The ROYAL COLLEGE of OPHTHALMOLOGISTS

ARTICLE

Check for updates

Feasibility, efficacy and safety of early lens extraction in patients with pseudoexfoliation glaucoma: a feasibility and pilot study

Sara Pose-Bazarra[1]✉, María Jesús López-Valladares[2], Ignacio López-de-Ullibarri[3] and Augusto Azuara-Blanco[4]

© The Author(s), under exclusive licence to The Royal College of Ophthalmologists 2022

PURPOSE: To evaluate the feasibility of a trial to compare the efficacy and safety of initial lens extraction surgery versus medical treatment for people with pseudoexfoliation glaucoma (PXFG) or ocular hypertension (OHT) and pseudoexfoliation syndrome.
METHODS: This is a feasibility and pilot randomized controlled trial (RCT) in patients with newly diagnosed PXFG and mild cataract. The study was prospectively registered at ClinicalTrials.gov. An online survey was conducted among members of UK and Eire Glaucoma Society (UKEGS) and Spanish Glaucoma Society (SEG) with the aim of understanding current practices related to interventions for PXFG, the role of phacoemulsification and the willingness to participate in a definite trial. Participants were randomized into either early lens extraction surgery or medical treatment and deferred surgery Primary clinical outcome was intraocular pressure (IOP) at 12 months.
RESULTS: The study was conducted between May 2019 and February 2021. Twelve patients were randomized, six in each group. Median IOP decreased significantly in both arms. Among the secondary outcomes of BVCA, reduction in the number of treatments and quality of life, statistically significant differences were found in favor of lens extraction. There were no differences in other secondary outcomes. No adverse effects occurred. Glaucoma experts would be willing to participate in a RCT.
CONCLUSIONS: A trial on early lens extraction surgery compared with medication in PXFG is feasible. Early lens extraction appears to be an effective treatment for PXFG, reducing the number of hypotensive drugs after surgery as well as improving patients' quality of life.

Eye (2023) 37:1878–1884; https://doi.org/10.1038/s41433-022-02271-4

INTRODUCTION

Pseudoexfoliation (PXF) is an age-related systemic disorder of the extracellular matrix that can affect several tissues and organs of the body with clinical consequences especially on the eye [1, 2]. PXF is associated with an increased risk of surgical complications in cataract surgery and it increases the risk of open-angle glaucoma [3, 4]. It has also been stated that the glaucoma is more severe in eyes with PXF than in primary open-angle glaucoma (POAG) [5].

The association between PXF and cataract has been established in previous studies [6–8] and because cataract usually occurs in the same demographic patients, the treatment of both entities at the same time is a relevant clinical problem [9, 10]. The co-existence of cataract and glaucoma in patients with PXF poses dilemmas about the optimal surgical approach.

Several studies over the last decade have consistently described reductions in intraocular pressure (IOP) following cataract surgery, nonetheless there is a large variability in the magnitude and duration of IOP reduction depending on the type of glaucoma. Clear lens extraction is highly effective and a first line option for some patients with primary angle closure glaucoma [11]. The IOP lowering effect of cataract surgery in patients with POAG is modest [12–15] but the reduction in IOP may be more significant in people with PXF [16–18]. The observations of IOP reduction associated with cataract surgery leads to the question whether clear lens extraction may be an option for people with PXFG.

The best therapeutic approach for PXFG remains uncertain [19]. In patients diagnosed with co-existing PXFG and relatively mild cataract a possible management strategy is to try to control the IOP first with medical or laser treatment followed with lens extraction associated or not with further glaucoma surgery depending on the efficacy of initial treatments. Alternatively, lens extraction surgery may be used as an initial option.

Due to the current uncertainty, we conducted this feasibility and pilot study to evaluate the effectiveness of clear or early lens extraction surgery for patients newly diagnosed with PXFG.

METHODS

Objective

The main objective of this pilot study is to inform a definite trial to determine whether clear or early lens extraction surgery is a clinically effective and safe intervention for the treatment of PXFG or ocular hypertension (OHT) and pseudoexfoliation syndrome compared to standard medical treatment.

[1]Department of Ophthalmology, University Hospital Complex Ferrol, Ferrol, Spain. [2]Department of Ophthalmology, University Hospital Complex Santiago de Compostela, Santiago de Compostela, Spain. [3]Department of Mathematics, University of A Coruña, A Coruña, Spain. [4]Centre for Public Health, Queen's University, Belfast, UK.
✉email: saraposeb@gmail.com

Received: 28 February 2022 Revised: 29 August 2022 Accepted: 16 September 2022
Published online: 26 September 2022

Study design

This pilot trial was carried out with patients recruited from the public health care system (SERGAS) in the Ophthalmology Units of the Hospital University Complex of Ferrol and Santiago de Compostela (Galicia, Spain) from May 2019 to February 2020. These hospitals serve a population of 182.751 and 450.136 patients, respectively. In this region there is a high prevalence of PXF [20]. Patients were randomized in two groups in equal proportion (1:1 ratio) by using sealed envelopes.

The pilot study was prospectively registered at ClinicalTrials.gov (NCT03494465, 03/21/2018) and it is described in line with CONSORT (Consolidated Standards of Reporting Trials) checklist for guidance for pilot and feasibility studies [21].

