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

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Corresponding Author:	Michele Figus, MD, PhD University of Pisa: Università degli Studi di Pisa Pisa, Pisa ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Pisa: Università degli Studi di Pisa
Corresponding Author's Secondary Institution:	
First Author:	Michele Figus, MD, PhD
First Author Secondary Information:	
Order of Authors:	Michele Figus, MD, PhD Alessandro Palma, MD Giuseppe Covello, MD Luca Agnifili, MD, PhD Chiara Posarelli, MD, PhD
Order of Authors Secondary Information:	
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Abstract:	<p>Purpose: This study aimed to evaluate the efficacy and safety of UCP in glaucoma patients with high-myopia.</p> <p>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.</p> <p>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.</p> <p>Conclusion: UCP seems to be an effective and well-tolerated strategy to lower IOP in glaucoma patients with high-myopia.</p>

UNIVERSITÀ DI PISA

Department of Surgical, Medical, Molecular Pathology and Critical Care
Medicine
Ophthalmology



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, FEBOPht

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:

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1 ~~Ultrasound Cyclo Plasty using High-Intensity Focused Ultrasound in open angle glaucoma~~
2 ~~myopic patients~~ **Ultrasound Cyclo Plasty in patients with open angle glaucoma patients and**
3 **high myopia**

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5 Michele Figus MD PhD¹, Alessandro Palma MD¹, Giuseppe Covello MD¹, Luca Agnifili MD PhD²,
6 Chiara Posarelli MD PhD¹

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7
8 ¹ Ophthalmology, Department of Surgical, Medical, Molecular Pathology and Critical Care Medicine,
9 University of Pisa, Pisa, Italy

10 ² Ophthalmology, Department of Medicine and Aging Science, University G. D'Annunzio, Chieti-
11 Pescara, Italy

12
13
14 Corresponding. Author

15 Prof. Michele Figus, MD, PhD

16 Via Savi, 10

17 56126 PISA, ITALY

18 Phone +39050997626

19 FAX +39050997656

20 Electronic address: michele.figus@unipi.it

21

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

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

26

27

28 **Abstract**

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

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

35 **Results:** Mean IOP significantly decreased in both groups after treatment ($p < 0.001$). Mean IOP
36 reduction from baseline to the last visit was 9.8 ± 6.6 mmHg (38.7%) in group A and 9.6 ± 6.3 mmHg
37 (34.8%) in group B ($p < 0.001$). Mean IOP at the last visit was 15.8 ± 4.1 mmHg in the myopic group
38 and 18.1 ± 5.6 mmHg in the non-myopic one. Regarding the number of IOP-lowering eyedrops being
39 taken by our patients, no statistically significant differences were found between groups A and B at
40 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 ;
41 $p = 0.762$). No major complications occurred. All minor adverse events resolved within a few days.

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

44

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

47 **Introduction**

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

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

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

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

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

75

76 **Materials and methods**

77 *Patients*

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

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

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

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

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

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

107 108 *UCP procedure*

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

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

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

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

129 130 *Statistical analysis*

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

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

146 147 **Results**

148 A total of 36 glaucoma patients (36 eyes), 17 men and 19 women, were enrolled for the study and all
149 of them were included for the statistical analysis. No patients were lost to follow-up. Group A
150 included 17 myopic eyes and group B 19 non-myopic eyes. The general characteristics of the patients
151 and baseline ophthalmic data are reported in Table 1. The two populations were similar except for
152 age and blood pressure, which were higher in the non-myopic group, and axial length: 27.61 ± 1.61
153 mm for myopic patients and 23.51 ± 0.68 mm for non-myopic patients ($p < 0.001$). Mean IOP before
154 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
155 number of anti-glaucoma medications was 2.8 ± 0.9 and 2.6 ± 1.0 , respectively ($p = 0.57$).

156 Thirteen patients, (5 from group A and 8 from group B), had a previous history of glaucoma surgery
157 with either trabeculectomy, Ex-Press P-200® (Alcon, Fort Worth, Texas, USA), Xen® 45 Gel Stent
158 (Allergan Plc., Dublin, Ireland), or Preserflo™ MicroShunt (Santen, Miami, Florida, USA). In all,
159 82.4% of patients in the myopic group and 68.4% in the non-myopic group ($p = 0.335$) had primary
160 open-angle glaucoma (Table 1). Mean deviation and pattern standard deviation on visual field testing
161 were analyzed in a small subpopulation only because many patients had very low visual acuity and
162 the perimetric data would have been unreliable (8/17 from group A, 47.1%; and 11/19 from group B,
163 57.9%).

