

ARTICLE



The effect of hypotensive drugs on intraocular lenses clarity

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OBJECTIVES: To assess the effect of hypotensive drugs on light absorbance, discoloration, opacification and precipitate formation of IOLs.

METHODS: In this laboratory study, four types of IOLs (two hydrophilic-acrylic—L1 and L2, and two hydrophobic-acrylic—B1 and B2) were soaked in solutions containing Timolol-maleate 0.5%, Dorzolamide 2%, Brimonidine-tartrate 0.2%, Latanoprost 0.005%, Brimonidine-tartrate/Timolol-maleate 0.2%/0.5% and Dorzolamide/Timolol-maleate 2%/0.5%. Non-treated IOLs and IOLs soaked in balanced salt solution (BSS) served as controls. All Treated lenses were sealed in containers and placed in an oven at 82 degrees Celsius for 120 days. Each IOL was examined using four different techniques: light microscopy imaging, light absorbance measurements at 550 nanometers through the optic's center, assessment of by a scanning electron microscope (SEM), and energy dispersive Xray spectrometry (EDX).

RESULTS: Ninety-eight IOLs were included. All BSS-soaked IOLs appeared clear with no significant discoloration or precipitate-formation. Light absorbance in these lenses was comparable to that of non-soaked, non-heated IOLs. No calcium or phosphate were detected in either of these groups. Light absorbance differed significantly between the four treated IOL types. The drops most affecting light absorbance differed between IOLs. Gross examination revealed brown and yellow discoloration of all IOLs soaked in Dorzolamide and Brimonidine-tartrate solutions, respectively. SEM demonstrated precipitates that differed in size, morphology and distribution, between different IOL-solution combinations. EDX's demonstrated the presence calcium and phosphor in the majority of precipitates and the presence of sulfur in brown discolored IOLs.

CONCLUSIONS: In vitro, interactions between hypotensive drugs and IOLs induce changes in light absorbance, discoloration and precipitate formation.

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INTRODUCTION

Cataract and Glaucoma are two of the most common ophthalmic conditions affecting hundreds of millions of patients worldwide [1, 2]. The treatment for cataract is surgical replacement of the natural lens with an implanted clear synthetic intraocular lens (IOL), which is meant to stay clear for the lifetime of the patient [3]. The mainstay of treatment for glaucoma is hypotensive drops, which patients take daily for many years, and often for their whole lifetime [4]. Thus, pseudophakia and chronic use of topical hypotensive drugs are two conditions which often co-exist [5].

IOLs are designed to remain clear for the patient's lifetime. However, when loss of optical clarity does occur, it can reduce the quality of vision and may even lead to explantation of the implant [6–11].

Loss of IOL clarity may manifest in different ways, namely opacification, discoloration, precipitate formation or glistening [12]. The effects of these on visual quality range from insignificant to visually debilitating [13, 14].

Multiple risk factors for loss of IOL clarity have been found: the characteristics of the polymer (water content, molecular arrangement and photochemical resistance among others), the production and packaging processes or implantation techniques

and more [15–17]. Opacification, discoloration, degradation and glistening were reported for polymethyl methacrylate, silicone, hydrogel, hydrophilic and hydrophobic acrylic lenses [17–19]. Intraocular exposure to drugs and materials such as silicone oil, gas and air have been shown to cause calcifications and opacifications of IOLs [20–24].

Correlations have also been found between IOL opacification and systemic conditions such as diabetes mellitus, or ophthalmic comorbidities such as diabetic retinopathy, history of retinal detachment or ocular trauma, and glaucoma [16].

Glaucoma has been shown to have an effect on aqueous humor composition and on its biochemical characteristics (altered metabolic state—proteome consistent, lipemic synthesis, inflammatory response and anti-oxidative action for instance) [25–28]. Glaucoma was proven to be a risk factor to both IOL opacification and glistening [16, 29, 30]. Additionally, several studies have shown a correlation between hypotensive glaucoma drops and nasolacrimal duct obstruction [31, 32], a fact which reinforces the suspicion of the tendency of hypotensive drugs to produce precipitates.

Yet, the effect of hypotensive drops on IOL clarity has not been reported to the best of our knowledge.

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In this study we aim to assess the effect of hypotensive drugs on opacification, precipitate formation, discoloration and glistening of IOLs.