Based on the recommendations of published studies on sample size calculations for pilot studies [22, 23], we estimated our sample size of 40 patients in order to obtain an accurate and concrete view of the objectives we aim to achieve.

Inclusion criteria

1. Mild or moderate PXFG or OHT over 25 mmHg + PXF syndrome. Glaucoma was defined as: reproducible defects (two or more contiguous points with a loss of $P < 0.01$, three or more contiguous points with a loss of $P < 0.05$ or greater) in the visual field (VF) or detectable damage to the optic nerve (cup-to-disc ratio ≥ 0.7 and/or focal thinning of the optic nerve rim and/or asymmetry of cup disc ratio ≥ 0.2 between both eyes). Mild glaucoma was defined as MD < −6 dB, and moderate glaucoma was defined as MD < −12 dB [24]. PXF was defined clinically by the presence of pseudoexfoliative material in the anterior capsule of the lens.
2. Presence of early cataract with some visual symptoms that justify the intervention, with best corrected visual acuity (BCVA) between range >0.4 and <0.7.
3. Naive diagnosed patients.
4. Age: patients > 60 years.
5. Willingness to participate in the trial and to defer cataract surgery for 12 months if randomized to initial medical treatment.

Exclusion criteria

1. Advanced glaucoma. It is defined as an average deviation > −12 dB [24] and/or threat of fixation (paracentral point with sensitivity of 0 dB), and/or cup-to-disc ratio > 0.9.
2. Corneal edema, corneal opacity or any other known corneal factor that may increase the risk of complications during surgery.
3. Previous cataract surgery in the eye considered for the study.
4. Axial length < 20 mm.
5. Estimated IOL power > 30 dioptres.
6. Signs of zonular weakness: phacodonesis, iridodonesis, lens subluxation, asymmetry of anterior chamber depth apparent on clinical exam.
7. Pupillary dilation < 5 mm.
8. Advanced cataract, with vision worse than 0.4.

Primary and secondary outcomes

The primary outcome was IOP at 12 months post-randomization.

Secondary outcomes included clinical, patient reported outcomes and safety, specifically: VF according to the global VF index (VFI), retinal nerve fibre layer (RNFL) global thickness by optical coherence tomography (OCT), need for glaucoma surgery, BCVA, quality of life using a visual function quality questionnaire: National Eye Institute Visual Function Questionnaire (NEI-VFQ39), number of antiglaucoma drugs, adverse events and rate of recruitment.

Investigators evaluating outcomes were masked for IOP measurements and interpretation of VF tests results. Patients were not masked.

Measurements and interventions

Target IOP was used in both groups to inform the need of escalation of therapy; in patients with OHT the target IOP was set at 21 mmHg. In patients with mild glaucoma target IOP was 18 mmHg, and in patients with moderate glaucoma the target IOP was set at 15 mmHg [25, 26]. Patients in both groups were treated in a staggered manner: 1. single topical medication with prostaglandin analogues; 2. double topical therapy; 3. triple topical therapy. If necessary, glaucoma surgical treatment was offered.

In lens extraction arm, patients underwent standard lens phacoemulsification with intraocular lens implant (IOL) within 60 days after randomization. Medical treatment was initiated at the time of diagnosis. If additional treatment was required, the stepped sequence of therapy described above was used.

Patients allocated to medical treatment were offered lens extraction surgery after 12 months post-randomization. Two ophthalmologists (SPB and MJVL), one per centre, performed the lens extraction surgeries. The calculation of the biometric power was made with an IOL Master (Carl Zeiss Meditec AG, Jena, Germany), and the formula SRK-T was used. IOL implanted was Clareon® Aspheric Hydrophobic Acrylic IOL, Model SY60WF (Alcon Laboratories, Inc., Fort Worth, TX). IOP measurement, with Perkins applanation tonometry, was masked by using a second observer. Humphrey Perimeter

Table 1. Online survey for glaucoma experts: multiple-choice questionnaire.

1. Do you see many patients with PXFG or PXF in your practice? • Yes, I see several patients every week • Not often, only a few patients every month • PXF is rare in my area
2. Do you think phaco + IOL improves IOP control in patients with PXFG or PXF and high IOP? • Yes, in my experience this is a common finding • Sometimes but typically the change in IOP is minor • No
3. Do you modify the timing of phaco in patients with cataract and PXFG? • Yes, I offer earlier phaco in patients with PXFG and early caratact, as I think surgery will be more difficult with denser cataract or it may help control the IOP • Occasionally • No
4. If there were evidence from a large trial that early lens extraction is safe and effective for IOP control in patients with PXFG, would you be willing to offer this option to your patients? • Yes, and this is already my current practice • Possibly, if the results of the trial are definite • No
5. Would you be willing to participate in a trial evaluating the efficacy and safety of lens extraction in patients with PXFG? • Yes • Possibly • No
6. What is your position? (e.g., consultant, ophthalmologist, hospital optometrist, trainee)

(SITA Standard 24-2) (Carl Zeiss Meditec AG, Jena, Germany) was used for VFs testing; RNFL determinations were carried out with Spectralis® spectral-domain OCT (Heidelberg Engineering, Inc., Heidelberg, Germany). The BCVA was taken on a Snellen scale. Complications related to cataract surgery and adverse events were collected.