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

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

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

172 No statistically significant differences between the two groups were found in mean IOP 1 year after
173 treatment ($p = 0.879$). Nor were any found in mean number of IOP-lowering medications, which was
174 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
175 1 year after the procedure ($p = 0.762$).

176 Figure 1 shows the trend of IOP reduction from baseline to the last follow-up visit in both populations.
177 Visual acuity (VA) did not change after UCP in either group, with no statistically significant
178 difference emerging from baseline to the last follow-up visit. Particularly, we observed VA mean
179 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
180 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)
181 for group B ($p = 0.25$). Moreover, we observed by the linear mixed models that the control variables
182 age, gender and myopia did not have a statistically significant effect in our results.

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

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

190

191 Discussion

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

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

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

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

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

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

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

232 A few minor adverse events were observed without any statistically significant difference between
233 groups. Conjunctival hyperemia, intraocular inflammation, and superficial punctate keratitis were the
234 main complications in both groups, and all resolved within a few days following topical
235 antibiotic/steroid combination therapy. Safety seems to be one of the most relevant advantages of this
236 procedure, including in myopic patients. UCP results in few intraoperative or postoperative
237 complications in refractory or surgery-naïve patients, be it conjunctival hyperemia, anterior chamber
238 inflammation, corneal edema, or transient IOP spikes (10). UCP has demonstrated a reduced rate of
239 severe complications compared to conventional cyclodestructive (39) and filtration procedures (40).

240 Filtration surgery may present a higher complication rate in myopic than non-myopic patients,
241 potentially causing choroidal detachment, hypotony maculopathy, and aqueous misdirection (41). All
242 of these severe complications appear to be reduced in patients who undergo UCP (9,10,15) and our
243 results are consistent with this finding.

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

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

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

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

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

271
272 In conclusion, UCP seems to be an effective and safe strategy to lower IOP in myopic patients with
273 medically uncontrolled glaucoma, since it may reduce the likelihood of the complications associated
274 with filtration surgery.

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386 **Figures/Tables/Supplementary Digital Content legend**

387

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

389 **Table 2** – Intraocular pressure measurements and number of topical medications

390 **Table 3** – Post-operative complications

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

392 **Supplementary Digital Content 1** – Linear mixed model. docx

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

2 Michele Figus MD PhD¹, Alessandro Palma MD¹, Giuseppe Covello MD¹, Luca Agnifili MD PhD²,
3 Chiara Posarelli MD PhD¹

4

5 ¹ Ophthalmology, Department of Surgical, Medical, Molecular Pathology and Critical Care Medicine,
6 University of Pisa, Pisa, Italy

7 ² Ophthalmology, Department of Medicine and Aging Science, University G. D'Annunzio, Chieti-
8 Pescara, Italy

9

10

11 Corresponding. Author

12 Prof. Michele Figus, MD, PhD

13 Via Savi, 10

14 56126 PISA, ITALY

15 Phone +39050997626

16 FAX +39050997656

17 Electronic address: michele.figus@unipi.it

18

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

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

23

24

25 **Abstract**

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

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

32 **Results:** Mean IOP significantly decreased in both groups after treatment ($p < 0.001$). Mean IOP
33 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 (34.8%) in group B ($p < 0.001$). Mean IOP at the last visit was 15.8 ± 4.1 mmHg in the myopic group
35 and 18.1 ± 5.6 mmHg in the non-myopic one. Regarding the number of IOP-lowering eyedrops being
36 taken by our patients, no statistically significant differences were found between groups A and B at
37 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 ;
38 $p = 0.762$). No major complications occurred. All minor adverse events resolved within a few days.

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

41

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

44 **Introduction**

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

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

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

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

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

72
73 **Materials and methods**

74 *Patients*

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

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

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

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

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

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

104 105 *UCP procedure*

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

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

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

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

126 127 *Statistical analysis*

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

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

143 144 **Results**

145 A total of 36 glaucoma patients (36 eyes), 17 men and 19 women, were enrolled for the study and all
146 of them were included for the statistical analysis. No patients were lost to follow-up. Group A
147 included 17 myopic eyes and group B 19 non-myopic eyes. The general characteristics of the patients
148 and baseline ophthalmic data are reported in Table 1. The two populations were similar except for
149 age and blood pressure, which were higher in the non-myopic group, and axial length: 27.61 ± 1.61
150 mm for myopic patients and 23.51 ± 0.68 mm for non-myopic patients ($p < 0.001$). Mean IOP before
151 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
152 number of anti-glaucoma medications was 2.8 ± 0.9 and 2.6 ± 1.0 , respectively ($p = 0.57$).

