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Ultrasound Cyclo Plasty in patients with open angle glaucoma and high myopia

--Manuscript Draft--

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Abstract:	Purpose: This study aimed to evaluate the efficacy and safety of UCP in glaucoma patients with high-myopia. Methods: In this retrospective, single-center study, we enrolled 36 eyes divided into two groups based on axial length: group A (≥ 26.00 mm) and group B (< 26.00 mm). We collected data about visual acuity, Goldmann applanation tonometry, biomicroscopy, and visual field before the procedure and at 1, 7, 30, 60, 90, 180, and 365 days after the procedure. Results: Mean IOP significantly decreased in both groups after treatment ($p<0.001$). Mean IOP reduction from baseline to the last visit was 9.8 ± 6.6 mmHg (38.7%) in group A and 9.6 ± 6.3 mmHg (34.8%) in group B ($p<0.001$). Mean IOP at the last visit was 15.8 ± 4.1 mmHg in the myopic group and 18.1 ± 5.6 mmHg in the non-myopic one. Regarding the number of IOP-lowering eyedrops being taken by our patients, no statistically significant differences were found between groups A and B at baseline (2.8 ± 0.9 and 2.6 ± 1.0; $p=0.568$) nor 1 year after the procedure (2.5 ± 1.1 and 2.6 ± 1.1; $p=0.762$). No major complications occurred. All minor adverse events resolved within a few days. Conclusion: UCP seems to be an effective and well-tolerated strategy to lower IOP in glaucoma patients with high-myopia.

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Chairman: Prof. Michele Figus

Dear Prof. Neeru Gupta,

We are pleased to submit the revised manuscript entitled: **Ultrasound Cyclo Plasty in patients with open angle glaucoma and high myopia** by Michele Figus, Alessandro Palma, Giuseppe Covello, Luca Agnifili and Chiara Posarelli for publication on the Journal of Glaucoma.

The manuscript has been revised according to JOG suggestions as follows:

Editorial Board Comments
Please change title: Ultrasound Cyclo Plasty in patients with primary open angle glaucoma patients and high myopia

Thanks to Editorial Board for this suggestion. We accepted the change of the title. However, we prefer to delete the word “primary” because some patients had diagnosis of secondary open angle glaucoma and “patients” that was redundant. So, we changed the title as follows: “Ultrasound Cyclo Plasty in patients with open angle glaucoma and high myopia”

Reviewer #2: Comments were addressed by authors.
In line 259 authors comment on a paper in which progression of the disease may have occurred in patients with IOP fluctuations, and the following sentence states that IOP spikes or changes were not observed after UCP in both groups. Did authors specifically look at spikes/fluctuations (ie: diurnal curves, water drinking test, measuring IOP at different times of the day, etc)?

We thank the Reviewer for this comment. In our series, we investigated the difference between mean IOP changes before and after surgery in two different groups. IOP fluctuations in the each patient were not explored. So, accordingly we left the comment regarding Park et al. study for completion and changed the sentence as follows “In our series we only observed mean IOP reduction at each follow-up visit so, we cannot confirm whether treatment was successful in halting IOP fluctuations and consequently visual field progression.” in the Discussion paragraph.

This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

Thank you once again for your consideration.

Sincerely,

Michele Figus MD, PhD, FEBOphth

Pisa, 2023 January 24th

Comments from the editors

We thank the Reviewers for his/her careful reading of our manuscript and insightful suggestions that allowed a substantial improvement of the paper

Reviewer Comments:

Editorial Board Comments
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~~Ultrasound Cyclo Plasty using High Intensity Focused Ultrasound in open angle glaucoma myopic patients~~ Ultrasound Cyclo Plasty in patients with open angle glaucoma ~~patients~~ and high myopia

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Disclosure: The authors declare that they have no conflicts of interest.

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Précis: Ultrasound cycloplasty (UCP) using high-intensity focused ultrasound (HIFU) is an effective and safe procedure in lowering intraocular pressure (IOP) in patients with glaucoma, even in those with high myopia.

Abstract

Purpose: This study aimed to evaluate the efficacy and safety of UCP in glaucoma patients with high-myopia.

Methods: In this retrospective, single-center study, we enrolled 36 eyes divided into two groups based on axial length: group A (≥ 26.00 mm) and group B (< 26.00 mm). We collected data about visual acuity, Goldmann applanation tonometry, biomicroscopy, and visual field before the procedure and at 1, 7, 30, 60, 90, 180, and 365 days after the procedure.

Results: Mean IOP significantly decreased in both groups after treatment ($p<0.001$). Mean IOP reduction from baseline to the last visit was 9.8 ± 6.6 mmHg (38.7%) in group A and 9.6 ± 6.3 mmHg (34.8%) in group B ($p<0.001$). Mean IOP at the last visit was 15.8 ± 4.1 mmHg in the myopic group and 18.1 ± 5.6 mmHg in the non-myopic one. Regarding the number of IOP-lowering eyedrops being taken by our patients, no statistically significant differences were found between groups A and B at baseline (2.8 ± 0.9 and 2.6 ± 1.0; $p=0.568$) nor 1 year after the procedure (2.5 ± 1.1 and 2.6 ± 1.1; $p=0.762$). No major complications occurred. All minor adverse events resolved within a few days.

Conclusion: UCP seems to be an effective and well-tolerated strategy to lower IOP in glaucoma patients with high-myopia.

Keywords: Ultrasound cycloplasty, high-intensity focused ultrasound, glaucoma, myopia, intraocular pressure, glaucoma surgery

Introduction

In 2020, glaucoma was second only to cataracts as a leading cause of blindness in the world among people over 50 years old, with about 3.6 million cases worldwide (1). To date, lowering intraocular pressure (IOP) is the most efficient way to reduce the retinal ganglion cells and optic nerve head damage (2,3). Hypotensive medications often are not sufficient to lower IOP and surgery is mandatory (2). However, in refractory glaucoma reducing aqueous humor inflow by destroying parts of the ciliary body epithelium can be a useful alternative technique to control IOP after failure of traditional filtering procedures. In recent decades, many approaches to destroying the ciliary body have been proposed using heating, freezing, or ultrasound, but they have generally been used as a last resort due to their severe adverse events (4). According to the literature, complications like ocular phthisis, chronic inflammation, decreased visual acuity, and corneal ulcer have been described as potential consequences of these treatments (3–8). Recently, the marketing of new, more selective devices that target tissues and are, theoretically, safer has made this approach feasible not only in refractory glaucoma, but also in patients with early to moderate disease and even as a first-line surgical treatment (9,10).