The visit schedule included a complete examination at baseline and at the end of the study (12 months), including visits at 4 and 8 months for IOP, BCVA, number of treatments, OCT RNFL and possible complications. Visual Function Questionnaire was completed at baseline and at the end of the study.

Table 2. Characteristics of the patients at baseline by treatment.

Characteristic	Control	Intervention	*p* value
Age	77.0 (72.3, 82.5)	76.5 (73.0, 78.5)	0.959
Gender[a]			
Female	83.3%	63.7%	1.000
Ocular history[a]			
Yes	16.7%	33.3%	1.000
Laterality[a]			
Right	33.3%	16.7%	1.000
Pachymetry	546.5 (521.5, 562.5)	541.5 (523.8, 553.2)	0.851
AXL	22.60 (22.68, 22.95)	23.14 (23.10, 23.42)	0.065
IOP	29.5 (28.3, 31.5)	29.5 (26.5, 31.8)	0.727
BCVA	0.65 (0.60, 0.70)	0.50 (0.50, 0.58)	0.074
BMO	276.0 (242.5, 321.5)	289.5 (261.5, 314.5)	1.000
RNFL	90.0 (84.0, 94.5)	90.5 (85.3, 94.3)	0.905
NT	1.0 (1.0, 1.0)	1.5 (1.0, 2.0)	0.545
ENDO	2366 (2308, 2592)	2314 (2188, 2616)	0.699
VFI	93.5 (90.8, 95.5)	94.0 (87.3, 94.8)	0.814
MD	−3.88 (−4.90, −3.28)	−6.56 (−6.70, −4.53)	0.180
VFQ-39	90.2 (83.0, 92.1)	83.4 (76.0, 89.0)	0.310

AXL axial length. mm, *IOP* intraocular pressure. mmHg, *BCVA* best corrected visual acuity. Snellen lines, *BMO* Bruch's membrane opening. µm, *RNFL* retinal nerve fiber layer. µm, *NT* number of treatments, *ENDO* endothelial cells count, *VFI* visual field index, *MD* median deviation, dB, *VFQ* visual function questionnaire.
[a]Under the columns 'Control' and 'Intervention' percentages are given. The column '*p* value' gives the *p* value of Fisher's test. For the other variables, the corresponding figures are median (1st quartile, 3rd quartile) and *p* value of the WMW test.

Statistical analysis

Statistical comparison of patient baseline characteristics between treatment arms was carried out using the exact Wilcoxon-Mann-Whitney (WMW) test or Fisher's exact test, according to the variable type. Changes in variables describing visual status were computed by subtracting final (i.e., at 12 months) measurements from baseline values. For these variables, 95% confidence intervals (95%CI) for the median change in each of both arms were computed using Bauer's procedure [27], based on the Wilcoxon signed rank statistic. Comparison of the change in these variables between treatment arms was performed using the exact WMW test.

For statistical computing and graphs, R [28] and the R packages *coin* [29], *exactRankTests* [30] and *ggplot2* [31] were used.

Ethical-legal aspects

The development of the project was carried out respecting the Declaration of Helsinki of the World Medical Association 1964 and successive ratifications. The present study was approved by the Research Ethics Committee (CEI). Any clinical data collected from the subjects was separated from the personal identification data, guaranteeing the confidentiality of the participants in the research and respecting the Law of Protection of Personal Data.

This study was supported in kind by the researchers' organizations.

Survey

An anonymous online survey was developed using a commercial website (SurveyMonkey, Palo Alto, California, USA) and was distributed to the members of the UK and Eire Glaucoma Society (UKEGS) (http://www.glaucoma-societyuke.org) and the Spanish Glaucoma Society (SEG) (https://www.sociedadglaucoma.com) in October 2019. A second e-mail survey was sent 4 weeks after as a reminder. Data were analyzed using surveymonkey.com analysis tools and Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

At the time of survey distribution, there were 116 glaucoma subspecialty consultants registered as UKEGS members, and 429 registered as SEG members.

Participants were asked questions about percentage of PXF patients treated in daily consultation, their current practices in the timing for phaco

Table 3. Comparison of visual status variables between treatment groups at 12 months.

	12 months[a]		Change from 0 to 12 months[b]		
Variable	Control	Intervention	Control	Intervention	*p* value
IOP	15.0 (14.0, 19.0)	16.0 (14.5, 16.8)	15.0 (8.8, 16.0) [6.0; 20.0]	11.0 (9.3, 16.5) [9.0; 19.5]	0.893
BCVA	0.50 (0.43, 0.58)	1.00 (0.93, 1.00)	0.15 (0.10, 0.20) [0.10; 0.30]	−0.45 (−0.50, −0.33) [−0.50; −0.20]	0.002
BMO	263.5 (237.0, 302.8)	273.0 (247.8, 305.0)	12.5 (7.8, 17.3) [7.0; 19.0]	8.5 (−8.0, 14.5) [−30.0; 85.0]	0.513
RNFL	89.5 (85.0, 91.8)	87.0 (78.8, 96.0)	3.5 (1.5, 4.0) [−5.0; 8.0]	3.5 (−0.8, 7.0) [−3.0; 8.0]	0.987
NT	1.0 (1.0, 1.8)	0.0 (0.0, 0.8)	0.0 (0.0, 0.0)	1.0 (1.0, 1.0)	0.013
ENDO	2252.5 (2152.8, 2537.5)	2171.0 (1996.8, 2309.3)	66.5 (30.5, 121.2) [−19.0; 637.0]	168.5 (82.3, 224.8) [10.0; 325.0]	0.394
VFI	93.0 (91.5, 93.0)	90.5 (88.9, 95.5)	2.0 (0.3, 3.0) [−1.0; 32.0]	−3.0 (−5.5, 4.8) [−7.0; 21.0]	0.223
MD	−4.77 (−6.11, −3.56)	−3.48 (−3.81, −2.57)	1.27 (0.70, 1.48) [−0.90; 6.97]	−2.12 (−3.63, −0.30) [−4.16; 3.92]	0.065
VFQ-39	89.2 (81.8, 95.7)	95.8 (86.0, 96.9)	−0.5 (−2.7, 4.2) [−4.5; 13.5]	−7.4 (−11.7, −7.0) [−20.1; −2.4]	0.009