MATERIALS AND METHODS

IOLs

We used four types of acrylic, monofocal, IOLs from three different manufacturers, two hydrophilic (marked L1 and L2), and two hydrophobic (marked B1 and B2). All IOLs used in this study are made of a well-known acrylic polymer which has been in widespread clinical use worldwide for decades. One type of hydrophobic IOL had a yellow tint (B2). As the lenses were donated, we could not control their dioptric power. The range of dioptric power of the IOLs used in this study ranged from $-10.0D$ to $+40.0D$, in accordance with the manufacturer's stock. In some IOLs, the dioptric power was unknown. All IOLs were donated to us by the manufacturer or their authorized distributor and were kept in their original packaging in accordance with the manufacturer's guidelines. All IOLs used in this study are routinely used in clinical practice with excellent results and have been for many years. Details of the manufacturers of the different lenses are not provided as the IOLs were donated for the purpose of the study on this condition.

Hypotensive drugs

The IOLs were soaked in 2 milliliters of a solution containing balanced salt solution (BSS) and a hypotensive drug in its original concentration in a ratio of 1:1. Six types of hypotensive ophthalmic drugs were used: Brimonidine-tartrate 0.2%, Timolol-maleate 0.5%, Dorzolamide 2%, Dorzolamide 2%/Timolol-maleate 0.5%, Latanoprost 0.005% and Brimonidine-tartrate 0.2%/Timolol-maleate 0.5%. The medications we used are commonly used in clinical practice worldwide, were purchased by the hospital's pharmacy and were kept according to manufacturer's instructions until use. For every solution used in this study, all ingredients (both active and non-active) were documented according to official drug leaflet (Supplementary Table 1).

Preparations and settings

We used silicone sealed glass containers, which were thoroughly rinsed with distilled water and completely dried prior to use.

Each IOL was soaked in 1 ml of study medication and 1 ml of BSS (6 containers) or with BSS alone (control). A mark was manually made on the bottle at the height of the solution to assure no evaporation or spillage occurred. Three duplicates of each IOL-drop combination were made. Samples of each IOL type were kept in the original packaging to serve as an additional control.

The containers were then placed in an opaque metal box and put in an oven at $82^{\circ}C$ for 4 months. Degradation of IOL material has been shown to develop over many years. The Arrhenius equation was used to simulate 10 years at a physiologic temperature of $37^{\circ}C$ [33].

IOL analysis

Each IOL underwent the following four examinations.

Light microscopy. After complete drying, each IOL was mounted on a glass slide and photographed by a retro-illuminating light microscope, at magnifications of $\times 10$, $\times 20$ and $\times 400$ (Leica Biosystems, San Diego, CA, USA).

Light absorbance. In order to ensure a reading through the center of the IOL optic, we printed three dimensional opaque polymeric inserts with an outer diameter designed to fit into a 24-well plate, and a central 3-millimeter opening (Supplementary Fig. 1). Light absorbance was measured at 5 central points at 550 nm light frequency of (approximately the middle of the visible light spectrum). For the measurement of photo-spectrometric light absorbance we used an ELISA reader (Infinite F200, Tecan Trading AG, Switzerland). Mean absorbance of the five measurements of each IOL were used for analysis.

Scanning electron microscope imaging and energy dispersive X-ray spectrometry readings. One representative IOL of each IOL-drug combination was scanned using a scanning electron microscope (SEM) (Quanta-200, Field Emission Instruments, the Netherlands). Back-scattered electron

mode was used to demonstrate difference in chemical composition within the samples, and a secondary electron (SE) mode was used to demonstrate the topographic characteristics of the samples. Selected areas of interest were demonstrated with high magnification ($\times 1000$). Then, the IOLs were scanned using the energy dispersive X-ray spectrometry (EDX) tool through areas of interest (i.e., precipitates) to obtain elemental spectrometric signatures.

Outcome measures and statistical analysis

All phenomena (discoloration, precipitates, opacification and glistening) detected in light microscopy and SEM were carefully documented. Absorbance of light was documented as percentage of the light transmitted by the machine. The presence of all chemical elements detected in EDX was also documented.

We found that a total sample size of 76 and 98 samples were required to detect a significant difference in light absorbance with a significance level of 0.05 and a power of 80% using one-way ANOVA comparing type of lenses and type of solutions respectively. Calculations were performed using G*Power software version 3.1.9.6.

Statistical analysis was performed using SPSS software for windows version 20.0 by IBM. *p* values < 0.05 on a two-sided test were considered statistically significant. For the analysis of continuous data, Student's independent *t* test was used for normally distributed variables. Kruskal–Wallis and post hoc Dunn test for pairwise comparisons with Bonferroni correction for multiple comparisons were carried out for non-parametric variables. One-way analysis of variance (ANOVA) was used for comparison of multiple group averages, Two-way ANOVA was used to determine interaction between IOL type and type of solution on mean light absorbance. Results are expressed as median (interquartile range (IQR)).

