring the endothelial cell loss, the variation in mean cell area of the endothelial cells (CV), the frequency of hexagonal cells, and the central corneal thickness. Data were recorded preoperatively and 3 months postoperatively.

Results: Preoperatively, no significant difference was observed in cell count, CV, hexagonal pattern or pachymetry among groups. Postoperatively, all three groups had a significant decrease in cell count, but the decrease was significantly less in the Vitrax group (6.97%) than in the Celoftal (18.03%) and Healon groups (18.46%). No changes in CV, hexagonality or corneal thickness were observed within any of the three groups or among the groups. There was an equal and significant increase in visual acuity.

Conclusions: Phacoemulsification with implantation of a posterior chamber lens is known to affect the density and morphology of corneal endothelial cells. Viscoelastics facilitate cataract surgery and protect the corneal endothelium during the procedure. Choosing a dispersive hyaluronate OVD during the phaco procedure may allow for protection of the endothelial cells while suppressing the formation of free radicals. This may be the reason for the superior protective effect on the corneal endothelial cells of Vitrax compared with Celoftal and Healon.

Key words: cataract surgery – viscoelastics – endothelium cell – free radicals – Vitrax

Introduction

The development of new surgical phaco techniques is aimed at restoring visual acuity (VA) in order to secure a fast return to normal social life and work. Small-incision phaco procedures have minimized postoperative astigmatism, and better pre- and peroperative antibacterial procedures have reduced the incidence of postoperative endophthalmitis. However, postoperative VA can still be seriously compromised by transient or permanent corneal oedema caused by a decrease in endothelial pump function.

Several factors lead to endothelial cell damage during phacoemulsification, including: incision size and design (Dick et al. 1996); phacoemulsification technique (Pirazzoli et al. 1996); hardness of the nucleus (Hayashi et al. 1996); amount of total ultrasonic energy (Hayashi et al. 1994; Walkow et al. 2000); the composition of the irrigation fluids (Joussen et al. 2000; Cameron et al. 2001), and formation of free radicals (Holst et al. 1993; Cameron et al. 2001; Takahashi et al. 2002).

To decrease postoperative endothelial cell loss, different ocular viscoelastic devices (OVDs) have been proposed to facilitate surgical manoeuvres, maintain space during surgery, and protect
the endothelial cells. These effects have been demonstrated in an animal model using rabbits (Glasser et al. 1989, 1991). Other researchers have since provided evidence of endothelial cell protection during phacoemulsification in humans (Ravalico et al. 1997; Schwenn et al. 2000; Holzer et al. 2001; Maar et al. 2001).

The clarity of the cornea is dependent on endothelial cell pump function (Shaw et al. 1978). If the number of cells decreases to below a certain density, corneal oedema appears. The critical density is estimated to be 600–800 cells/mm². Other important descriptors of the endothelial cell population are the coefficient of variation of the mean cell area (CV) and the cellular shape (the frequency of hexagonal cells). An estimation of these two parameters is useful in following cellular reorganisation after cataract surgery (Schultz et al. 1986). In addition to cell density measurements, the results may provide an indication of endothelial cell damage.

Adult human corneal endothelium must be considered a non-replicative tissue (Mishima 1982). Throughout life there is a natural decrease in endothelial cell density, from 4000 cells/mm² in childhood to 2500 cells/mm² in people aged 80 years and over (Yee et al. 1985). Increased age and ocular traumas such as cataract surgery cause the endothelial cell area to become less uniform, which is reflected in an increase in CV value and a decrease in the frequency of hexagonal cells (Yee et al. 1985).

Pachymetry reflects endothelial functional status. The corneal endothelium acts as a barrier between the anterior chamber and the corneal stroma. If this barrier function is damaged during cataract surgery, swelling of the cornea will occur. An increase in central corneal thickness in the first postoperative week, measured by pachymetry, may be a useful clinical predictor of longterm endothelial cell loss (Cheng et al. 1988; Beneyto et al. 1996), although the correlation between corneal thickness and endothelial cell count is not quite clear (Koch et al. 1993).

