A multicentric, randomized double-masked study comparing the efficacy of fermented sodium hyaluronate vs. rooster comb sodium hyaluronate in cataract surgery.

Dr. Volker Rasch, Potsdamer Augenklinik im Graefe-Haus GmbH, Potsdam, Germany

Dr. Hans Ulrich Frank & Dr. Hendrik Fuchs, BELENUS Augenzentrum, Siegen, Germany

Dirk Krüger, Ph.D., ALBOMED® GmbH, Schwarzenbruck, Germany

Abstract

Purpose:

To compare the efficiency, performance and ease-of-use of Ophthalmic Viscosurgical Devices (OVDs) with either 1.4% or 1.6% sodium hyaluronate (HA) of bacterial origin by biofermentation with a product with 1.0% native sodium hyaluronate from rooster comb.

Methods:

Seventy-six eyes were included in this trial. A number of parameters were obtained: intraocular pressure (IOP), endothelial cell density, corneal thickness, ease-of-use (by questionnaire to the ophthalmosurgeon), time needed to drain off the OVD, severity of the cataract, phacoenergy, and time needed for phaco-extraction. Secondary data obtained were: total duration of surgery, specifications of inserted intraocular lens (IOL), balanced salt solution (BSS), best corrected visual acuity (BCVA), ease-of-use by questionnaire, any other medication taken, anamnesis. Statistical analysis was performed in standardized software.

Results and Conclusions:

In almost all parameters, the control viscoelasticum (VE) product of avian origin scored similar to the VEs from bio-fermentation, with their lower viscosity, was evaluated better in terms of the loss during phacoemulsification and need to reinject more VE. The fermented HA VE products are a safe, cost-effective alternative compared to the OVD with HA of avian origin for the standard cataract surgery.

Study „Äquivalenzstudie Hyaluron F“
Ethics Commission Approvals under 2012-308-f-S and AS 159(bB)/2013

Introduction

Since the late 1970s viscoelastic (VE) substances are commonly used in ophthalmic surgery (Lloyd et al 2001, Arshinoff & Jafari 2005). In providing stability and support in the anterior chamber as well as protection for the corneal endothelium, their availability meant a revolutionary progress for surgery of patients with senile cataract that includes the phacoemulsification of the aged lens and its replacement by an intraocular lens (IOL). The primary gels now used as medical products termed OVDs (Ophthalmic Viscosurgical Devices) are based on either the sodium salt of hyaluronic acid (HA) or hydroxypropyl methylcellulose (HPMC). HA is commonplace in extracellular spaces of almost all animal tissues and plays manifold roles (Fraser et al 1997), hence it is nowadays also commonly used in aesthetic surgery, as health supplemental, and as pharmaceutical for various conditions including a potential effect in cancer treatment (Lokeshwar et al 2014). HA naturally has the capacity to hold a large amount of water, such as in the vitreous body of the eye (Theocharis et al 2008) and it interacts with a number of proteoglycans in interstitial spaces. The sodium salt of HA is produced either from rooster combs, thus of avian origin, or biofermented by genetically modified bacteria. HPMC however, is fully synthetical and in contrast to the biological macromolecule HA much shorter-chained. HA itself is a GAG (glucosaminoglycan), an unbranched polysaccharide consisting of repetitive disaccharides. Here these monomers are D-glucuronic acid and N-acetyl-D-glucosamine. HA VEs differ in the chain lenght and the degree of artifical, synthetically achieved cross-linkage and possibly addition of other substances with gelling and/or pharmacological character, such as anesthetic lidocaine or endothelium-protecting mannitol (Augustin & Dick 2004, Belda et al 2005) and also the proteoglycan chondroitin sulfate. Due to strict quality necessities of OVDs that include sterility and optical clarity, international standardisation in form of EN ISO 15798 applies. Of great importance is that application of the gel to the eye does not post-operatively raise the intraocular pressure (IOP) above 30 mmHg. A protection of the corneal endothelium can be seen by measuring corneal thickness by pachymetry (the thicker the more pressure on it) as well as by measuring cell density by endothel microscopy.

Goal of this work was to prove that biofermented, non-crosslinked, medium-chain length sodium hyaluronate gels in two concentrations are similar or better in performance and safety compared with long-chain length, classical sodium hyaluronate gels of avian origin. To be observed were effects on corneal endothelium, risks for raising IOP beyond a critical point, risk of intraocular infection and performance during cataract surgery. For the parameters of the three OVDs included in the study, see Table 1, and for the parameters to be obtained, see Table 2.