RESULTS

A total of 98 acrylic IOLs were included in the study. Forty-nine hydrophilic lenses and 49 hydrophobic lenses. Eighty-four IOLs were soaked (72 in solutions containing hypotensive drugs and 12 in BSS) and then heated, and 14 IOLs served as untreated, unheated controls. Thus, two types of controls were available: an untreated, unsoaked and unheated group ("non-treated"), and a BSS-soaked and heated group ("BSS group"), which was intended to reduce the confounding effects of the heating process.

Light microscopy imaging

Five types of gross changes were identified in the treated IOLs—opacification, brown discoloration, yellow discoloration, precipitate formation and glistening. Figure 1 shows distribution of phenomena by drug type and by IOL type, along with controls. Glistening occurred almost exclusively in one hydrophobic IOL (B2). The glistening occurred with all solutions, including BSS. Opacification and discoloration of both yellow and brown color were seen in all four IOL types.

Opacification. Opacification was noted in all four IOL types soaked in three types of solutions (containing Latanoprost, Brimonidine-tartrate and Brimonidine-tartrate/Timolol-maleate) (Supplementary Fig. 2). Three types of lenses presented a diffuse opacification pattern (L1, L2 and B2), and the fourth type (B1) presented a patchy opacification pattern.

Hydrophilic IOLs soaked in either Latanoprost or in Brimonidine-tartrate/Timolol-maleate, appeared opaque when dried, but immediately cleared when rehydrated. Higher magnification imaging demonstrated an alteration to the surface topography in both the wet and dry states (Supplementary Fig. 3).

Discoloration. IOLs soaked in solutions containing Brimonidine-tartrate showed different degrees of yellow discoloration. Discoloration was more prominent in Brimonidine-tartrate/Timolol-maleate combination drug than in Brimonidine-tartrate alone and appeared more intense in hydrophilic lenses than in hydrophobic lenses. IOLs which were soaked in solutions

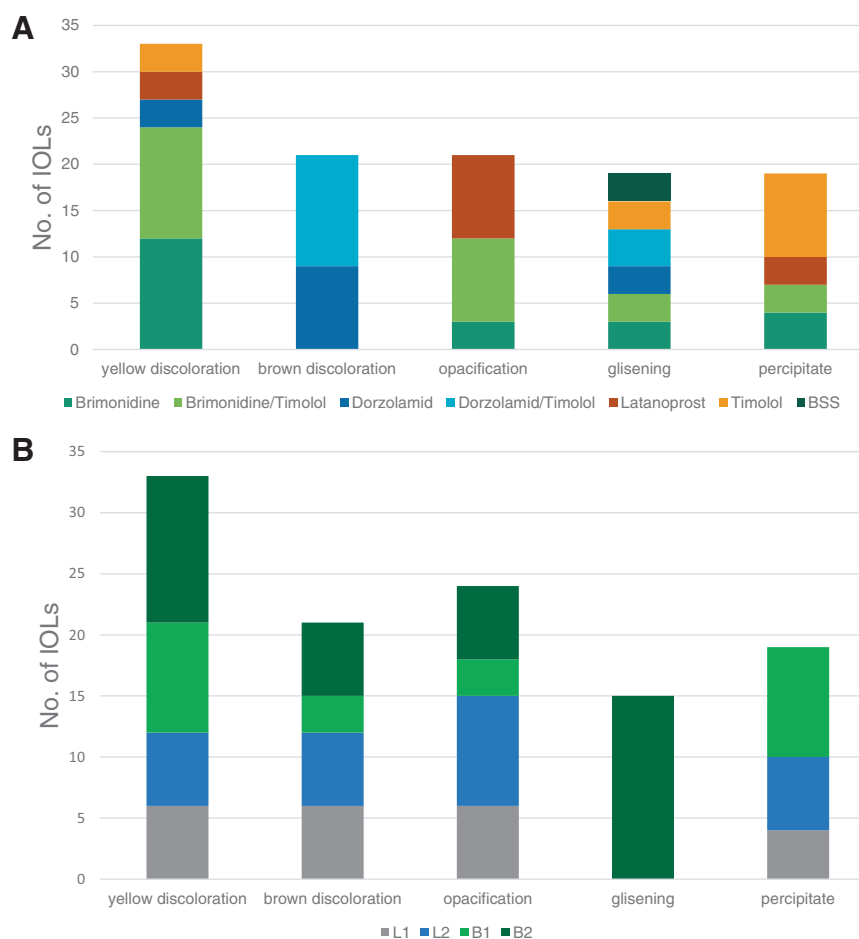


Fig. 1 Different phenomena identified by gross inspection. **A** Distribution of phenomena by drug type. **B** Distribution of phenomena by IOL type. L1 first type of hydrophilic acrylic IOL, L2 second type of hydrophilic acrylic IOL, B1 first type of hydrophobic acrylic IOL, B2 second type of hydrophobic acrylic IOL.

containing Dorzolamide and Dorzolamide/Timolol-maleate showed different degrees of brown discoloration. Three of the IOLs (duplicate of B1) which were soaked in Dorzolamide alone showed a minor discoloration which was difficult to classify. Since the change in color was very mild, it appeared yellow to the naked eye. All other IOL soaked in solutions containing Dorzolamide showed a brown discoloration. This phenomenon was more prominent in hydrophilic lenses and in Dorzolamide rather than in the combination drug (Fig. 2).