Ultrasound cycloplasty (UCP) using high-intensity focused ultrasound effectively reduces IOP through selective transscleral coagulation necrosis of the ciliary body epithelium and increases suprachoroidal and transscleral aqueous humor outflow (11). The new generation of probe seems to be easier to use, faster, and safer compared to previous models (12,13).

High myopia is defined as axial length ≥ 26 mm and is recognised as a risk factor for glaucoma. The elongation of the eyeball as well as the morphological changes in the intrapapillary and peripapillary region of the optic nerve seemed to be the reasons for this greater risk (14).

Because of the potential vision-threatening complications induced by standard filtration procedures, the surgical management of glaucoma in highly myopic patients remains challenging, with no consensus as yet on the best approach (14). To date, no study has investigated whether UCP can be considered a therapeutic option in high-myopia glaucoma.

This study aimed to evaluate the efficacy and safety of UCP in patients with medically uncontrolled high-myopia glaucoma.

Materials and methods

Patients

In this single-center, retrospective, non-randomized, double-arm clinical study, we included a cohort of 36 patients (36 eyes) with glaucoma who underwent UCP treatment between January and November 2020 at the Ophthalmology Unit of the Department of Surgical, Medical, and Molecular Pathology and Critical Care Medicine at the University of Pisa, Italy. The study design was approved by the Area Vasta Nord Ovest Ethics Committee (ID 22395). All procedures were conducted in adherence to the tenets of the Declaration of Helsinki and every patient provided a signed informed consent form.

We included patients diagnosed with glaucoma with IOP > 21 mmHg refractory to maximum medical therapy (topical and systemic), with or without a history of previous glaucoma surgery (filtration or tube shunt), and aged older than 18 years. All patients have received a diagnosis of open angle glaucoma.

We excluded patients who could not complete the post-operative follow-up, were pregnant, or had ocular trauma, ocular tumor, previous cyclodestructive procedures, any ocular surgery other than glaucoma surgery, uveitis, or ocular infection in the last year, as well as those requiring unavailable probe sizes (<11 or > 13 mm).

Patients were divided in two groups based on eye axial length: group A (myopic patients) with an axial length ≥ 26.00 mm and group B (non-myopic patients) with an axial length < 26.00 mm. Axial length was calculated with non-contact optical biometry (IOL Master, Carl Zeiss Meditech, Jena, Germany).

A complete ophthalmic evaluation was performed before the UCP procedure, including best-corrected visual acuity (LogMAR), Goldmann applanation tonometry, biomicroscopy, IOP determination, gonioscopy, fundus examination, and visual field (Humphrey, Carl Zeiss Meditech, Jena, Germany). The follow-up visits were conducted 1, 7, 30, 60, 90, 180, and 365 days after the treatment.

Based on previous studies (10,15) it has been observed that UCP reduces IOP without any difference on medical treatments. Consequently, qualified success was defined as a lowering of IOP by $\geq$ 20% and by > 5 mmHg from baseline (9). Complete success was defined as a lowering of IOP by $\geq$ 20% without any new additional medication or re-intervention and by > 5 and < 21 mmHg according to previous studies (10,15).

UCP procedure

Before treatment, the white-to-white corneal diameter and the axial length were measured to select the appropriate probe size (11, 12, or 13 mm). The UCP procedures were performed by the same glaucoma surgeon (M.F.) with the EyeOP1 device (EyeTechCare, Rillieux-la-Pape, France) under peribulbar anesthesia (13).

The procedure was conducted as follows. Firstly, the positioning cone was placed on the ocular surface in direct contact with the peri-limbal sclera without touching the cornea to focus the ultrasound beam directly on the ciliary body. A suction ring created a low-level vacuum to keep the cone steady during the procedure. Secondly, the treatment probe, containing six active piezo-electric elements (transducers), was inserted inside the cone. Balanced saline solution (Alcon Laboratories, Inc., Forth Worth, Texas, USA) was used to fill the space between the probe, cone, and eye to guarantee acoustic propagation. After filling the system, the procedure started by pressing a footpedal connected to the control unit, which initiated sequential activation of the transducers. The second generation of UCP probes deliver ultrasound for 8 seconds per transducer, followed by a 20-second interval (13). All patients were insonified in eight sectors.

The procedure was fully automated, ensuring treatment was standardized and reproducible. High-frequency ultrasound (21 MHz) elicits a well-controlled coagulation of the ciliary body epithelium without explosion and independent of cell pigmentation (13).

As per protocol, patients received a set combination of topical antibiotics and steroids (chloramphenicol/dexamethasone) five times a day for 10 days after the procedure, and cycloplegic eyedrops (cyclopentolate) twice a day for 1 week.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 26 (IBM Corporation, Armonk, NY, USA). Kolmogorov-Smirnov normality was tested to assess the normal or skewed distribution of all variables. Data were presented as mean ± standard deviation or median and interquartile range. Quantitative variables between the two groups were compared using the independent t-test or corresponding non-parametric Mann-Whitney U-test, where appropriate. Comparisons within each group at baseline and at follow-up used the dependent t-test or corresponding non-parametric Wilcoxon signed-rank test, where appropriate. The chi-squared test was used to compare categorical variables. A two-tailed p-value < 0.05 was considered significant for all analyses. In addition to the t-tests, we evaulated the effect of the treatment controlling for possible confounding variables such as age, gender and myopia through use of a linear mixed model (16).

Linear mixed models are akin to classical linear models, but account for the fact that the observations do not come from 72 different subjects, but from 36 subjects measured at two different time points. The model thus includes an additional random term for each subject, allowing to account for intra-subject variability without giving up too much power. Details are given in the supplementary digital content 1 (SDC1).