The aim of the present study was to evaluate the efficacy of Vitrax® (Advanced Medical Optics, Inc., Santa Ana, CA, USA) in protecting the corneal endothelium during in-the-bag phacoemulsification with implantation of a foldable acrylic lens. Healon® (Advanced Medical Optics, Inc., Santa Ana, CA, USA) was used as the reference gold standard. We found only one study on Vitrax evaluating endothelial cell loss after extracapsular cataract extraction (ECCE) (Colin et al. 1995). To our knowledge there are no reports on endothelial damage after phacoemulsification using Vitrax.

Materials and Methods
We designed a clinical prospective, randomized study including 60 eyes of 60 consecutive patients scheduled to undergo cataract surgery at our department. The study protocol was approved by the local ethical committee. All patients gave full informed consent. The authors have no proprietary or financial interest in any of the products discussed.

The 60 patients were randomly assigned into three groups based on the OVDs used: Celofal, Vitrax or Healon. The three viscoelastics differ from each other in molecular weight, concentration, viscosity, pseudoplasticity, cohesiveness and coatability. The rheological and clinical features of the three OVDs are presented in Table 1.

Exclusion criteria were corneal abnormalities, traumas or previous intraocular surgery, history of intraocular inflammation, diabetes, preoperative pupil dilatation < 4 mm, age less than 40 years, preoperative endothelial cell count < 1500 cells/mm² and surgical complications. Preoperatively all patients underwent slit-lamp and retinal examination followed by measurement of best corrected visual acuity (BCVA) and intraocular pressure (IOP). The endothelial cell parameters including cell density, variation in CV, percentage of hexagonal cells and pachymetry were analysed using a non-contact specular microscope (SP 2000P; Topcon, Tokyo, Japan) with the Image-Net™ imaging system (version 2.1, Topcon, Tokyo, Japan). Specular microscopy was repeated 3 months postoperatively.

All operations were performed by one surgeon (JT) following a standardized procedure: sterile draping with Povidone-Iodine (PVD-Iodine) 5%; topical anaesthesia on the cornea (lidocaine 2% in gel suspension); a 2.75-mm, self-sealing, temporal, clear corneal incision; intracameral injection of lidocaine 1% followed by one of the three OVDs; capsulorhexis; one-handed divide-and-conquer removal of the nucleus; cortical clean-up; implantation of a foldable acrylic lens (AR 40e; Allergan, Advanced Medical Optics, Inc., Santa Ana, CA, USA) using an injector system, and aspiration of the OVD. At the end of the operation all patients received an injection of 4–5 cc cefuroxime (2.5 mg/ml) into the anterior chamber and behind the intraocular lens (IOL), followed by one drop of topical apraclonidine and one drop of PVP-Iodine. No sutures were applied.

The surgeon used a Storz Millennium phaco machine (Millennium, Bausch & Lomb, Inc., St. Louis, MO, USA) with a Kelman-type microtip and standardized machine settings. The patients were dismissed from our ambulatory centre 30 mins after

<table>
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<th>Table 1. Rheological characteristics of different viscoelastics (data provided by the manufacturers).</th>
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<tr>
<td>Classification</td>
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<tr>
<td>Ingredient</td>
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<tr>
<td>Concentration mg/ml</td>
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<tr>
<td>Molecular weight (Dalton)</td>
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<tr>
<td>Viscosity (V0)</td>
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<td>Shear rate = 0 cps</td>
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<td>Viscosity (V1000)</td>
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<tr>
<td>Shear rate = 1000 cps</td>
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<tr>
<td>Pseudoplasticity (V0/V1000)</td>
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<td>Cohesiveness</td>
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surgery. Postoperatively, dexametha-
sion (1 mg/ml) was given three times
daily for 3 weeks. No attempt was made
to mask the surgeon as to which viscoelastic was used because of the
different properties and behaviour of the OVDs. The surgeon had similar
experiences with all three OVDs. The two observers who performed the pre-
and postoperative measurements were not aware of the OVD used.