Precipitates. Surface precipitates were seen on IOLs soaked in Brimonidine-tartrate (L1, L2, B2), Brimonidine-tartrate/Timolol-maleate (L1, L2, B1, B2), Latanoprost (L1, L2, B1, B2) and Timolol-maleate (L1, L2, B1). No precipitates were seen on IOLs soaked in Dorzolamide or Dorzolamide/Timolol-maleate. Precipitates were observed on both hydrophilic and hydrophobic IOLs. Size, shape and distribution of the precipitates were specific to IOL-drug combinations (Fig. 3).

Glisening. Glisening occurred mainly in one type of hydrophobic IOL (B2) with all solutions including BSS but excluding Latanoprost. In the other hydrophobic model used in this study, glisening occurred infrequently with two types of solutions and without repetitions in the IOL duplicates (Supplementary Fig. 4).

Light absorbance

A two-way ANOVA was conducted to examine the effect of the IOLs and the solutions on the mean light absorbance. There was a

statistically significant interaction between the effects of IOL type and type of solution on mean light absorbance, $F(21, 66) = 3.863$, $p = 0$. Light absorbance depended on the IOL-solution combination. The drops most affecting light absorbance differed between IOLs. IOL type and water content (hydrophilic versus hydrophobic) did not affect mean light absorbance (Fig. 4A).

Light absorbance divided by IOL type. No statistically significance difference in light absorbance was seen between non-treated IOLs of different models ($p = 0.148$). When comparing all the treated lenses analyzed by the type of lens, the difference in the median absorbance between lenses B1 and L2 and between B1 and B2 was statistically significant. The difference between B1 and L1 was not significant. The median absorbance and IQR were 0.21 (0.1) for L1, 0.21 (0.21) for L2, 0.16 (0.02) for B1 and 0.28 (0.16) for B2. B1 showed a trend of lower light absorbance with different solutions, but this trend was not statistically significant. Figure 4B is a boxplot which depicts the absorbance divided by type of lenses.

Light absorbance divided by drug type. Light absorbance of IOLs in the BSS group was comparable to that seen in non-treated controls ($p > 0.05$). The difference between the mean light absorbance of IOLs soaked in hypotensive solutions and non-treated controls was statistically significant ($p = 0.003$). Light absorbance was significantly higher in IOLs soaked in Brimonidine-tartrate/Timolol-maleate, Dorzolamide/Timolol-maleate and Latanoprost as compared to non-treated controls ($p < 0.006$), and

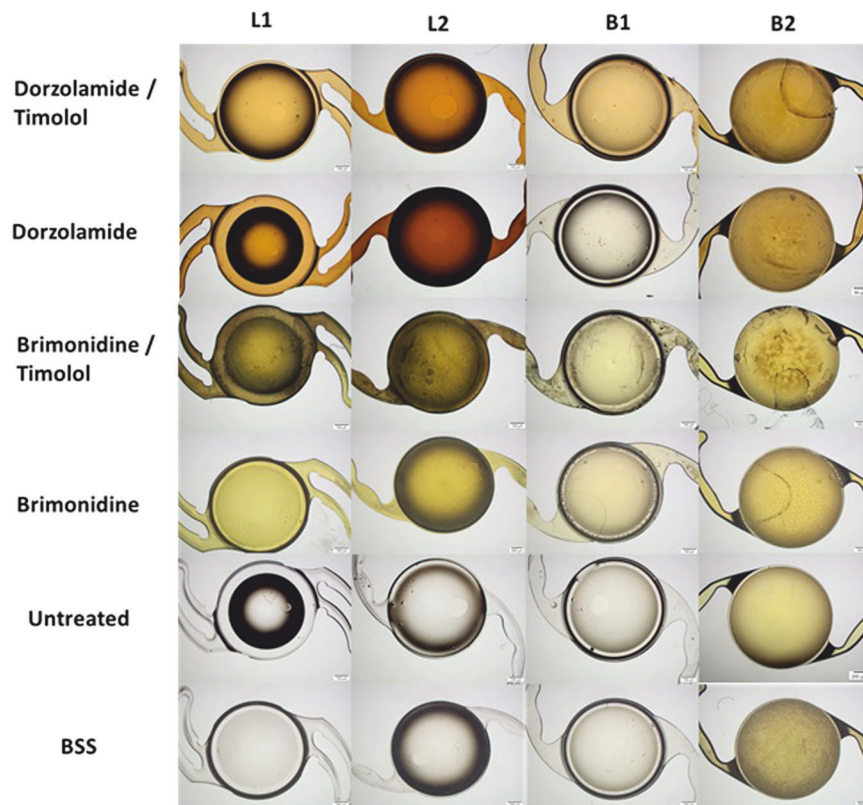


Fig. 2 Discoloration of IOLs. IOLs soaked in Brimonidine showing yellow discoloration and IOLs soaked in Dorzolamide showing brown discoloration as compared to untreated controls and BSS-soaked controls.