Table 1. Product specifications of the viscoelastica used in the clinical study, according to manufacturers.

	1.4% biofermented HA	1.6% biofermented HA	original 1.0% HA
	Study Group A	Study Group B	Control Group
molecular weight [MDa]	1.1 to 2.0	1.2 to 2.0	4.0
viscosity [m Pa*s]	approx. 60 000	approx. 80 000	200 000
osmolality [m Osm/kg]	270 to 400	270 to 400	304
pH	6.8 to 7.4	6.8 to 7.4	7.0 to 7.5
source	bacterial fermentation (*Streptococcus equi* Sand & Jensen subsp. *equi* (Sand & Jensen) Farrow & Collins)		rooster comb
sodium hyaluronate / ml	14.0 mg	16.0 mg	10.0 mg
sodium chloride / ml	8.5 mg	8.5 mg	8.5 mg
disodium hydrogen phosphate dihydrate / ml	0.563 mg	0.563 mg	0.04 mg
sodium dihydrogen phosphate dihydrate / ml	0.045 mg	0.045 mg	0.28 mg

Bacterial vs. non-bacterial hyaluronate study

Table 2. Time scheme and variables.

Data		pre-op	operation	1 day	1 week	1 month	3 months	any other time as needed
				+/- 4 hours	+/- 2 days	(4-6 weeks)	(12-16 weeks)	
inclusion and exclusion criteria		yes						
demographics and anamnesis		yes						
medication		yes		yes	yes	yes	yes	yes
patient agreement		yes						
general eye status		yes		yes	yes	yes	yes	
cataract degree	primary parameter	yes						
IOP	primary parameter	yes		yes	yes	yes	yes	(yes)
IOP over 30 mmHg				yes	yes	yes	yes	(yes)
endothelial cell density	primary parameter	yes		yes	yes	yes	yes	
central cornea thickness	primary parameter	yes		yes	yes	yes	yes	
handling, ease-of-use	primary parameter		yes					
time required for removal of VE	primary parameter		yes					
phaco energy	primary parameter		yes					
phaco time	primary parameter		yes					
operation duration	secondary parameter		yes					
other information on operation			yes					
IOL specifications	secondary parameter		yes					
BSS specifications	secondary parameter	yes			yes	yes	yes	
ease-of-use by questionnaire	secondary parameter		(yes)	(yes)	(yes)	(yes)	(yes)	(yes)
adverse/severe adverse effects				(yes)	(yes)	(yes)	(yes)	(yes)
stop of study				(yes)	(yes)	(yes)	(yes)	(yes)

Methods

Study design and data analysis were perfomed by an external service provider.The study was structured as a double-blinded, concealed, block-randomized design (Roberts & Torgerson 1998) that included two biofermented HA OVDs (Pe-Ha-Luron® F 1.4% 1.0 ml, Pe-Ha-Luron® F 1.6% 1,0 ml) by ALBOMED® GmbH (Schwarzenbruck, Germany) vs. standard avian-derived HA OVD (Healon® 11.0% 0.55 ml) by Abbott Medical Optics (Santa Ana, CA, USA; meanwhile Johnson & Johnson Vision), see Table 1. Power analysis for IOP, endothelial cell density, central corneal thickness and time needed for removal of OVD was done using a significance of .05. after Rosner (2010) and Blackwelder (1982) and basing this on literature reports (Behndig & Lundberg 2002, Lüchtenberg et al 2000, Rainer et al 2007, Storr-Paulsen et al 2007, Adina 2008, Auffarth et al 2004).

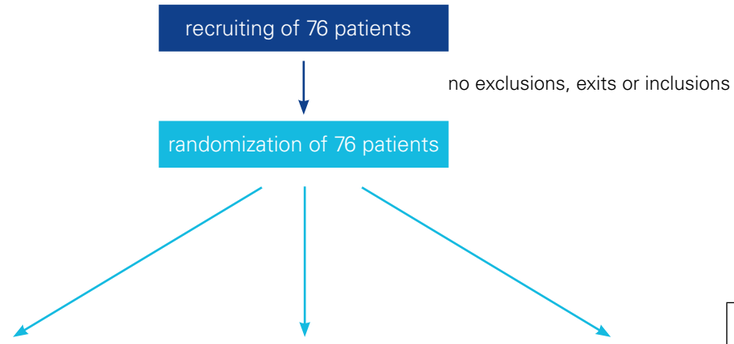
Thus a number of 25 eyes per group was deemed appropriate for this study. Hence 75 eyes with senile cataract were to be included. All operations and post-operative surveillance was performed by medical personnel trained in cataract surgery, with the post-operative surveillance physicians unaware of which OVD was used, while during surgery itself this was not possible. Ethics commissions approved the study before starting. For the recruitment flow chart and inclusion/exclusion criteria see Table 3. An approximately equal number of the three OVDs was used in each study center.