153 Thirteen patients, (5 from group A and 8 from group B), had a previous history of glaucoma surgery
154 with either trabeculectomy, Ex-Press P-200[®] (Alcon, Fort Worth, Texas, USA), Xen[®] 45 Gel Stent
155 (Allergan Plc., Dublin, Ireland), or Preserflo[™] MicroShunt (Santen, Miami, Florida, USA). In all,
156 82.4% of patients in the myopic group and 68.4% in the non-myopic group ($p = 0.335$) had primary
157 open-angle glaucoma (Table 1). Mean deviation and pattern standard deviation on visual field testing
158 were analyzed in a small subpopulation only because many patients had very low visual acuity and
159 the perimetric data would have been unreliable (8/17 from group A, 47.1%; and 11/19 from group B,
160 57.9%).

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

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

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

169 No statistically significant differences between the two groups were found in mean IOP 1 year after
170 treatment ($p = 0.879$). Nor were any found in mean number of IOP-lowering medications, which was
171 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
172 1 year after the procedure ($p = 0.762$).

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

174 Visual acuity (VA) did not change after UCP in either group, with no statistically significant
175 difference emerging from baseline to the last follow-up visit. Particularly, we observed VA mean
176 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
177 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)
178 for group B ($p = 0.25$). Moreover, we observed by the linear mixed models that the control variables
179 age, gender and myopia did not have a statistically significant effect in our results.

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

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

187

188 Discussion

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

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

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

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

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

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

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

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

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

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

247 successful in halting IOP fluctuations and consequently visual field progression. Due to severe
248 glaucoma damage, several patients were unable to undergo visual field testing. We therefore had data
249 on only 53% of the whole population, which represents a major limitation of our statistical analysis.
250 Tanaka D. et al published their results about the influence of high myopia on trabeculectomy
251 outcomes (42). They hypothesized that high myopia could lead to surgery failure due to the high
252 levels of inflammatory cytokines and growth factors detected in the aqueous humor (43,44).
253 However, they demonstrated that high myopia was not a risk factor for trabeculectomy failure,
254 although these controversial data remain unexplained. Our results showed a significant efficacy in
255 lowering IOP. This seems to corroborate the finding by Tanaka et al. that high myopia is not a risk
256 factor for trabeculectomy failure, even if surgical procedure, patient age, and glaucoma type and
257 severity were different.

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

265
266 In conclusion, UCP seems to be an effective and safe strategy to lower IOP in myopic patients with
267 medically uncontrolled glaucoma, since it may reduce the likelihood of the complications associated
268 with filtration surgery.

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380 **Figures/Tables/Supplementary Digital Content legend**

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

383 **Table 2** – Intraocular pressure measurements and number of topical medications