IOP intraocular pressure. mmHg, *BCVA* best corrected visual acuity. Snellen lines, *BMO* Bruch's membrane opening. µm, *RNFL* retinal nerve fiber layer. µm, *NT* number of treatments, *ENDO* endothelial cells count, *VFI* visual field index, *MD* median deviation, dB, *VFQ* visual function questionnaire.
[a]Median (1st quartile, 3rd quartile) of the measurements at 12 months.
[b]Median (1st quartile, 3rd quartile) of the differences computed by subtracting measurements at 12 months from baseline measurements. Within square brackets, a 95% confidence interval for the median of differences is given (for NT it is omitted, due to the extreme discreteness of the data). The last column collects the *p* values of the WMW test.

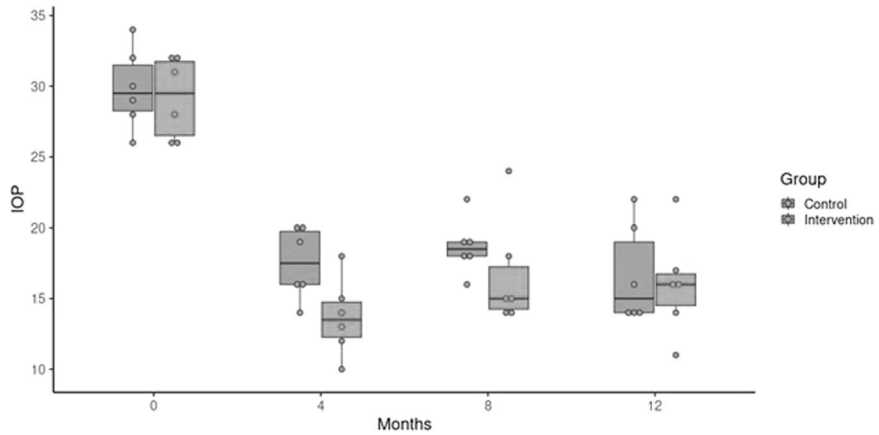

Fig. 1 Post-treatment IOP outcome. Combined box and dot plots of IOP by time and treatment group.

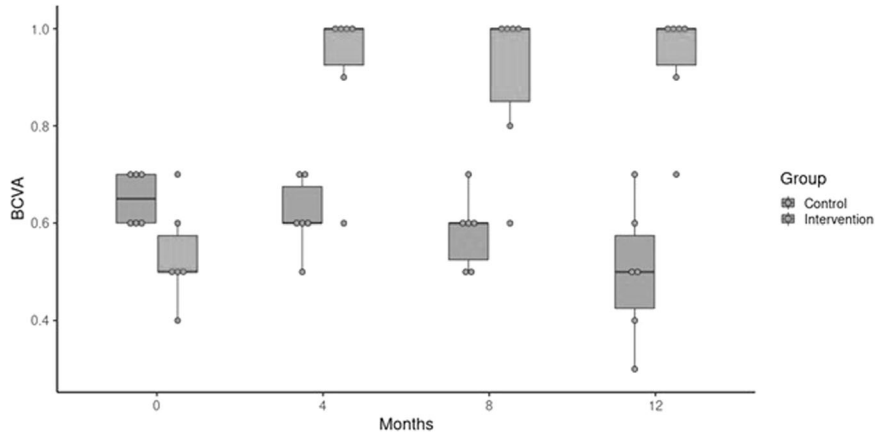

Fig. 2 Post-treatment BCVA outcome. Combined box and dot plots of BCVA by time and treatment group.

in PXF cases, their approaches on cataract surgery as an intervention for controlling IOP, and if the existence of a clinical trial confirming the conclusions found in previous studies could imply a change in their clinical practice. The referred questions are presented in detail in Table 1.

RESULTS

From May 2019 to February 2020, 19 patients were assessed for eligibility in the study. Recruitment was halted due to the COVID-19 pandemic. The number of patients declining to participate in the trial was 7 (39%). Finally, 12 patients were randomized to either phaco-intervention group ($n = 6$) or control group ($n = 6$) and none were lost to follow-up. Participants in both arms were comparable at baseline and no statistically differences at the 0.05 significance level were found between groups. Table 2 provides a detailed description of baseline patient characteristics.