The recruitment was stopped when the 75 eyes were randomely assigned into groups by the external, independent study monitor. Occurence of severe adversary effects (SAE) was deemed to potentially warrant stopping ths study. Given GCP guidelines during emergency the group identity would have been allowed to be revealed.

Safety of the OVDs was gauged by differences in IOP and occurance of IOP > 30 mmHg 1 day and 1 week post-op (measured contact-free on NCT TOPCON CT-80, Oakland, NJ, USA), differences in endothelial cell density (measured with Tomey EM 3000, Phoenix, AZ, USA or TOPCON SP 2000, Oakland, NJ, USA), differences in corneal thickness 1 day and 1 week post-op, differences the condition of the eye 1 day and 1 week post-op. Performance was judged by handling during surgery, injectability, occurance of bubbles, visibility during surgery, leakage of OVD during phacoemulsification, necessity to replenish OVD, preparation of the anterior chamber, removability after surgery, handling of syringe. Grades 1 (for best) to 5 (for worst) were used by the physicians and it was tested for siginificant differences. Data were documented in standard Microsoft® software. Arythmetic mean, standard deviation, minima and maxima were calculated and t-tests performed. Diagrams were made using R (R Core Team 2013) with package ggplot2 (Wickham 2009).

Bacterial vs. non-bacterial hyaluronate study

Table 3. Recruitment scheme, exclusion and inclusion criteria, case numbers.



Study Group A	Study Group B	Control Group	List of Inclusion Criteria
n=26	n=25	n=25	- cataract operation - cataract degree 1-3 - endothelial cell density over 1600/mm² - adult
operation received: n=26	operation received: n=25	operation received: n=25	**List of Exclusion Criteria**
one day: n=25; 1 patient missed appointment	one day: n=25	one day: n=25	- glaucoma - corneal pathology - iritis - iridocyclitis - luxatio lentis, sublaxation - pseudoexfoliation - iris synechien - other current or prior ophthalmic diseases/surgery that may have to be tended to during course of study - concurrent iridectomy - piggyback lens, anterior chamber lens - hypertonism - insulin-dependent diabetes
one week: n=25	one week: n=25	one week: n=23; 1 patient excluded, 1 patient missed appointment	
one month: n=26	one month: n=25	one month: n=23; 1 patient excluded, 1 patient missed appointment	
analyzed after one day: n=24	analyzed after one day: n=25	analyzed after one day: n=25	
analyzed after one week: n=25	analyzed after one week: n=25	analyzed after one week: n=23	
analyzed after one month: n=25	analyzed after one month: n=25	analyzed after one month: n=23	
analyzed after three months: n=25	analyzed after three months: n=24	analyzed after three months: n=24	

Results

The number of recruited eyes was 76 initially. Due to a case of cornea guttata overseen during the pre-op examination, one patient with decreased endothelial cell density was excluded later on and replaced by another patient. One patient of the control group missed appointments 1 week and 1 month post-surgery, however, this patient was otherwise included in analyses.

An additional 2% was excluded from statistical analyses: 1 patient from Group A because of an additional, surgery-prolonging vitrectomy, and the 3 month post-op data from a patient in Group B because of appearing almost 3 months late for this appointment. Table 4 summarizes the observance of appointment time frames in the three groups.

The independent monitor also recognized that all laws, guidelines and standards governing clinical studies and medical devices were fulfilled throughout the study finished in October 2014, MPG (German Medical Device Law) 2009, MPKPV (German Ordinance on Medical Device Clinical Trials) 2010, MDD 2007, Helsinki Declaration on Ethical Principles for Medical Research, ICH-GCP, EN ISO 14155, EN ISO 14971, EN ISO 10993, EN ISO 15798.