Statistical analysis
Tests for difference among groups in
demographic and clinical characteris-
tics were carried out using chi-square
tests for categorical variables and one-
way analysis of variance (anova) tables
for continuous variables. If differences
were observed using anova, least signi-
ficant difference tests were performed
between all groups of pairs. Noron-
roni correction was used to adjust for
multiple comparisons. Similar p-values
were obtained using non-parametric
tests (data not shown).

Mean VA was calculated based on
logMAR transformation. Visual acu-
ity is presented as Snellen decimal
fractions. The sample size was based
on power calculations (power 0.90,
$p = 0.05$) using a standard deviation
obtained in previous studies from our
institutions. For the power calculation
a clinical important change in cell
count was defined as a loss of one
standard deviation (300 cells/mm²).

Results
Sixty patients were enrolled but eight
patients did not attend the planned
postoperative examination despite two
calls to participate. A complete 3-
month follow-up examination was
obtained in the remaining 52 patients,
of whom 17 were in the Celofal
group, 16 in the Vitrax
group and 19 in the Healon
group.

Baseline preoperative demographic
data are given in Table 2. There were
no statistically significant differences
among the three groups in age, sex,
visual acuity or IOP (Table 2). No sig-
nificant difference was observed pre-
operatively among groups in any of
the cell parameters or in central cor-
neal thickness (Tables 3 and 4).

Postoperatively, all groups had a
significant decrease in endothelial cells
(Table 3). The mean endothelial cell
loss was 484 cells/mm² (18.03%) in
the Celofal group, 186 cells/mm²
(6.97%) in the Vitrax group, and
523 cells/mm² (18.46%) in the Healon
group. The Vitrax group had a signifi-
cantly lower rate of cell loss than the
other two groups (anova, $p = 0.04$;
Table 3).

There was no significant change in
variance in endothelial cell size
(CV), percentage of hexagonal cells or
central corneal thickness among the
groups (anova, $p > 0.05$; Table 4).
There was an equal and significant
increase in VA ($p < 0.5$). Postopera-
tive IOP did not differ significantly
from preoperative IOP within any
of the groups or among the three
groups.

Discussion
In the present study we investigated
the effect on the corneal endothelium
of phacoemulsification with implanta-
tion of a posterior foldable acrylic
lens using three different viscoelastics.
Preoperatively, demographic as well
as endothelial cell parameters were
similar in the three groups, indicating
that no sampling bias was present.
Loss of endothelial cells is compen-
sated by cellular enlargement, cell
gliding, rearrangement and cell
coalescence (Mishima 1982; Yee et al.
1985). Specular microscopy should be
performed at least 3 months postopera-
tively, when this reorganization has
started, when this reorganization has
started.
guideline was followed in the present study.

Postoperatively, all three groups had a significant decrease in cell density, but the cell loss was significantly lower in the Vitrax group than in the other two groups. Several factors may explain this observation.

Ophthalmic viscoelastic devices have been shown to decrease endothelial cell damage during phacoemulsification by facilitating the surgical manoeuvres, maintaining space and protecting the endothelial cells during surgery. The viscoelastics can be described by their rheological properties (Table 1). However, in clinical life it is more convenient to divide OVDs into two main groups of cohesive and dispersive OVDs according to their behaviour during surgery (Liesegang 1990).

A cohesive hyaluronate OVD with high molecular weight, such as Healon, contains long polysaccharide chains with glycosidic connections, which gives it higher viscosity, pseudoplasticity and cohesiveness. Cohesive OVDs are good at maintaining space and stabilizing tissue during surgery. They are easy to inject and to remove from the anterior chamber (McDermott et al. 1998; Poyer et al. 1998). However, the vulnerable aspect of these OVDs concerns their tendency to escape from the anterior chamber as a solid mass during phacoemulsification, leaving the endothelial cells without sufficient protection (Koch et al. 1993; Miyata et al. 2002).