Table 3 shows summaries of the variables characterizing the visual status of the patients at 12 months from randomization in both treatment groups. In Table 3 the measurements are also expressed in terms of the change from baseline.

Primary outcome

Figure 1 illustrates the time profile of IOP at baseline, 4, 8 and 12 months by treatment. Median IOP decreased in both control and intervention groups, from 29.5 mmHg baseline to 15.0 mmHg and 16.0 mmHg at 12 months, respectively (95% CI's for the median change from baseline [6; 20] and [9; 19.5], for control and intervention groups, respectively). At the 0.05 significance level, no location shift in the distribution of the change of IOP between treatment arms was found (p value = 0.893).

Secondary outcomes

For BCVA, the time profile at baseline, 4, 8 and 12 months by treatment is displayed in Fig. 2 by means of a grouped box (and dot) plot. Median BCVA decreased in standard medical treatment from 0.65 at baseline to 0.5 at 12 months (95% CI for the median change: [0.1; 0.3]), while it improved in the surgery arm from 0.5 to 1 (95% CI for the median change: [−0.5, −0.2]).

The evolution of the number of antiglaucoma treatments (NT) along time is shown with the conditional bar chart displayed in Fig. 3. Median NT remained stable in the control group, but in the lens extraction group it was reduced from 1.5 at baseline to 0 at 12 months (no 95% CI for the median change is given, because the technique cannot be reliably applied due to extreme data discreteness).

As for the VFQ-39 questionnaire, Fig. 4 shows box (and dot) plots of the scores by time and treatment group. The median VQF-39 score showed a worsening in the visual status of the patients treated with standard therapy, decreasing from 90.2 at the baseline to 89.2 at the final visit (95% CI for the median change: [−4.5; 13.5]). On the contrary, it showed an improvement in the surgery group, increasing from 83.4 to 95.8 (95% CI for the median change: [−20.1; −2.4]).

For all of BCVA, NT and VQF-39, the distribution of the change from baseline to 12 months showed a significant location shift between treatment groups at the 0.05 level (p value = 0.002, 0.013 and 0.009, respectively). On the other hand, at the same significance level, no between-group differences were found for any of the other secondary outcomes (OCT parameters, VF index and mean deviation and endothelial cell count). In Table 2, 95%

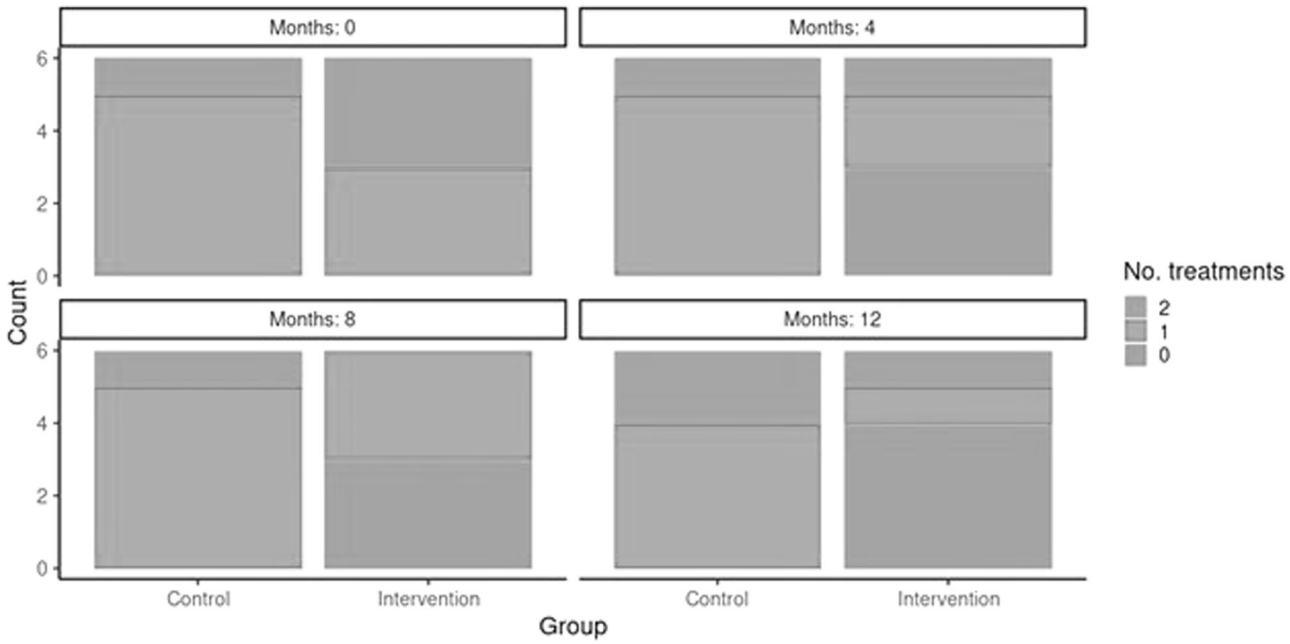

Fig. 3 Changes in NT. Bar chart of NT by time and treatment group.