Table 4. Average time of examinations.

day post-op examination	Study Group A				according to study plan
	mean	SD	min	max	mean
one day	1.00	0.00	1.00	1.00	1.00
one week	7.30	2.60	5.00	19.00	5.00 - 9.00
one month	31.00	3.00	26.00	36.00	28.00 - 42.00
three months	94.90	8.90	82.00	120.00	84.00 - 112.00
	Study Group B				
	mean	SD	min	max	mean
one day	1.00	0.00	1.00	1.00	1.00
one week	7.20	0.80	6.00	9.00	5.00 - 9.00
one month	32.00	3.20	28.00	40.00	28.00 - 42.00
three months	95.50	5.20	85.00	108.00	84.00 - 112.00
	Control Group				
	mean	SD	min	max	mean
one day	1.00	0.00	1.00	1.00	1.00
one week	7.00	1.20	5.00	9.00	5.00 - 9.00
one month	33.50	4.70	28.00	43.00	28.00 - 42.00
three months	95.40	8.60	81.00	128.00	84.00 - 112.00

Table 5 includes the baseline data as well as comparability of study groups. All 75 eyes, belonging to 61 patients of Caucasian race, were subjected to surgery on senile cataracts and treated with the same medication and BSS. One eye each of Group A and Group B showed post-op degeneration of the macula. In Group A turbidity remained on one posterior capsule, two eyes had vis a tergo, two had narrowed pupillae, and one eye required staining due to a cataracta matura. In Group B there also was one chronic turbidity, one visa tergo, one case of Floppy Iris Syndrome and one case with long paracentesis. In the Control Group two turbid posterior capsules remained, one damaged thin posterior capsule without further medical consequences, one eye showed vis a tergo vitrous body and enlarged rhesis. Two eyes had narrowed pupillae.

In six cases of the Control Group the OVD was insufficient in the delivered amount, and one was reported to drain too quickly. Tables 6a, 6b and Supplemental Table 1 (available upon request) summarize aforementioned findings, including the SAE of a macular edema in Control Group that was followed up. This was successfully treated with medication, leading to a BCVA of 1.0.

Table 5. Baseline data on the study population

population	n	n (Study Group A)	n (Study Group B)	n (Control Group)
number of eyes	75 (61 patients)	25	25	25
Study Center 1	53 (45 patients)	18	18	17
Study Center 2	22 (16 patients)	7	7	8
age [years]	72.1+/-8.6 (45–85)	71+/-10	72+/-8	73+/-8
male	19	8	5	6
female	56	17	20	19
right eye	37	13	15	9
left eye	37	12	10	15

Table 6a. Various parameters measured in Study Center 1.

		mean	SD	min	max
cataract degree [log]	Study Group A n=19	2.0	0.0	2.0	2.0
	Study Group B n=18	2.1	0.2	2.0	3.0
	Control Group n=17	2.0	0.0	2.0	2.0
phaco energy [%]	Study Group A n=19	13.7	6.5	5.0	30.0
	Study Group B n=18	11.4	5.5	5.0	29.0
	Control Group n=17	13.2	5.1	6.0	22.5
phaco time [s]	Study Group A n=19	17.2	28.6	3.0	124.0
	Study Group B n=18	8.2	5.9	2.0	24.0
	Control Group n=17	9.6	13.9	2.0	62.0
operation duration [min]	Study Group A n=19	12.7	6.6	7.9	38.0
	Study Group B n=18	10.6	2.2	7.9	17.4
	Control Group n=17	10.5	1.8	8.8	16.8
time VE removal [s]	Study Group A n=19	37.7	15.9	8.0	67.0
	Study Group B n=18	43.8	17.4	16	104.0
	Control Group n=17	35.4	13.0	18.0	60.1

Table 6b. Various parameters measured in Study Center 2.

		mean	SD	min	max
cataract degree [log]	Study Group A n=7	1.7	0.5	1.0	2.0
	Study Group B n=7	1.3	0.5	1.0	2.0
	Control Group n=8	1.8	0.5	1.0	2.0
phaco energy [%]	Study Group A n=7	80.0	0.0	80.0	80.0
	Study Group B n=7	80.0	0.0	80.0	80.0
	Control Group n=8	80.0	0.0	80.0	80.0
phaco time [s]	Study Group A n=7	12.7	6.7	2.2	20.0
	Study Group B n=7	8.3	6.3	2.8	18.0
	Control Group n=8	11.7	8.2	3.5	28.0
operation duration [min]	Study Group A n=7	7.9	1.3	6.0	10.0
	Study Group B n=7	7.1	1.6	5.0	10.0
	Control Group n=8	8.3	0.8	7.5	10.0
time VE removal [s]	Study Group A n=7	5.3	2.9	3.0	10.0
	Study Group B n=7	5.3	2.0	3.0	8.0
	Control Group n=8	5.4	2.7	3.0	10.0