in IOLs soaked in Dorzolamide as compared to both types of controls.

The median absorbance and IQR from low to high were 0.13 (0.01) for non-treated controls; 0.13 (0.05) for BSS-soaked controls; 0.16 (0.04) for Brimonidine-tartrate; 0.18 (0.05) for Timolol-maleate; 0.23 (0.14) for Latanoprost; 0.24 (0.1) for Dorzolamide/Timolol-maleate; 0.26 (0.15) for Brimonidine-tartrate/Timolol-maleate; and 0.37 (0.27) for Dorzolamide. Light absorbance for all IOLs in the different solutions is shown in Fig. 4C.

Scanning electron microscopy (SEM)

SEM demonstrated three main phenomena: precipitates, mild and scattered surface alterations, and homogenous film-like coating. The precipitates' distribution, size, and morphology were specific to IOL-drug combination. The appearance under SEM mirrored that in light microscopy (Fig. 3). Mild and scattered surface alterations appeared in all soaked IOLs.

Homogenous film-like coating appeared in several IOL-drug combinations. This phenomenon mirrored an opacified appearance under light microscopy (Supplementary Fig. 5).

SE scans confirmed that the changes described above occurred on the surface of the IOLs (as the penetration of electron scanning is limited to a few microns) [34]. All treated IOLs demonstrated surface alterations of different nature compared to non-treated IOL of the same type.

When comparing SEM scans with high-magnification light microscopy images, a clear correlation arose: IOLs which looked grossly clear did not demonstrate precipitates or showed mild and scattered surface alterations. IOLs that presented circumscribed round precipitates in gross inspection, demonstrated the same pattern of changes in SEM scans (Fig. 3).

Morphology, size, distribution and density of the precipitates differed according to IOL-solution combinations. For some

solutions, morphology of the precipitates seemed similar with different IOL types (Supplementary Fig. 6).

EDX spectrometric signature

Reading through clear portions of nearly all IOLs demonstrated exclusive presence of carbon (C) and oxygen (O), the main components of most acrylic polymers. Readings through precipitates demonstrated signatures of Calcium (Ca) and Phosphor (P) in all IOLs soaked in Brimonidine-tartrate/Timolol-maleate, Latanoprost, and Timolol-maleate. Calcium and Phosphor were not detected in Dorzolamide, Dorzolamide/Timolol-maleate, Brimonidine-tartrate, BSS alone or non-treated IOLs. Lenses that underwent brown discoloration (all IOLs soaked in Dorzolamide or Dorzolamide/Timolol-maleate) showed presence of Sulfur (S). This chemical element was not detected in IOLs which were soaked in other solutions. Silicon was identified in several samples. Other chemical components of unknown origin were detected in different drugs, IOLs and areas of sampling (Aluminum, Brom, Magnesium, Potassium, Fluorine and more).

Data on chemical elements found with each IOL-drug combination are shown in Table 1.

A summary of the morphological and optical changes of the different IOL types in the various hypotensive drugs solutions are summarized in Supplementary Table 2.

DISCUSSION

In this *in vitro* study, hypotensive drugs affected IOL clarity. Significant and repeatable differences in light absorbance, precipitate formation and discoloration were seen in IOLs treated with hypotensive drugs compared with those treated with BSS or left untreated.