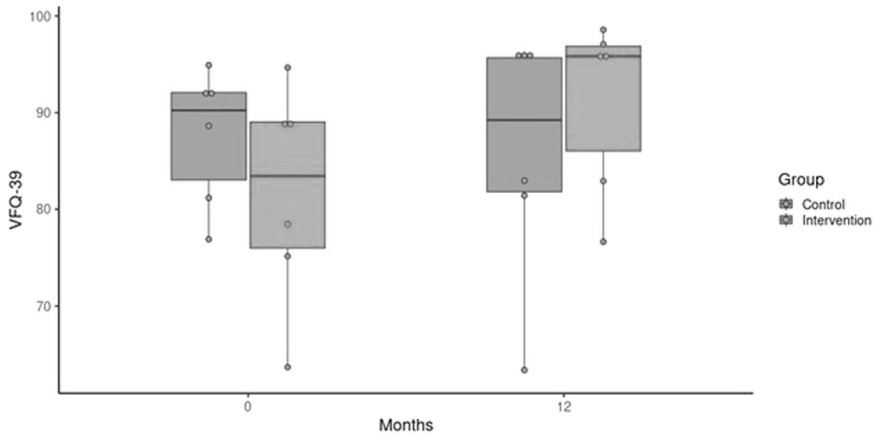

Fig. 4 Post-treatment VFQ-39 outcome. Combined box and dot plots of VFQ-39 by time and treatment group.

CI's for the median change of these variables between visits can be found, both for control and intervention groups.

Adverse events

No adverse events were encountered in either arm of the trial. No complications occurred during cataract surgery. No patients required additional glaucoma surgery during the study follow-up period.

Survey

A total of 72 glaucoma experts from Spain, UK and Ireland completed the survey representing a 14% response rate from eligible experts. Most respondents (94%) were glaucoma specialists. All survey questions were completed.

PXFG is a common disease in the daily practice of glaucoma clinicians of both societies. The majority (over 50%) see several patients with PXFG every week.

Overall, glaucoma experts considered phaco to be an effective lowering IOP procedure, but discrepancies were seen between answers in both societies. In UK/Eire, nearly half of respondents (46%), considered that phaco was an effective option and an adequate initial procedure while a similar proportion considered that the efficacy was limited. In Spain, less (30%) of survey respondents thought that phaco was sufficient to control de IOP at least in some cases, while the majority (63%) thought that it could control IOP in certain cases but usually it did not provide a satisfactory control.

UK/Eire and Spain respondents agreed (79% and 88% respectively) to early cataract extraction in order to avoid possible complications of denser cataracts and weaker zonules.

On the question about the possibility of changing practice if there was evidence from a large trial proving that early lens extraction is safe and effective for IOP control in patients with PXFG, 50% of the specialists surveyed would be willing to offer this option, as is already their current practice. The rest of the participants (49%) would be keen to do it if the results show efficacy with a good safety profile.

The majority of respondents (71%) expressed an interest in participating in a trial evaluating the efficacy and safety of lens extraction in patients with PXFG.

DISCUSSION

The results of this randomized pilot and feasibility study provide preliminary confirmation that a large trial of early lens extraction for PXFG would be feasible as it would have support from glaucoma experts from Spain, UK and Ireland, although some challenges remain.

Similar to previous studies, in patients with mild to moderate PXFG controlled with 1 or 2 medications, phacoemulsification has resulted in a moderate decrease in IOP (20%) and in the number of medications required after surgery (35%) [32]. This IOP reduction seems to be maintained over time, even 7 years after cataract surgery [33]. In a very recent study, the results of phacoemulsification alone are comparable in terms of IOP decrease versus viscocanalostomy in patients with mild to moderate PXFG [34]. Patients with advanced stages of PXFG were excluded from the study due to uncertainty about the efficacy and safety of this intervention. In a future trial it will be useful to stratify the population according to the severity of disease and IOP level.

The sample size was lesser than expected and was halted because of the COVID pandemic. Of 19 eligible patients, 12 were included, achieving a recruitment rate of over 50% (65%). The most frequent reason for declining participation was refusal of surgery given the insufficient visual limitations they presented. This was surprising considering that patients had cataract and some degree of vision loss.

The mean age of the patients included in the trial was 77 years, influenced by our inclusion criteria, which used a visual acuity cut-off point. The indication for cataract surgery in clinical practice is individualized and typically based on the presence of a visual symptoms and limitations, without any fixed visual acuity criterium. Participants enrolled in our pilot study had early or moderate cataracts but were willing to defer surgery. Actually, some patients who had reduced vision due to early cataract and fulfilled other inclusion criteria declined to participate in the study because they were asymptomatic and would not consider surgery. In our study, a BCVA between 0.4 and 0.7 on the Snellen scale was used, avoiding dense cataracts. In a future RCT it will be interesting to target patients with an earlier stage of lens opacity and better visual acuity. However, the possibly of including patients with clear lens and perfect vision will raise clinical and ethical challenges that will need to be addressed.

Lens removal in patients with PXF is a procedure with higher complication rates due to its smaller pupillary diameter and its greater zonular weakness [35]. However earlier cataract surgery in people with PXF may decrease the risk of surgical complications [36] if zonules are not yet compromised. In our small sample, we have not found any adverse event related to the surgery or a lower endothelial cell count after the intervention. A prospective study has been published [37] analyzing endothelial damage secondary to cataract surgery in pseudoexfoliative patients compared to a non-PXF control group. The results show that there are no significant differences at 2 years between groups in the corneal endothelial cell loss. However, even though our pilot study was not associated with serious adverse events we acknowledge that our study and even a larger randomized trial may not have sufficient power to quantify the incidence of uncommon severe complications. Many of the complications may be late and would require a longer follow-up than 1 year to be observed and larger sample size.