Table 6c. Various parameters measured in both study centers combined.

		mean	SD	min	max	n	t-test
cataract degree [log]	Study Group A n=25	1.9	0.3	1.0	2.0	25	1.00
	Study Group B n=25	1.8	0.5	1.0	3.0	25	0.47
	Control Group n=25	1.9	0.3	1.0	3.0	25	1.00
phaco energy [%]	Study Group A n=25	32.4	30.8	5.0	80.0	25	0.81
	Study Group B n=25	30.6	31.8	5.0	80.0	25	0.66
	Control Group n=25	34.6	32.1	6.0	80.0	25	1.00
phaco time [s]	Study Group A n=25	16.4	25.0	2.2	124.0	25	0.28
	Study Group B n=25	8.3	5.9	2.0	24.0	25	0.47
	Control Group n=25	10.2	12.2	2.0	62.0	25	1.00
operation duration [min]	Study Group A n=25	10.3	2.8	6.0	18.4	25	0.48
	Study Group B n=25	9.6	2.6	5.0	17.4	25	0.76
	Control Group n=25	9.8	1.9	7.5	16.8	25	1.00
time VE removal [s]	Study Group A n=25	28.7	20.4	3.0	67.0	25	0.59
	Study Group B n=25	33.0	23.0	3.0	104.0	25	0.22
	Control Group n=25	25.8	17.9	3.0	60.1	25	1.00

IOP

IOP and IOP deviation pre-op vs. post-op is shown in Figure 1. There were no statistically significant differences. IOPs exceeding 30 mmHg were in no case measured, but in Study Group A one value of 30 mmHg 1 day post-op requiring IOP controlling medication. By 3 months post-op IOP has decreased significantly in all three groups (A: p=2.4 10-5, B: p=0.0015, C: p=0.0019, chi square test) by an average of 3.5 mmHg.

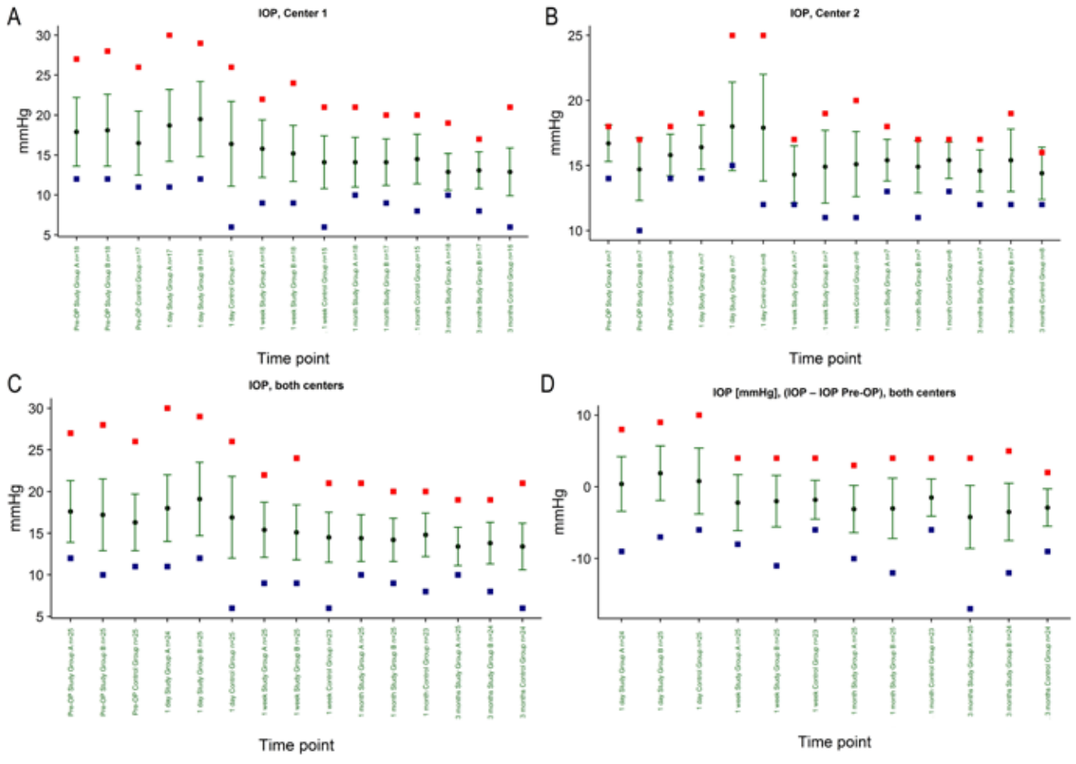


Figure 1. Intraocular pressure vs. time course. Study Center 1 (A) and 2 (B). Both study centers (C). Intraocular pressure differences vs. time courset. Both study centers (D). Blue = minimum, red = maximum, black dot = mean +/- SD (green bars).