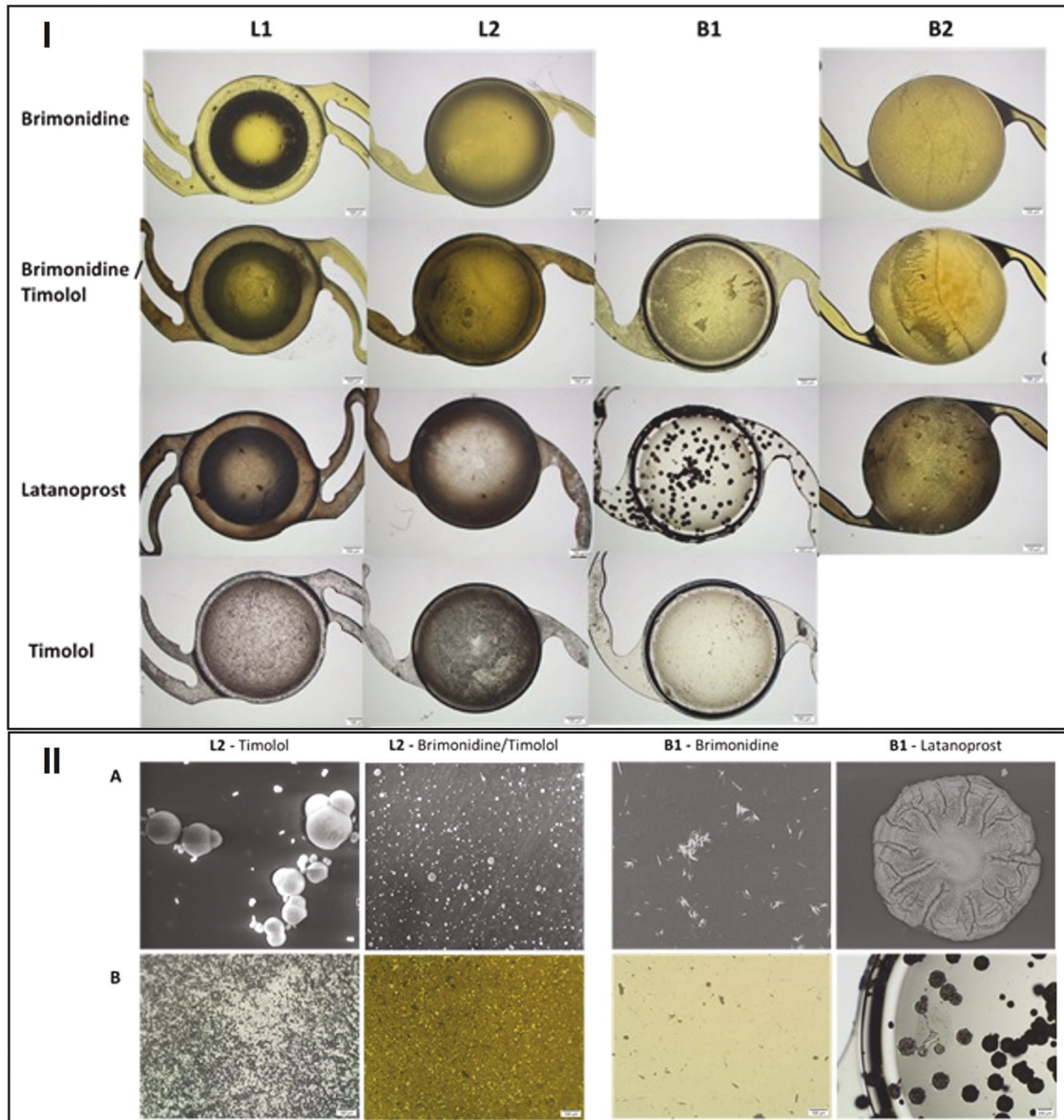


Fig. 3 Precipitates. I—Precipitates formed on different IOLs with different hypotensive drugs. II—Precipitates on hydrophilic and hydrophobic IOLs soaked in different solutions. Precipitates differ in distribution, size, and morphology in different IOL-drug combinations. There is a good correlation between SEM (A) and light microscopy imaging (B) in different IOLs and different solutions.

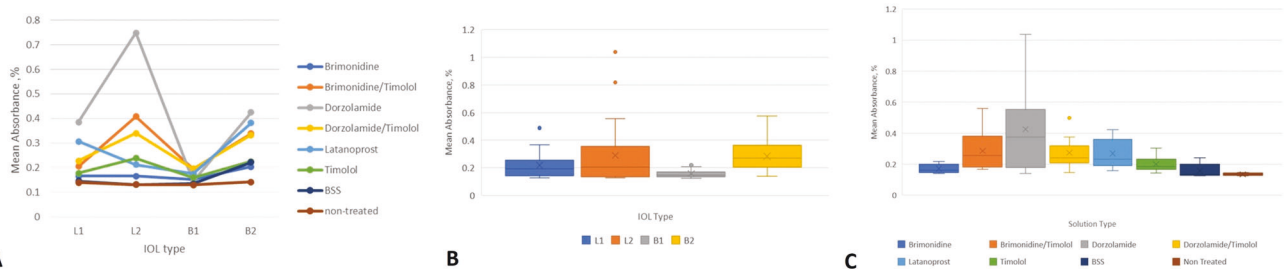


Fig. 4 Light absorbance. A Light absorbance (percentage of light transmitted) of different IOL models which were soaked in different solutions. There was a statistically significant interaction between the effects of IOL type and type of solution on mean light absorbance. B a boxplot that depicts the absorbance divided by type of lenses. C Light absorbance for all IOLs in the different solutions.