Results

A total of 36 glaucoma patients (36 eyes), 17 men and 19 women, were enrolled for the study and all of them were included for the statistical analysis. No patients were lost to follow-up. Group A included 17 myopic eyes and group B 19 non-myopic eyes. The general characteristics of the patients and baseline ophthalmic data are reported in Table 1. The two populations were similar except for age and blood pressure, which were higher in the non-myopic group, and axial length: 27.61 ± 1.61 mm for myopic patients and 23.51 ± 0.68 mm for non-myopic patients ($p<0.001$). Mean IOP before the procedure was 25.8 ± 8.5 mmHg in group A and 27.7 ± 7.7 mmHg in group B ($p=0.48$). The mean number of anti-glaucoma medications was 2.8 ± 0.9 and 2.6 ± 1.0, respectively ($p=0.57$).

Thirteen patients, (5 from group A and 8 from group B), had a previous history of glaucoma surgery with either trabeculectomy, Ex-Press P-200® (Alcon, Fort Worth, Texas, USA), Xen® 45 Gel Stent (Allergan Plc., Dublin, Ireland), or Preserflo™ MicroShunt (Santen, Miami, Florida, USA). In all, 82.4% of patients in the myopic group and 68.4% in the non-myopic group ($p=0.335$) had primary open-angle glaucoma (Table 1). Mean deviation and pattern standard deviation on visual field testing were analyzed in a small subpopulation only because many patients had very low visual acuity and the perimetric data would have been unreliable (8/17 from group A, 47.1%; and 11/19 from group B, 57.9%).

Table 2 shows mean IOP, percentage IOP reduction from baseline, and number of topical hypotensive medications of the two groups. The mean IOP in both groups was significantly reduced ($p<0.001$) from baseline to the last visit, respectively 15.8 ± 4.1 mmHg in the myopic group and 18.1 ± 5.6 mmHg in the non-myopic group.

Mean IOP reduction from baseline at the last follow-up visit was 9.8 ± 6.6 mmHg (38.7%) in group A, and 9.6 ± 6.3 mmHg (34.8%) in group B ($p<0.001$ for both groups).

Qualified success was achieved in 76% of patients for group A and 74% for group B, while complete success was observed in 59% of patients for group A and 53% for group B.

No statistically significant differences between the two groups were found in mean IOP 1 year after treatment ($p=0.879$). Nor were any found in mean number of IOP-lowering medications, which was 2.8 ± 0.9 and 2.6 ± 1.0 at baseline ($p=0.568$) in group A and group B, and 2.5 ± 1.1 and 2.6 ± 1.1 1 year after the procedure ($p=0.762$).

Figure 1 shows the trend of IOP reduction from baseline to the last follow-up visit in both populations.

Visual acuity (VA) did not change after UCP in either group, with no statistically significant difference emerging from baseline to the last follow-up visit. Particularly, we observed VA mean values of 1.2 (0.3 – 1.3) for group A and 1.0 (0.2 -1.4) for group B at baseline whereas at last follow up visit the mean VA values were respectively 1.3 (0.4 -1.4) for group A ($p=0.18$) and 1.1 (0.3 – 1.4) for group B ($p=0.25$). Moreover, we observed by the linear mixed models that the control variables age, gender and myopia did not have a statistically significant effect in our results.

Only one patient from Group B had to repeat UCP 6 months after the first procedure due to increased IOP despite hypotensive medications.

No major complications occurred and no statistically significant differences were observed between the two groups. We collected data about minor postoperative complications such as conjunctival hyperemia, intraocular inflammation, and superficial punctate keratitis (Table 3). All these complications resolved within a few days with the use of topical antibiotic/steroid combination therapy.

Discussion

This study aimed to compare the effectiveness of UCP with a second-generation probe in myopic and non-myopic patients. We considered patients to be myopic if their axial length was > 26.00 mm, as reported in previous studies (17–19). We decided to use this cut-off for axial eye length to include in the myopic group only patients highly likely to have myopia.

IOP was significantly decreased at 12 months in both groups without any differences between the two populations. No statistically significant differences were found in mean IOP 1 year after treatment between both populations.

IOP reduction has been statistically significant from baseline to 1-year control across populations in studies on UCP in patients with open-angle glaucoma (9,15,20–24). Particularly, Bolek et al. in 2020 and Marques et al. in 2021 reported mean IOP reductions of 28.1% and 34%, respectively, during the first year of follow-up. Both studies highlighted a significant reduction throughout the first year, which is in line with our results (20,23).

Myopia is a well-known risk factor for glaucoma (25,26). However, how it causes or worsens the disease is not well understood. Many studies suggest that myopia, especially high myopia, is a risk factor for glaucomatous progression (25–27). The myopic scleral canal is unusually large and abnormally shaped and tilted, while the myopic lamina cribrosa and peripapillary sclera are unusually thin. This may heighten stress at a given level of IOP (28–30). Neverthless, to date, these hypotheses have not yet been validated.

Chihara et al. observed that only severe myopia (> -4.00 diopters) is associated with progressive visual field loss, whereas mild myopia (-0.25 to -4.00 diopters) and emmetropic or hyperopic eyes did not appear to have the same association of severe myopia (25). Optic nerve head shape in severe myopia seems to relate to a higher glaucomatous risk. The optic disk in the severely myopic eye is frequently pale in color and accompanied by a wide crescent. Peripapillary choroidal atrophy is associated with primary open-angle glaucoma, may lead to an additional ischemic insult, and may influence the susceptibility of nerve fibers to glaucomatous insult (25,31). Moreover, uneven distribution of the extracellular matrices and retinal vessels in the optic nerve head also affects the local susceptibility of nerve fibers to damage (32,33). The same results have been published by other authors (34,35).

Axial elongation in myopic eyes is associated with scleral remodeling, which causes considerable thinning of the sclera, especially at the posterior pole. Particularly, a reduced production and, consequently, a disorganization of glycosaminoglycan and collagen content have been observed in myopic eyes. These changes affect the sclera's mechanical properties, making the sclera of the myopic eye more extensible and less resistant to the expansive forces of normal IOP. As a result, the eye elongates, myopia develops, and the sclera thins (36).

Based on this knowledge, we investigated whether high-intensity focused ultrasound might be effective in myopic as well as non-myopic eyes. The device is placed on the anterior bulbar surface and directed at the ciliary body according to a well-standardized procedure. Although myopic patients have a thinner sclera, such thinning does not involve the anterior part of the eyeball. Rather, it mainly affects the region behind the equator (37,38). For this reason, the efficacy of UCP should not be invalidated. Our data confirmed this hypothesis, showing similar efficacy in both groups.