Endothelial Cell Density

Starting out from statistically insignificant cell number differences, by 3 months post-op on average, in all three groups, 140 cells/mm^2 less were measured (Figure 2, in partiular Figure 2D).
Throughout the study, the three groups did not differ significantly.

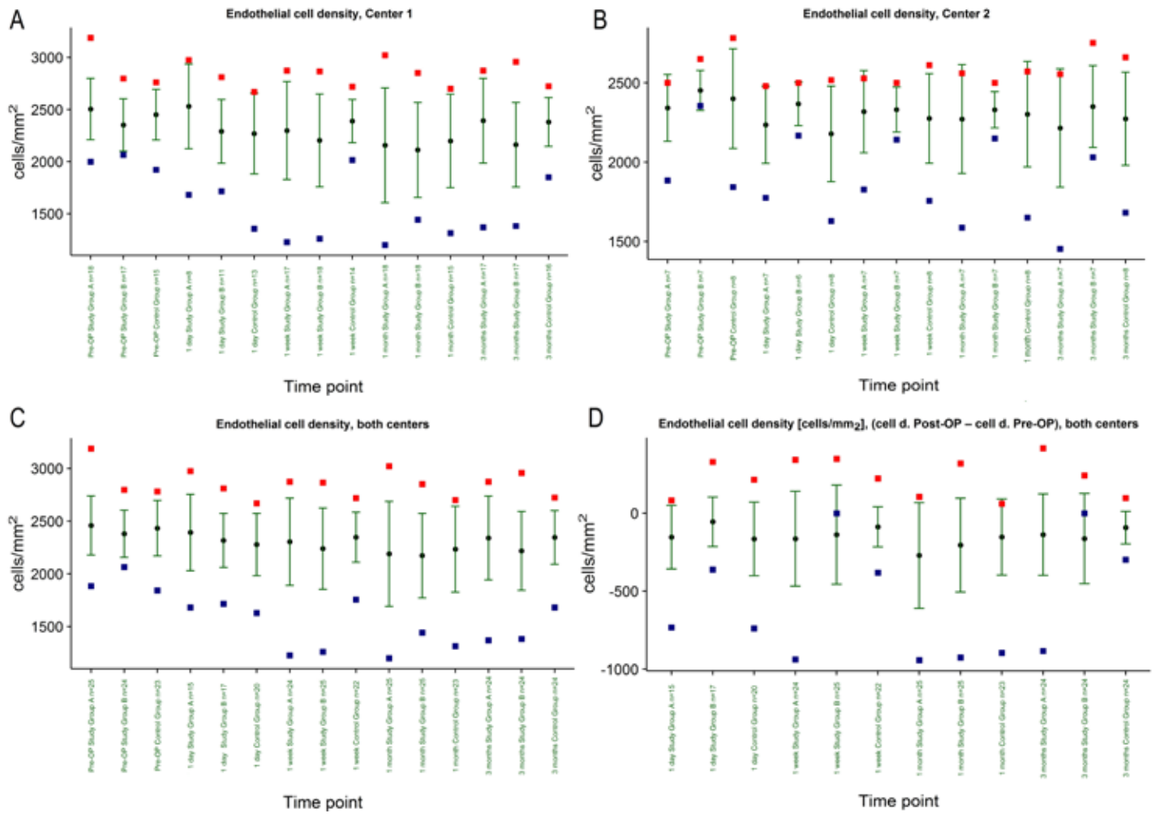


Figure 2. Endothelial cell density vs. time course. Study Center 1 (A) and 2 (B). Both study centers (C). Endothelial cell density differences vs. time course. Both study centers (D). Blue = minimum, red = maximum, black dot = mean +/- SD (green bars).

Cornea Thickness

As depicted in Figure 2 there were no significant differences in pachymetrically measured corneal thickness. Groups A and B showed 1 day post-op a mere tendency to slightly thicker corneas compared with the Control Group. This accompanies findings of slightly more stromal edema in Groups A and B. Supplemental Table 1 (available upon request) contains additional information gathered on the cornea. Groups A and B fared well in comparison with Control Group, especially in receiving better grades for not requiring additional injection of the OVD.