The morphology of the precipitates did not correlate solely to drug or IOL type, but rather to specific combinations. Different duplicates of the same IOL-drug combinations showed similar results. This suggests that both the drug type

and the nature of the polymer influence the precipitate formation. For some solutions, the shape of the precipitates was similar on all different IOLs, while their size and distribution varied.

Table 1. Main chemical elements composition in different combinations of IOL type and drug type found via energy dispersive X-ray spectrometry (EDX).

	Brimonidine	Brimonidine/ Timolol	Dorzolamid	Dorzolamide/ Timolol	Latanoprost	Timolol	BSS
L1	other	Ca-P, other	Sulfur, other	Sulfur, other	Ca-P, other	Ca-P, other	other
L2	other	Ca-P, other	sulfur	Sulfur, other	Ca-P, other	Ca-P, other	other
B1	other	Ca-P, other	Sulfur, other	Sulfur, other	Ca-P, other	Ca-P, other	other
B2	other	Ca-P, other	Sulfur, other	Sulfur, other	Ca-P, other	Ca-P, other	other

The cells of the table were colored according to the elements' composition detected in each combination in order to emphasize the correlation between drug type and composition of elements.
Ca-P calcium-phosphate.

Most precipitates contained Calcium and phosphorus. Calcium is present in the aqueous humor in normal conditions, and has been shown to form calcium phosphate deposits on explanted IOLs in previous studies [35–39]. In our *in vitro* study, BSS, which was added to all solutions, contains calcium [40] to simulate the environment in the posterior chamber [41]. While phosphorus is absent in BSS, it does exist in some of the hypotensive drugs we examined in our study (Timolol-maleate, Brimonidine-tartrate/Timolol-maleate and Latanoprost). Calcium-phosphate precipitates formed only in IOLs treated with the above drugs. Supplementary Table 1 elaborates different solutions ingredients, as specified in solutions' official leaflet.

We observed two different types of discolorations in our study. Yellow discoloration was observed in IOLs soaked in Brimonidine-tartrate and in its combination with Timolol-maleate. This yellow discoloration was not associated with increased light absorbance.

Dorzolamide, alone and in its combination with Timolol-maleate caused brown discoloration in all treated IOLs. One type of hydrophobic IOL (B2) showed a very mild discoloration which was difficult to classify, and appeared yellow to the naked eye. Since we detected sulfur on these lenses, as detected in other IOLs soaked in Dorzolamide we assume that this yellow appearance might be a milder form of sulfur accumulation. All these lenses showed a higher light absorbance and the presence of sulfur. No precipitates were formed with either of these solutions, and calcium and phosphorus were not detected. These findings suggest that the brown discoloration may be more disruptive to the passage of light with a wavelength of 550 nm as compared to the yellow discoloration.

Light microscopy demonstrated an opaque appearance of some hydrophilic IOLs which were soaked in Brimonidine-tartrate, Brimonidine-tartrate/Timolol-maleate and Latanoprost. This phenomenon was not visible in the primary gross examination of those lenses when kept in the containers within the solution. We recognized subtle surface alterations in high magnification of their light microscopy images. Interestingly, these IOLs seemed opaque when dry, and re-cleared when re-hydrated. We hypothesize that this phenomenon may be explained by light scattering caused at the surface of the IOLs, which was shown to have negligible effect on visual function in *in vitro* and *in vivo* studies [42, 43]. Kang et al. have shown that hydration status and temperature induced changes in IOLs' appearance [44]. The hypothesis requires further study.

We observed glistening formation in one of the two models of hydrophobic IOLs. Unlike previously published data by Schweitzer

et al. [29] who described a correlation between the use of hypotensive drops in glaucomatous eyes and glistening, glistening in our study seemed to be related to the IOL type, and not to the hypotensive drug exposure. Glistening also appeared in the BSS soaked IOLs. Previous reports demonstrated that glistening has a negligible effect on visual function in most cases [42, 45].

A clear effect of hypotensive drugs on light absorbance of IOLs was demonstrated. While BSS soaked IOLs showed low light absorbance similar to that of non-treated IOLs, all the IOLs soaked in hypotensive drugs showed different levels of increased light absorbance as compared to controls.

A clear correlation between light absorbance and specific types of solutions or IOLs was not found, since no significant difference could be proven. The effect seemed to be related to IOL-solution combination.

No clear conclusion can be drawn regarding the effect of the precipitates on the light absorbance of the IOL, since most of the precipitates were discrete and surrounded by clear areas, and the light absorbance readings were made through five central locations. Correlating the readings to specific precipitate location was not possible in the setting of our study. Clinically, the presence of small discrete opacifications on the IOL is not considered by many physicians (authors included) to be clinically significant, though the effect is likely related to their size, density, opacity, location in relation to the visual axis and distribution.