A few minor adverse events were observed without any statistically significant difference between groups. Conjunctival hyperemia, intraocular inflammation, and superficial punctate keratitis were the main complications in both groups, and all resolved within a few days following topical antibiotic/steroid combination therapy. Safety seems to be one of the most relevant advantages of this procedure, including in myopic patients. UCP results in few intraoperative or postoperative complications in refractory or surgery-naive patients, be it conjunctival hyperemia, anterior chamber inflammation, corneal edema, or transient IOP spikes (10). UCP has demonstrated a reduced rate of severe complications compared to conventional cyclodestructive (39) and filtration procedures (40). Filtration surgery may present a higher complication rate in myopic than non-myopic patients, potentially causing choroidal detachment, hypotony maculopathy, and aqueous misdirection (41). All of these severe complications appear to be reduced in patients who undergo UCP (9,10,15) and our results are consistent with this finding.

Moreover, no statistically significant difference in visual acuity was found between our groups at the last follow-up visit. Our results underline the safety of UCP (13) although the baseline visual acuity of our patients was very low.

Park H-YL et al. reported a higher risk of progressive visual field damage after filtration surgery in myopic than non-myopic eyes if they were exposed to IOP fluctuations (40). In our series we only observed mean IOP reduction at each follow-up visit so, we cannot confirm whether treatment was

successful in halting IOP fluctuations and consequently visual field progression. ~~IOP spikes or changes were not observed during follow-up after UCP in either of our groups. However, we cannot confirm whether treatment was successful in halting the progression of visual field damage because we could not collect perimetric data for all patients.~~ Due to severe glaucoma damage, several patients were unable to undergo visual field testing. We therefore had data on only 53% of the whole population, which represents a major limitation of our statistical analysis.

Tanaka D. et al published their results about the influence of high myopia on trabeculectomy outcomes (42). They hypothesized that high myopia could lead to surgery failure due to the high levels of inflammatory cytokines and growth factors detected in the aqueous humor (43,44). However, they demonstrated that high myopia was not a risk factor for trabeculectomy failure, although these controversial data remain unexplained. Our results showed a significant efficacy in lowering IOP. This seems to corroborate the finding by Tanaka et al. that high myopia is not a risk factor for trabeculectomy failure, even if surgical procedure, patient age, and glaucoma type and severity were different.

Our study had several limitations such as the small sample size and relatively short follow-up. The statistical analysis included all types of open-angle glaucoma, with or without previous glaucoma surgery. Patients could not be divided into subgroups, otherwise statistical power would have been lost. Perimetric data are fundamental to evaluate the progression of visual field damage. The very low visual acuity of our patients made our perimetric data unreliable. To overcome these limitations and confirm our findings, future multicenter, prospective studies with strict protocols, larger sample sizes, and longer follow-up would be desirable.

In conclusion, UCP seems to be an effective and safe strategy to lower IOP in myopic patients with medically uncontrolled glaucoma, since it may reduce the likelihood of the complications associated with filtration surgery.

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Table 1 – General characteristics of the study population and baseline ophthalmic data

Table 2 – Intraocular pressure measurements and number of topical medications

Table 3 – Post-operative complications

Figure 1 – Intraocular pressure (mean values and SD) at each follow-up visit

Supplementary Digital Content 1 – Linear mixed model. docx

Ultrasound Cyclo Plasty in patients with open angle glaucoma and high myopia

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Précis: Ultrasound cycloplasty (UCP) using high-intensity focused ultrasound (HIFU) is an effective and safe procedure in lowering intraocular pressure (IOP) in patients with glaucoma, even in those with high myopia.

Abstract

Purpose: This study aimed to evaluate the efficacy and safety of UCP in glaucoma patients with high-myopia.

Methods: In this retrospective, single-center study, we enrolled 36 eyes divided into two groups based on axial length: group A (≥ 26.00 mm) and group B (< 26.00 mm). We collected data about visual acuity, Goldmann applanation tonometry, biomicroscopy, and visual field before the procedure and at 1, 7, 30, 60, 90, 180, and 365 days after the procedure.

Results: Mean IOP significantly decreased in both groups after treatment ($p<0.001$). Mean IOP reduction from baseline to the last visit was 9.8 ± 6.6 mmHg (38.7%) in group A and 9.6 ± 6.3 mmHg (34.8%) in group B ($p<0.001$). Mean IOP at the last visit was 15.8 ± 4.1 mmHg in the myopic group and 18.1 ± 5.6 mmHg in the non-myopic one. Regarding the number of IOP-lowering eyedrops being taken by our patients, no statistically significant differences were found between groups A and B at baseline (2.8 ± 0.9 and 2.6 ± 1.0; $p=0.568$) nor 1 year after the procedure (2.5 ± 1.1 and 2.6 ± 1.1; $p=0.762$). No major complications occurred. All minor adverse events resolved within a few days.

Conclusion: UCP seems to be an effective and well-tolerated strategy to lower IOP in glaucoma patients with high-myopia.

Keywords: Ultrasound cycloplasty, high-intensity focused ultrasound, glaucoma, myopia, intraocular pressure, glaucoma surgery

Introduction

In 2020, glaucoma was second only to cataracts as a leading cause of blindness in the world among people over 50 years old, with about 3.6 million cases worldwide (1). To date, lowering intraocular pressure (IOP) is the most efficient way to reduce the retinal ganglion cells and optic nerve head damage (2,3). Hypotensive medications often are not sufficient to lower IOP and surgery is mandatory (2). However, in refractory glaucoma reducing aqueous humor inflow by destroying parts of the ciliary body epithelium can be a useful alternative technique to control IOP after failure of traditional filtering procedures. In recent decades, many approaches to destroying the ciliary body have been proposed using heating, freezing, or ultrasound, but they have generally been used as a last resort due to their severe adverse events (4). According to the literature, complications like ocular phthisis, chronic inflammation, decreased visual acuity, and corneal ulcer have been described as potential consequences of these treatments (3–8). Recently, the marketing of new, more selective devices that target tissues and are, theoretically, safer has made this approach feasible not only in refractory glaucoma, but also in patients with early to moderate disease and even as a first-line surgical treatment (9,10).