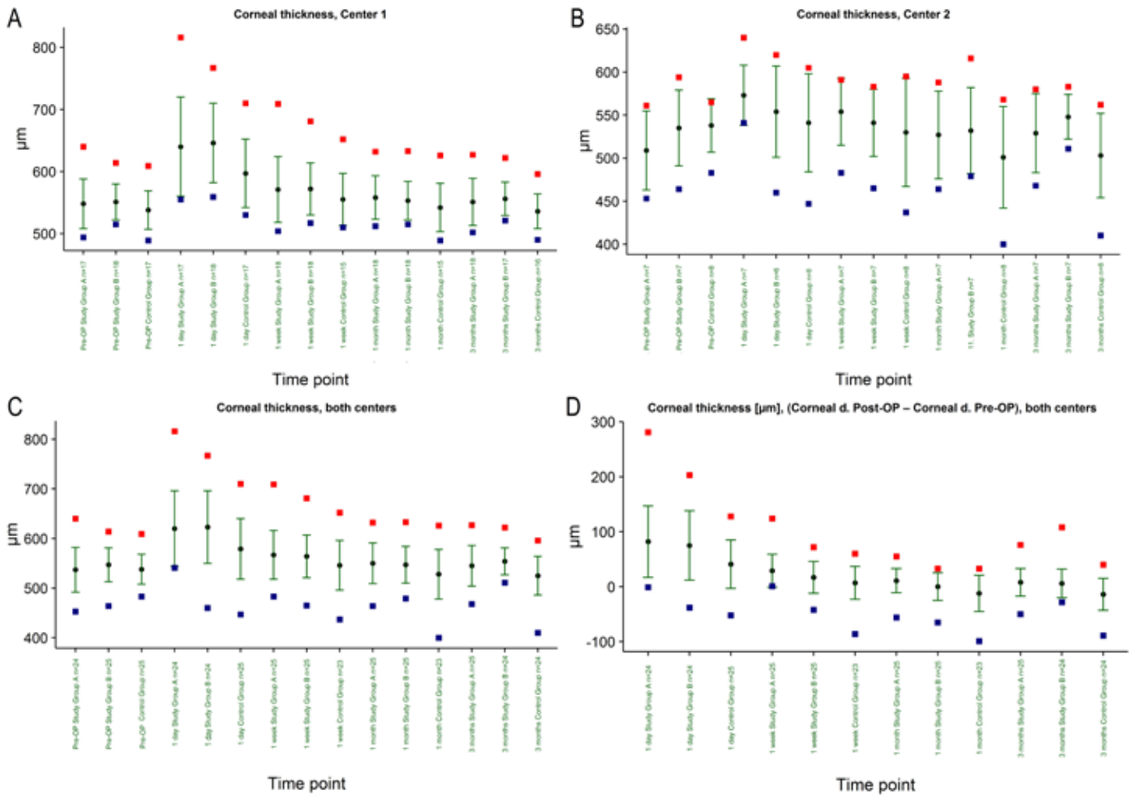


Figure 3. Corneal thickness vs. time plot. Study Center 1 (A) and 2 (B). Both study centers (C). Corneal thickness differences vs. time plot. Both study centers (D). Blue = minimum, red = maximum, black dot = mean +/- SD (green bars).

Evaluation Grades

Supplemental Table 1 (available upon request) contains all evaluation grades regarding surgery outcomes, and Supplemental Table 2 (available upon request) regarding package, preperedness and information of use. Generally, grades were better for the biofermented HA OVDs.

Visus

BCVA values are summarized in Figure 4. The results were comparable for all three groups..