Our survey found consistent agreement among glaucoma specialists about the importance of an early cataract surgery in patients with PXF in order to avoid possible difficulties associated denser cataracts, weaker zonular support and poor pupillary dilation. Early cataract surgery is a feasible option and chosen by many surgeons to improve control IOP while improving the visual and life quality of their patients. The majority of the respondents would be willing to participate in a multicentre study evaluating the efficacy of early lens extraction for IOP control in PXFG patients without cataract.

The following are the limitations of the study. First, our original target for our pilot study was not met, in part due to the COVID pandemic. However, we consider our study has been able to answer key questions regarding the feasibility of a larger, definite trial.

Another limitation of this study is the relatively low response rate to the survey, lower than other online glaucoma surveys in the United Kingdom [38], but in common with other previously published online surveys of glaucoma surgical preferences [39]. Since it has been conducted in different countries and we have achieved similar opinions, we can have more confidence in the generalizability of our findings.

The main methodological strength of this trial is its prospective randomized design and the rigorous methodology, with masked investigators evaluating the primary outcome. Despite the small sample size, we obtained statistically significant results in relation to quality of life, number of treatments and BVCA, and confirmed the efficacy of the intervention up to 12 months. In addition, this pilot study will serve to calculate the sample size of a larger study that will allow us to analyze the hypothesis in depth.

To the best of our knowledge, this is the first randomized clinical trial (RCT) investigating the feasibility and preliminary effect of early cataract surgery as a treatment for PXFG. The evidence from RCT on surgical interventions for PXFG is still very scarce. Our study supports the need for a definitive larger RCT to evaluate early or clear lens extraction in patients with PXFG.

SUMMARY

What was known before

- Lens removal has been demonstrated by multiple retrospective studies as an effective hypotensive treatment in almost all types of glaucoma.
- Only in cases of narrow angles has it been further demonstrated by prospective well-designed trials.

What this study adds

- First RCT to demonstrate the feasibility of lens extraction for the treatment of glaucoma or hypertension with pseudoexfoliation syndrome.
- Survey of glaucoma experts supporting the hypotheses put forward in the study.

DATA AVAILABILITY

Anonymised datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Ritch R. Perspective on exfoliation syndrome. J Glaucoma. 2001;10(5 Suppl 1):S33–5. Epub 2002/03/14
2. Schlotzer-Schrehardt U, Naumann GO. Ocular and systemic pseudoexfoliation syndrome. Am J Ophthalmol. 2006;141:921–37. Epub 2006/05/09
3. Ritch R. Exfoliation syndrome-the most common identifiable cause of open-angle glaucoma. J Glaucoma. 1994;3:176–7. Epub 1994/07/01
4. Mitchell P, Wang JJ, Hourihan F. The relationship between glaucoma and pseudoexfoliation: the Blue Mountains Eye Study. Arch Ophthalmol. 1999;117:1319–24. Epub 1999/10/26
5. Vesti E, Kivela T. Exfoliation syndrome and exfoliation glaucoma. Prog Retinal Eye Res. 2000;19:345–68. Epub 2000/04/05