Ultrasound cycloplasty (UCP) using high-intensity focused ultrasound effectively reduces IOP through selective transscleral coagulation necrosis of the ciliary body epithelium and increases suprachoroidal and transscleral aqueous humor outflow (11). The new generation of probe seems to be easier to use, faster, and safer compared to previous models (12,13).

High myopia is defined as axial length ≥ 26 mm and is recognised as a risk factor for glaucoma. The elongation of the eyeball as well as the morphological changes in the intrapapillary and peripapillary region of the optic nerve seemed to be the reasons for this greater risk (14).

Because of the potential vision-threatening complications induced by standard filtration procedures, the surgical management of glaucoma in highly myopic patients remains challenging, with no consensus as yet on the best approach (14). To date, no study has investigated whether UCP can be considered a therapeutic option in high-myopia glaucoma.

This study aimed to evaluate the efficacy and safety of UCP in patients with medically uncontrolled high-myopia glaucoma.

Materials and methods

Patients

In this single-center, retrospective, non-randomized, double-arm clinical study, we included a cohort of 36 patients (36 eyes) with glaucoma who underwent UCP treatment between January and November 2020 at the Ophthalmology Unit of the Department of Surgical, Medical, and Molecular Pathology and Critical Care Medicine at the University of Pisa, Italy. The study design was approved by the Area Vasta Nord Ovest Ethics Committee (ID 22395). All procedures were conducted in adherence to the tenets of the Declaration of Helsinki and every patient provided a signed informed consent form.

We included patients diagnosed with glaucoma with IOP > 21 mmHg refractory to maximum medical therapy (topical and systemic), with or without a history of previous glaucoma surgery (filtration or tube shunt), and aged older than 18 years. All patients have received a diagnosis of open angle glaucoma.

We excluded patients who could not complete the post-operative follow-up, were pregnant, or had ocular trauma, ocular tumor, previous cyclodestructive procedures, any ocular surgery other than glaucoma surgery, uveitis, or ocular infection in the last year, as well as those requiring unavailable probe sizes (<11 or > 13 mm).

Patients were divided in two groups based on eye axial length: group A (myopic patients) with an axial length ≥ 26.00 mm and group B (non-myopic patients) with an axial length < 26.00 mm. Axial length was calculated with non-contact optical biometry (IOL Master, Carl Zeiss Meditech, Jena, Germany).

A complete ophthalmic evaluation was performed before the UCP procedure, including best-corrected visual acuity (LogMAR), Goldmann applanation tonometry, biomicroscopy, IOP determination, gonioscopy, fundus examination, and visual field (Humphrey, Carl Zeiss Meditech, Jena, Germany). The follow-up visits were conducted 1, 7, 30, 60, 90, 180, and 365 days after the treatment.

Based on previous studies (10,15) it has been observed that UCP reduces IOP without any difference on medical treatments. Consequently, qualified success was defined as a lowering of IOP by $\geq$ 20% and by > 5 mmHg from baseline (9). Complete success was defined as a lowering of IOP by $\geq$ 20% without any new additional medication or re-intervention and by > 5 and < 21 mmHg according to previous studies (10,15).

UCP procedure

Before treatment, the white-to-white corneal diameter and the axial length were measured to select the appropriate probe size (11, 12, or 13 mm). The UCP procedures were performed by the same glaucoma surgeon (M.F.) with the EyeOP1 device (EyeTechCare, Rillieux-la-Pape, France) under peribulbar anesthesia (13).

The procedure was conducted as follows. Firstly, the positioning cone was placed on the ocular surface in direct contact with the peri-limbal sclera without touching the cornea to focus the ultrasound beam directly on the ciliary body. A suction ring created a low-level vacuum to keep the cone steady during the procedure. Secondly, the treatment probe, containing six active piezo-electric elements (transducers), was inserted inside the cone. Balanced saline solution (Alcon Laboratories, Inc., Forth Worth, Texas, USA) was used to fill the space between the probe, cone, and eye to guarantee acoustic propagation. After filling the system, the procedure started by pressing a footpedal connected to the control unit, which initiated sequential activation of the transducers. The second generation of UCP probes deliver ultrasound for 8 seconds per transducer, followed by a 20-second interval (13). All patients were insonified in eight sectors.

The procedure was fully automated, ensuring treatment was standardized and reproducible. High-frequency ultrasound (21 MHz) elicits a well-controlled coagulation of the ciliary body epithelium without explosion and independent of cell pigmentation (13).

As per protocol, patients received a set combination of topical antibiotics and steroids (chloramphenicol/dexamethasone) five times a day for 10 days after the procedure, and cycloplegic eyedrops (cyclopentolate) twice a day for 1 week.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 26 (IBM Corporation, Armonk, NY, USA). Kolmogorov-Smirnov normality was tested to assess the normal or skewed distribution of all variables. Data were presented as mean ± standard deviation or median and interquartile range. Quantitative variables between the two groups were compared using the independent t-test or corresponding non-parametric Mann-Whitney U-test, where appropriate. Comparisons within each group at baseline and at follow-up used the dependent t-test or corresponding non-parametric Wilcoxon signed-rank test, where appropriate. The chi-squared test was used to compare categorical variables. A two-tailed p-value < 0.05 was considered significant for all analyses. In addition to the t-tests, we evaulated the effect of the treatment controlling for possible confounding variables such as age, gender and myopia through use of a linear mixed model (16).

Linear mixed models are akin to classical linear models, but account for the fact that the observations do not come from 72 different subjects, but from 36 subjects measured at two different time points. The model thus includes an additional random term for each subject, allowing to account for intra-subject variability without giving up too much power. Details are given in the supplementary digital content 1 (SDC1).

Results

A total of 36 glaucoma patients (36 eyes), 17 men and 19 women, were enrolled for the study and all of them were included for the statistical analysis. No patients were lost to follow-up. Group A included 17 myopic eyes and group B 19 non-myopic eyes. The general characteristics of the patients and baseline ophthalmic data are reported in Table 1. The two populations were similar except for age and blood pressure, which were higher in the non-myopic group, and axial length: 27.61 ± 1.61 mm for myopic patients and 23.51 ± 0.68 mm for non-myopic patients ($p<0.001$). Mean IOP before the procedure was 25.8 ± 8.5 mmHg in group A and 27.7 ± 7.7 mmHg in group B ($p=0.48$). The mean number of anti-glaucoma medications was 2.8 ± 0.9 and 2.6 ± 1.0, respectively ($p=0.57$).