We chose to measure light absorbance at 550 nm to represent the visible spectrum. Studies of different wavelengths could provide more insight into the effect of different solutions on light absorption through IOLs.

This study has several important limitations. The conditions in this study significantly differ from the conditions in the human eye. Drug concentration was dramatically higher in our study as compared to that inside the posterior chamber. The duration and intensity of IOL-drug exposure was significantly higher in our study as compared to a real-life scenario. The IOLs were constantly soaked in the solutions for months, while in real life the patient applies drops one to three times a day, and there is some washout from tears. The remaining drug must then travel through the different layers of the cornea and eventually penetrate into the anterior and posterior chambers [46]. Latanoprost, is a pro-drug, which is modulated by the tear film and corneal enzymes. No enzymes or other non-active ingredients were added to the containers. The effects of non-active ingredients (including those of the preservative), were not assessed.

Despite the fact that heating of IOLs were shown to approximate aging of IOL polymer material [33], we assume that heating to high temperature for an extended period of time is not fully comparable to physiologic aging of the polymer. In addition, the effect of heating on different drugs is unknown. Especially susceptible to change may be those drugs which the manufacturer recommends keeping refrigerated. As heating drugs may change their chemical and physical characteristics, we conducted a photo-spectrometry analysis of the heated solutions. Since the absorbance readings were low and the difference between the solutions was insignificant, we found it did not contribute to our understanding of the findings and was thus not included in the final manuscript. Further studies including administration of drops according to their recommended use instructions are warranted.

Laboratory conditions do not simulate an organic, living environment. Though BSS was added to each container in order to approximate the chemical composition of the aqueous humor, a large variety of factors play a role in its maintenance (proteins, immune mediators, secretion and absorption of materials, pressure, acidity, etc.).

Visual significance of our findings, both in vitro and in vivo, needs to be further assessed, but were beyond the scope of this preliminary study. As previously shown, changes in optical qualities of an IOL may have an effect on modulation transfer function, light scattering, contrast sensitivity and more. These investigations are planned in further studies. Glaucoma has been shown to be a risk factor for IOL opacification [16]. However, the pathomechanism for this is unclear. The causes for deterioration in visual function of glaucoma patients are variable and include changes in ocular surface secondary to intensive drop use [47], retinal nerve fiber layer damage [48], loss of contrast sensitivity and more. For these patients, separating loss of IOL clarity as a significant reason for a decrease of visual function may prove very difficult. On the other hand, the multiple insults described highlight the importance of controlling as many variables as possible.

Significance of our study and future directions

This in vitro study preliminarily demonstrated a clear correlation between IOLs' loss of clarity and exposure to hypotensive drugs. To better characterize this correlation and its clinical importance, further research is needed. Some important questions that must be addressed include the effect of drug concentrations closer to the relevant clinical scenario, the effect of hypotensive drugs on additional IOL types, the effect of other hypotensive drugs on different IOL types, light absorbance through more wavelengths in the visual spectrum and the effect of heat on different solutions.

Correlating our findings to clinical practice is impossible at present. Different methods of in vitro and in vivo studies are required before this can be properly addressed. It is possible that in the future, knowledge of hypotensive drugs-IOL interactions can facilitate better, evidence-based pairings.

CONCLUSIONS

Hypotensive drugs significantly affect hydrophobic and hydrophilic IOL clarity in vitro. This manifests as changes in light absorbance, discoloration, and precipitate formation.

SUMMARY

What was known before

- Cataract and Glaucoma are two of the most common ophthalmic conditions, Glaucoma was shown to be a risk factor to both IOL opacification and Glistening, yet the effect of hypotensive drops on IOL clarity has not been studied

What this study adds

- Hypotensive drugs significantly affect hydrophobic and hydrophilic IOL clarity in vitro. This manifests as changes in light absorbance, discoloration, and precipitate formation.

DATA AVAILABILITY

The data that support the findings of this study are not openly available due to the specific condition of the IOL donators. Data are available from the corresponding author upon reasonable request and may be shown under blindness of the IOL manufacture and model.

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AUTHOR CONTRIBUTIONS

TS conceived and directed the project and wrote the manuscript. LNBH collected data, performed statistical analysis and critically revised the manuscript. NR, DK and AK collected data, YT, ALE and EIA contributed to the discussion and critically revised the manuscript. AB conceived the project, wrote the manuscript and directed the project.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

This study was exempted by the Institutional Review Board (IRB) at Meir Medical Center, since no use of human data was used.

ADDITIONAL INFORMATION

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