Dispersive hyaluronates and methylcellulose OVDs such as Vitrax and Celoftal have lower molecular weight and shorter, weaker chains which give them less viscosity, pseudoplasticity and cohesiveness. Dispersive OVDs do not maintain space as well as the cohesive agents. However, they are less entangled, so they do not leave the anterior chamber during surgery as easily as cohesive OVDs, which means dispersive OVDs are better able to coat and protect the corneal endothelium (Koch et al. 1993; McDermott et al. 1998; Poyer et al. 1998).

This ability is convenient during surgery, but it is more difficult to remove dispersive OVDs from the anterior chamber at the end of the operation. The complete removal of these OVDs may prolong aspiration/irrigation time and be responsible for increased endothelial cell loss (Holzer et al. 2001). This has been demonstrated for Viscoat® (Alcon Laboratories, Inc., Fort Worth, TX, USA), another dispersive OVD. Using the Miyake video technique, Assia et al. (1992) showed that Viscoat was more time-consuming to remove from the anterior chamber than a 2% methylcellulose OVD (Ocucoats®; Storz, St. Louis, MO, USA). In the present study, the OVD was not meticulously removed, but most visible OVD was aspirated, and the patients were given an antiglaucomatous eyedrop (apraclonidine) at the end of operation.

Although Vitrax and Celoftal are both dispersive OVDs, less cell loss was observed with Vitrax. This may be explained by the ability of Vitrax to reduce formation of free radicals. Phacoemulsification produces free hydroxyl radicals and reports suggest that these are destructive to corneal endothelial cells (Shimmura et al. 1992; Holst et al. 1993). The amount of free radicals is proportional to phaco time (Holst et al. 1993; Cameron et al. 2001). Hyaluronate OVDs have been shown to suppress the formation of free radicals and exert anti-inflammatory properties (Camilleri et al. 2004). It has been demonstrated that dispersive hyaluronate OVDs (Vitrax) suppress free radicals better than cohesive hyaluronate OVDs (Healon) (Takahashi et al. 2002). Others have shown that cohesive hyaluronate OVDs (Healon) suppress the formation of free radicals significantly more than methylcellulose (Augustin & Dick 2004). Results similar to ours have been published for the dispersive OVD Viscoat. In a study by Koch et al. (1993), significantly better endothelial protection was observed using Viscoat compared with a cohesive OVD (Healon).

A new group of OVDs, the viscoadaptives (Healon5®, Advanced Medical Optics, Inc., Santa Ana, CA, USA, and I-Visc®, Bohus BioTech, Stromstad, Sweden), behave differently from both the cohesive and the dispersive OVDs because they are able to change from being highly viscous cohesive to fracturable pseudo-dispersive (Arshinoff & Jafari 2003) according to the flow rate. It has been suggested that these new viscoadaptives may offer better protection of endothelial cells because they are well retained during lower flow rates, and are easily evacuated under higher flow at the conclusion of the operation (Arshinoff & Wong 2003). Healon5® and GV (Advanced Medical Optics, Inc., Santa Ana, CA, USA) have been compared with the dispersive Viscoat and seem to offer comparable protection to endothelial cells (Ravalico et al. 1997; Miller & Colvard 1999; Schwenn et al. 2000; Vajpayee et al. 2005).

In summary, Vitrax is a dispersive hyaluronate OVD which is well retained in the anterior chamber during the phaco procedure, and thus offers mechanical protection to endothelial cells while suppressing the formation of free radicals. These abilities may explain the better protection provided by Vitrax compared with both Celoftal and Healon. Our results encourage further investigations of the protective characteristics of Vitrax and similar dispersive, low molecular, hyaluronate OVDs.

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