Thirteen patients, (5 from group A and 8 from group B), had a previous history of glaucoma surgery with either trabeculectomy, Ex-Press P-200® (Alcon, Fort Worth, Texas, USA), Xen® 45 Gel Stent (Allergan Plc., Dublin, Ireland), or Preserflo™ MicroShunt (Santen, Miami, Florida, USA). In all, 82.4% of patients in the myopic group and 68.4% in the non-myopic group ($p=0.335$) had primary open-angle glaucoma (Table 1). Mean deviation and pattern standard deviation on visual field testing were analyzed in a small subpopulation only because many patients had very low visual acuity and the perimetric data would have been unreliable (8/17 from group A, 47.1%; and 11/19 from group B, 57.9%).

Table 2 shows mean IOP, percentage IOP reduction from baseline, and number of topical hypotensive medications of the two groups. The mean IOP in both groups was significantly reduced ($p<0.001$) from baseline to the last visit, respectively 15.8 ± 4.1 mmHg in the myopic group and 18.1 ± 5.6 mmHg in the non-myopic group.

Mean IOP reduction from baseline at the last follow-up visit was 9.8 ± 6.6 mmHg (38.7%) in group A, and 9.6 ± 6.3 mmHg (34.8%) in group B ($p<0.001$ for both groups).

Qualified success was achieved in 76% of patients for group A and 74% for group B, while complete success was observed in 59% of patients for group A and 53% for group B.

No statistically significant differences between the two groups were found in mean IOP 1 year after treatment ($p=0.879$). Nor were any found in mean number of IOP-lowering medications, which was 2.8 ± 0.9 and 2.6 ± 1.0 at baseline ($p=0.568$) in group A and group B, and 2.5 ± 1.1 and 2.6 ± 1.1 1 year after the procedure ($p=0.762$).

Figure 1 shows the trend of IOP reduction from baseline to the last follow-up visit in both populations.

Visual acuity (VA) did not change after UCP in either group, with no statistically significant difference emerging from baseline to the last follow-up visit. Particularly, we observed VA mean values of 1.2 (0.3 – 1.3) for group A and 1.0 (0.2 -1.4) for group B at baseline whereas at last follow up visit the mean VA values were respectively 1.3 (0.4 -1.4) for group A ($p=0.18$) and 1.1 (0.3 – 1.4) for group B ($p=0.25$). Moreover, we observed by the linear mixed models that the control variables age, gender and myopia did not have a statistically significant effect in our results.

Only one patient from Group B had to repeat UCP 6 months after the first procedure due to increased IOP despite hypotensive medications.

No major complications occurred and no statistically significant differences were observed between the two groups. We collected data about minor postoperative complications such as conjunctival hyperemia, intraocular inflammation, and superficial punctate keratitis (Table 3). All these complications resolved within a few days with the use of topical antibiotic/steroid combination therapy.

Discussion

This study aimed to compare the effectiveness of UCP with a second-generation probe in myopic and non-myopic patients. We considered patients to be myopic if their axial length was > 26.00 mm, as reported in previous studies (17–19). We decided to use this cut-off for axial eye length to include in the myopic group only patients highly likely to have myopia.

IOP was significantly decreased at 12 months in both groups without any differences between the two populations. No statistically significant differences were found in mean IOP 1 year after treatment between both populations.

IOP reduction has been statistically significant from baseline to 1-year control across populations in studies on UCP in patients with open-angle glaucoma (9,15,20–24). Particularly, Bolek et al. in 2020 and Marques et al. in 2021 reported mean IOP reductions of 28.1% and 34%, respectively, during the first year of follow-up. Both studies highlighted a significant reduction throughout the first year, which is in line with our results (20,23).

Myopia is a well-known risk factor for glaucoma (25,26). However, how it causes or worsens the disease is not well understood. Many studies suggest that myopia, especially high myopia, is a risk factor for glaucomatous progression (25–27). The myopic scleral canal is unusually large and abnormally shaped and tilted, while the myopic lamina cribrosa and peripapillary sclera are unusually thin. This may heighten stress at a given level of IOP (28–30). Neverthless, to date, these hypotheses have not yet been validated.

Chihara et al. observed that only severe myopia (> -4.00 diopters) is associated with progressive visual field loss, whereas mild myopia (-0.25 to -4.00 diopters) and emmetropic or hyperopic eyes did not appear to have the same association of severe myopia (25). Optic nerve head shape in severe myopia seems to relate to a higher glaucomatous risk. The optic disk in the severely myopic eye is frequently pale in color and accompanied by a wide crescent. Peripapillary choroidal atrophy is associated with primary open-angle glaucoma, may lead to an additional ischemic insult, and may influence the susceptibility of nerve fibers to glaucomatous insult (25,31). Moreover, uneven distribution of the extracellular matrices and retinal vessels in the optic nerve head also affects the local susceptibility of nerve fibers to damage (32,33). The same results have been published by other authors (34,35).

Axial elongation in myopic eyes is associated with scleral remodeling, which causes considerable thinning of the sclera, especially at the posterior pole. Particularly, a reduced production and, consequently, a disorganization of glycosaminoglycan and collagen content have been observed in myopic eyes. These changes affect the sclera's mechanical properties, making the sclera of the myopic eye more extensible and less resistant to the expansive forces of normal IOP. As a result, the eye elongates, myopia develops, and the sclera thins (36).

Based on this knowledge, we investigated whether high-intensity focused ultrasound might be effective in myopic as well as non-myopic eyes. The device is placed on the anterior bulbar surface and directed at the ciliary body according to a well-standardized procedure. Although myopic patients have a thinner sclera, such thinning does not involve the anterior part of the eyeball. Rather, it mainly affects the region behind the equator (37,38). For this reason, the efficacy of UCP should not be invalidated. Our data confirmed this hypothesis, showing similar efficacy in both groups.