384 **Table 3** – Post-operative complications

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

386 **Supplementary Digital Content 1** – Linear mixed model. docx

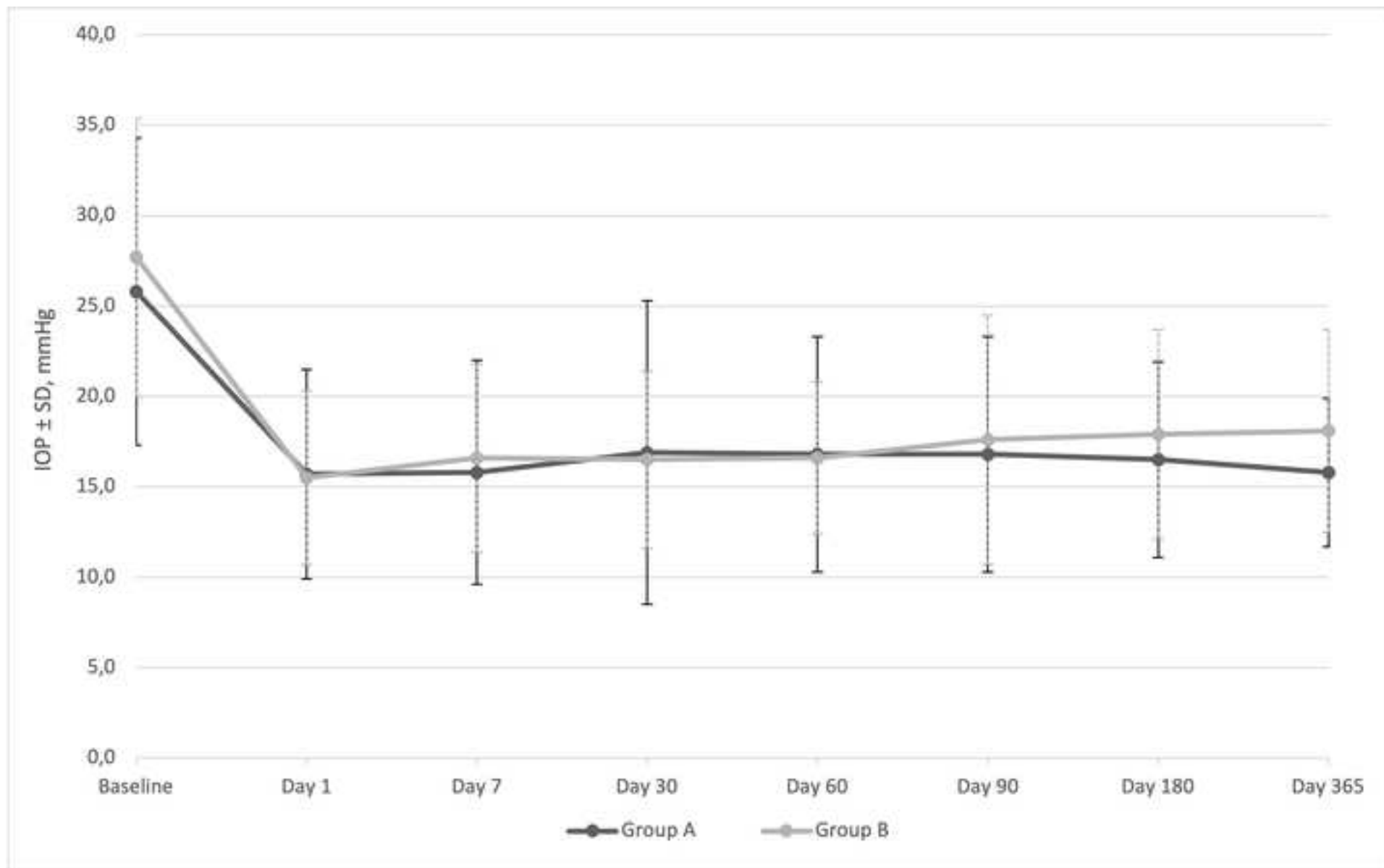


Table 1 – General characteristics of the study population and baseline ophthalmic data

	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	χ ² 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	χ ² test
Smoking, % (n)	19.4 (7)	11.8 (2)	26.3 (5)	0.272	χ ² test
Comorbidities					
Diabetes, % (n)	13.9 (5)	5.9 (1)	21.1 (4)	0.189	χ ² 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	χ ² test
Previous glaucoma surgery, % (n)	36.1 (13)	29.4 (5)	42.1 (8)	0.429	χ ² test
Type of glaucoma, % (n)					
POAG	75.0 (27)	82.4 (14)	68.4 (13)	0.335	χ ² test
Secondary glaucoma (PEX, PG)	22.2 (8)	11.8 (2)	31.6 (6)	0.153	χ ² test
Congenital glaucoma	2.8 (1)	5.9 (1)	0.0 (0)	0.284	χ ² 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	χ ² test
Pseudophakic	77.8 (24)	58.8 (10)	73.7 (14)	0.345	χ ² 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: pseudoexfoliation 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

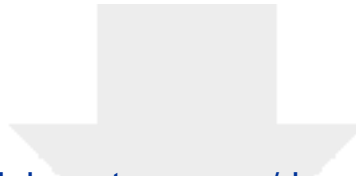
	Group A (n=17)			Group B (n=19)		
	Mean IOP, mmHg	IOP reduction (%)	n° of medications	Mean IOP, mmHg	IOP reduction (%)	n° of medications
Baseline	25.8 ± 8.5		2.8 ± 0.9	27.7 ± 7.7		2.6 ± 1.0
Day 1	15.7 ± 5.8	39.1		15.5 ± 4.8	43.7	
Day 7	15.8 ± 6.2	38.9	2.4 ± 1.1	16.6 ± 5.2	39.7	2.4 ± 0.9
Day 30	16.9 ± 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	χ^2 test
Subconjunctival haemorrhage	3 (17.6%)	2 (10.5%)	0.537	χ^2 test
Superficial punctuated keratitis	4 (23.5%)	6 (31.6%)	0.590	χ^2 test
Anterior chamber flare	4 (23.5%)	5 (26.3%)	0.847	χ^2 test
Corneal edema	1 (5.9%)	2 (10.5%)	0.615	χ^2 test

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



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