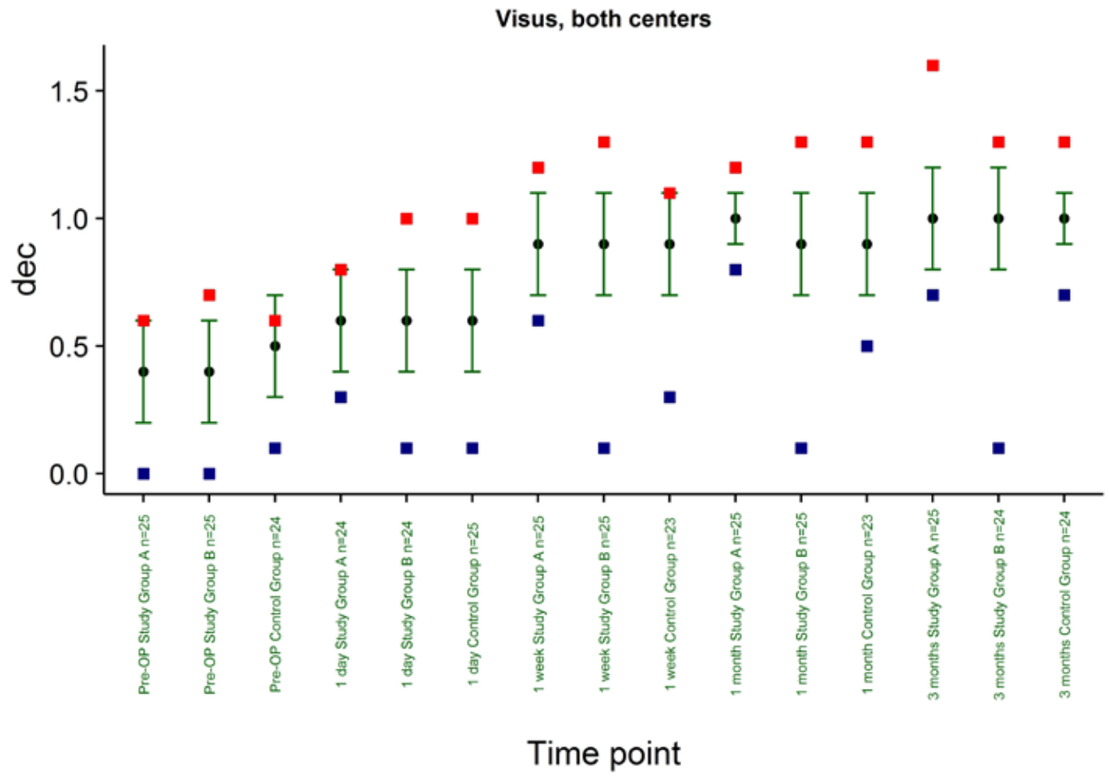


Figure 4. BCVA vs. time course. Both study centers. Blue = minimum, red = maximum, black dot = mean +/- SD (green bars).

Discussion

We are confident that by using standard measurements for IOP, the finding of no significant differences between groups are solid. Endothelial cell density measurements were done automatized on CE marked equipment. The eyes/patients of the three groups were equally treated and examined the two study centers having differently branded equipment. Pachymetry showed no significant differences, except for the slight tendency at day one post-op that in Groups A and B the cornea is slightly thicker and shows slightly more stromal edema than the Control Group. Generally in all three groups transient traumata were expectedly seen without differences between groups. The data are rather interpreted qualitatively than quantitatively, mostly due to the grading into categories after examination with a slit lamp microscope. The Groups A and B appeared better in terms of amount of OVD lost during surgery and need to reinject more of it. In 24% of the cases where the control OVD was used, the amount available to the surgeon was judged as insufficient, in 4% as barely sufficient. In difficult cases such as with Floppy Iris it seems necessary to use or at least add a highly viscous OVD. Parameters concerning the packaging were generally better in the Study Groups A and B than in the Control Group, while the information of use showed no statistically differences. However, it is not possible to draw strict statistics-confounded conclusions with this study.

It should be noted that only patients with senile cataract were included, and also patients with comorbidities were excluded, thus the results detailed here may be of limited applicability in such cases. The results are very similar to a study of Behndig & Lundberg (2002) where in 62 eyes beyond day 1 post-op a decrease in IOP was noted while at day 1 and pre-surgery the IOP were comparable. Rainer et al (2007) showed similar results in 60 eyes of 30 patients. Behndig & Lundberg (2002) also reported similar results in terms of corneal thickness. Storr-Paulsen et al (2007) reported decrease in corneal thickness (60 eyes), especially strongly in their group of 20 eyes (same as control OVD in our group), but with higher error bars than in our study. Our Groups A and B performed better (ca.400 cells / mm^2 lost) in comparison with a study that included similar OVD (compared with HPMC), where 140-160 cells / mm^2 were lost (Espindola et al 2012).

Conclusions

The standard rooster comb OVD bears no significant advantage over biofermented HA OVDs for example in terms of endothelial protection, intraoperative handling or in prevention of higher post-op IOP. The tested bacterial-derived OVDs contained 1.0 ml hydrogel, which provides more safety than the OVD with 0.55 ml hydrogel per syringe. This is an additional advantage especially for deeper anterior chambers, making sure there is enough material per syringe for the surgery.

Author Contributions

Wrote the article: DK, performed the surgeries and compiled data: VR, HUF, HF.

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