A few minor adverse events were observed without any statistically significant difference between groups. Conjunctival hyperemia, intraocular inflammation, and superficial punctate keratitis were the main complications in both groups, and all resolved within a few days following topical antibiotic/steroid combination therapy. Safety seems to be one of the most relevant advantages of this procedure, including in myopic patients. UCP results in few intraoperative or postoperative complications in refractory or surgery-naive patients, be it conjunctival hyperemia, anterior chamber inflammation, corneal edema, or transient IOP spikes (10). UCP has demonstrated a reduced rate of severe complications compared to conventional cyclodestructive (39) and filtration procedures (40). Filtration surgery may present a higher complication rate in myopic than non-myopic patients, potentially causing choroidal detachment, hypotony maculopathy, and aqueous misdirection (41). All of these severe complications appear to be reduced in patients who undergo UCP (9,10,15) and our results are consistent with this finding.

Moreover, no statistically significant difference in visual acuity was found between our groups at the last follow-up visit. Our results underline the safety of UCP (13) although the baseline visual acuity of our patients was very low.

Park H-YL et al. reported a higher risk of progressive visual field damage after filtration surgery in myopic than non-myopic eyes if they were exposed to IOP fluctuations (40). In our series we only observed mean IOP reduction at each follow-up visit so, we cannot confirm whether treatment was

successful in halting IOP fluctuations and consequently visual field progression. Due to severe glaucoma damage, several patients were unable to undergo visual field testing. We therefore had data on only 53% of the whole population, which represents a major limitation of our statistical analysis.
Tanaka D. et al published their results about the influence of high myopia on trabeculectomy outcomes (42). They hypothesized that high myopia could lead to surgery failure due to the high levels of inflammatory cytokines and growth factors detected in the aqueous humor (43,44). However, they demonstrated that high myopia was not a risk factor for trabeculectomy failure, although these controversial data remain unexplained. Our results showed a significant efficacy in lowering IOP. This seems to corroborate the finding by Tanaka et al. that high myopia is not a risk factor for trabeculectomy failure, even if surgical procedure, patient age, and glaucoma type and severity were different.
Our study had several limitations such as the small sample size and relatively short follow-up. The statistical analysis included all types of open-angle glaucoma, with or without previous glaucoma surgery. Patients could not be divided into subgroups, otherwise statistical power would have been lost. Perimetric data are fundamental to evaluate the progression of visual field damage. The very low visual acuity of our patients made our perimetric data unreliable. To overcome these limitations and confirm our findings, future multicenter, prospective studies with strict protocols, larger sample sizes, and longer follow-up would be desirable.

In conclusion, UCP seems to be an effective and safe strategy to lower IOP in myopic patients with medically uncontrolled glaucoma, since it may reduce the likelihood of the complications associated with filtration surgery.

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Figure 1 – Intraocular pressure (mean values and SD) at each follow-up visit

Supplementary Digital Content 1 – Linear mixed model. docx

Figure (one figure per file)

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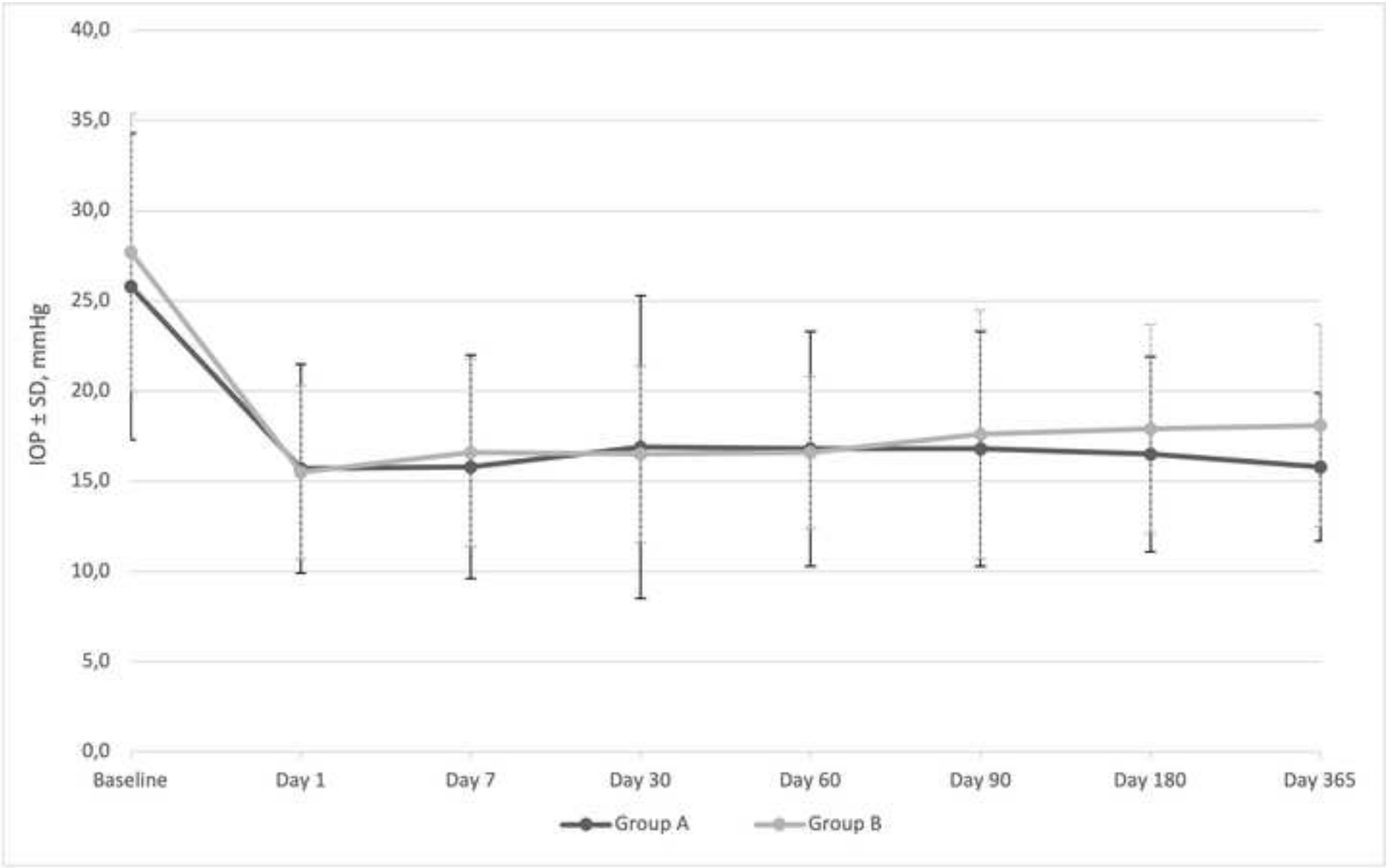

Table (WORD only. 1 per file. Do not embed in text)

Table 1 – General characteristics of the study population and baseline ophthalmic data

	Whole population (n=36)	Group A (n=17)	Group B (n=19)	p	Test
Age, years	71±13	65±15	76±7	**0.008**	t-test
Caucasian, %	100	100	100	---	
Gender				0.985	χ2 test
Male % (n)	47 (17)	47 (8)	47 (9)		
Female % (n)	53 (19)	53 (9)	53 (10)		
Family glaucoma history, % (n)	5.6 (2)	5.9 (1)	5.3 (1)	0.927	χ2 test
Smoking, % (n)	19.4 (7)	11.8 (2)	26.3 (5)	0.272	χ2 test
Comorbidities					
Diabetes, % (n)	13.9 (5)	5.9 (1)	21.1 (4)	0.189	χ2 test
Hypertension, % (n)	66.7 (24)	41.2 (7)	89.5 (17)	**0.002**	
ASCVD, % (n)	22.2 (8)	17.6 (3)	26.3 (5)	0.532	
Neurological disease, % (n)	5.6 (2)	0 (0)	10.5 (2)	0.169	
Intraocular pressure, mmHg	26.8 ± 8.0	25.8 ± 8.5	27.7 ± 7.7	0.482	t-test
N° of hypotensive eye-drops (n)	2.7 ± 1.0	2.8 ± 0.9	2.6 ± 1.0	0.568	t-test
Oral acetazolamide, % (n)	25.0 (9)	17.6 (3)	31.6 (6)	0.335	χ2 test
Previous glaucoma surgery, % (n)	36.1 (13)	29.4 (5)	42.1 (8)	0.429	χ2 test
Type of glaucoma, % (n)					
POAG	75.0 (27)	82.4 (14)	68.4 (13)	0.335	χ2 test
Secondary glaucoma (PEX, PG)	22.2 (8)	11.8 (2)	31.6 (6)	0.153	χ2 test
Congenital glaucoma	2.8 (1)	5.9 (1)	0.0 (0)	0.284	χ2 test
Years of eye-drops	12 ± 10	12 ± 11	11 ± 9	0.804	t-test
Axial length, mm	25.45 ± 2.41	27.61 ± 1.61	23.51 ± 0.68	**<0.001**	t-test
Visual acuity, LogMAR	1.0 (0.2-1.4)	1.2 (0.3-1.3)	1.0 (0.2-1.4)	0.925	M-W
MD	-22.29 ± 8.41	-21.72 ± 8.82	-22.76 ± 8.41	0.628	t-test
PSD	7.80 ± 3.64	8.07 ± 3.57	7.57 ± 3.85	0.628	t-test
WTW, mm	12.0 ± 0.7	12.3 ± 0.7	11.8 ± 0.6	0.356	t-test
Lens status, % (n)					
Phakic	33.3 (12)	41.2 (7)	26.3 (5)	0.345	χ2 test
Pseudophakic	77.8 (24)	58.8 (10)	73.7 (14)	0.345	χ2 test
Pachymetry, micron	536 ± 40	535 ± 38	538 ± 43	0.793	t-test

Group A: myopic; Group B: non-myopic; n: number; ASCVD: atherosclerotic cardiovascular disease; POAG: primary open angle glaucoma; PEX: psedoexfoliation glaucoma; PG: pigmentary glaucoma; MD: mean deviation; PSD: pattern standard deviation; WTW: white-to-white; t-test: independent t-test; χ2 test: chi-squared test; M-W: Mann-Whitney U-test; bold: statistically significant value ($p < 0.05$).

Table 2 – Intraocular pressure measurements and number of topical medications

	Group A (n=17)			**Group B (n=19)**		
	Mean IOP, mmHg	IOP reduction (%)	n° of medications	Mean IOP, mmHg	IOP reduction (%)	n° of medications
Baseline	25.8 ± 8.5		2.8 ± 0.9	27.7 ± 7.7		2.6 ± 1.0
Day 1	15.7 ± 5.8	39.1		15.5 ± 4.8	43.7	
Day 7	15.8 ± 6.2	38.9	2.4 ± 1.1	16.6 ± 5.2	39.7	2.4 ± 0.9
Day 30	16.9 ± 8.4	34.6	2.4 ± 1.1	16.5 ± 4.9	40.3	2.5 ± 0.7
Day 60	16.8 ± 6.5	35.0	2.4 ± 1.1	16.6 ± 4.2	39.7	2.6 ± 1.0
Day 90	16.8 ± 6.5	32.5	2.4 ± 1.1	17.6 ± 6.9	36.3	2.5 ± 1.0
Day 180	16.5 ± 5.4	35.9	2.4 ± 1.2	17.9 ± 5.8	35.0	2.6 ± 1.0
Day 365	15.8 ± 4.1	38.7	2.5 ± 1.1	18.1 ± 5.6	34.8	2.6 ± 1.1

IOP: intraocular pressure; Group A: myopic; Group B: non-myopic; n°: number.

Table 3. Post-operative complications

	Group A, n (%)	Group B, n (%)	p	Test
Conjunctival hyperaemia	7 (42.2%)	7 (36.8%)	0.788	$\chi 2$ test
Subconjunctival haemorrhage	3 (17.6%)	2 (10.5%)	0.537	$\chi 2$ test
Superficial punctuated keratitis	4 (23.5%)	6 (31.6%)	0.590	$\chi 2$ test
Anterior chamber flare	4 (23.5%)	5 (26.3%)	0.847	$\chi 2$ test
Corneal edema	1 (5.9%)	2 (10.5%)	0.615	$\chi 2$ test

Group A: myopic patients; Group B: non myopic patients; n: number; $\chi 2$ test: chi-squared test; bold: statistically significant value ($p < 0.05$).