6. Hiller R, Sperduto RD, Krueger DE. Pseudoexfoliation, intraocular pressure, and senile lens changes in a population-based survey. Arch Ophthalmol. 1982;100:1080–2. Epub 1982/07/01
7. Hirvela H, Luukinen H, Laatikainen L. Prevalence and risk factors of lens opacities in the elderly in Finland. A population-based study. Ophthalmology. 1995;102:108–17. Epub 1995/01/01
8. Arvind H, Raju P, Paul PG, Baskaran M, Ramesh SV, George RJ, et al. Pseudoexfoliation in South India. Br J Ophthalmol. 2003;87:1321–3. Epub 2003/11/12
9. Futa R, Shimizu T, Furuyoshi N, Nishiyama M, Hagihara O. Clinical features of capsular glaucoma in comparison with primary open-angle glaucoma in Japan. Acta Ophthalmologica. 1992;70:214–9. Epub 1992/04/01
10. Puska P, Vesti E, Tomita G, Ishida K, Raitta C. Optic disc changes in normotensive persons with unilateral exfoliation syndrome: a 3-year follow-up study. Graefe's Arch Clin Exp Ophthalmol = Albrecht von Graefes Arch fur klinische und experimentelle Ophthalmologie. 1999;237:457–62. Epub 1999/06/24
11. Azuara-Blanco A, Burr J, Ramsay C, Cooper D, Foster PJ, Friedman DS, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. Lancet. 2016;388:1389–97. Epub 2016/10/07
12. Chang TC, Budenz DL, Liu A, Kim WI, Dang T, Li C, et al. Long-term effect of phacoemulsification on intraocular pressure using phakic fellow eye as control. J Cataract Refractive Surg. 2012;38:866–70. Epub 2012/03/01
13. Iancu R, Corbu C. Intraocular pressure after phacoemulsification in patients with uncontrolled primary open angle glaucoma. J Med Life. 2014;7:11–6. Epub 2014/03/22
14. Bhandari S, Pandyal I, Khanal SP, Thapa SS. Effect of phacoemulsification surgery on various parameters in patients with glaucoma. Nepal J Ophthalmol: a Biannu peer-reviewed academic J Nepal Ophthalmic Soc: NEPJOPH. 2014;6:46–55. Epub 2014/10/25
15. Thomas R, Walland M, Thomas A, Mengersen K. Lowering of Intraocular Pressure After Phacoemulsification in Primary Open-Angle and Angle-Closure Glaucoma: a bayesian analysis. Asia Pac J Ophthalmol (Philos). 2016;5:79–84. Epub 2016/02/18
16. Altan-Yaycioglu R, Canan H, Pelit A, Akova YA. Intraocular pressure after phacoemulsification in eyes with pseudoexfoliation. J Cataract Refractive Surg. 2009;35:952–4. Epub 2009/04/28
17. Merkur A, Damji KF, Mintsioulis G, Hodge WG. Intraocular pressure decrease after phacoemulsification in patients with pseudoexfoliation syndrome. J Cataract Refractive Surg. 2001;27:528–32. Epub 2001/04/20
18. Damji KF, Konstas AG, Liebmann JM, Hodge WG, Ziakas NG, Giannikakis S, et al. Intraocular pressure following phacoemulsification in patients with and without exfoliation syndrome: a 2 year prospective study. Br J Ophthalmol. 2006;90:1014–8. Epub 2006/05/05
19. Pose-Bazarra S, Lopez-Valladares MJ, Lopez-de-Ullibarri I, Azuara-Blanco A. Surgical and laser interventions for pseudoexfoliation glaucoma systematic review of randomized controlled trials. Eye (Lond). 2021;35:1551–61. Epub 2021/02/11
20. Viso E, Rodriguez-Ares MT, Gude F. Prevalence of pseudoexfoliation syndrome among adult Spanish in the Salnes eye Study. Ophthalmic Epidemiol. 2010;17:118–24. Epub 2010/03/23
21. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355:i5239. Epub 2016/10/26
22. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res. 2016;25:1057–73. Epub 2015/06/21
23. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. J Clin Epidemiol. 2012;65:301–8. Epub 2011/12/16
24. Hodapp E, Parrish RK II, Anderson DR. Clinical decisions in glaucoma. St Louis: The CV Mosby Co;1993. p. 52–61.
25. European Glaucoma Society. Terminology and Guidelines for Glaucoma. 3rd ed. Savona: Dogma; 2008.
26. Damji KF, Behki R, Wang L, Target IOP Workshop participants. Canadian perspectives in glaucoma management: setting target intraocular pressure range. Can J Ophthalmol. 2003;38:189–97.
27. Bauer DF. Constructing confidence sets using rank statistics. J Am Stat Assoc. 1972;67:687–90.
28. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; 2021. https://www.R-project.org/.
29. Hothorn T, Hornik K, van de Wiel MA, Zeileis A. Implementing a class of permutation tests: the coin package. J Stat Softw. 2008;28:1–23.
30. Hothorn T, Hornik K. exactRankTests: exact distributions for rank and permutation tests. R package version 0.8-34; 2021. https://CRAN.R-project.org/package=exactRankTests
31. Wickham H. ggplot2: elegant graphics for data analysis. New York:Springer-Verlag; 2016.
32. Chen PP, Lin SC, Junk AK, Radhakrishnan S, Singh K, Chen TC. The Effect of Phacoemulsification on Intraocular Pressure in Glaucoma Patients: A Report by the American Academy of Ophthalmology. Ophthalmology. 2015;122:1294–307. Epub 2015/05/07
33. Shingleton BJ, Laul A, Nagao K, Wolff B, O'Donoghue M, Eagan E, et al. Effect of phacoemulsification on intraocular pressure in eyes with pseudoexfoliation: single-surgeon series. J Cataract Refractive Surg. 2008;34:1834–41. Epub 2008/11/14
34. Zarei R, Azimi A, Fakhraei G, Eslami Y, Naderan M, Nouri-Mahdavi K, et al. Combined phacoviscocanalostomy versus phacoemulsification alone in patients with coexisting cataract and mild-to-moderate open-angle glaucoma; a randomized-controlled trial. Eye (Lond). 2022. Online ahead of print. Epub 2022/06/26.
35. Shingleton BJ, Neo YN, Cvintal V, Shaikh AM, Liberman P, O'Donoghue MW. Outcome of phacoemulsification and intraocular lens implantion in eyes with pseudoexfoliation and weak zonules. Acta Ophthalmol. 2017;95:182–7. Epub 2016/05/28
36. Vazquez-Ferreiro P, Carrera-Hueso FJ, Fikri-Benbrahim N, Barreiro-Rodriguez L, Diaz-Rey M, Ramon Barrios MA. Intraocular lens dislocation in pseudoexfoliation: a systematic review and meta-analysis. Acta Ophthalmol. 2017;95:e164–9. Epub 2016/08/30
37. Kristianslund O, Pathak M, Ostern AE, Drolsum L. Corneal endothelial cell loss following cataract surgery in patients with pseudoexfoliation syndrome: a 2-year prospective comparative study. Acta Ophthalmol. 2020;98:337–42. Epub 2019/11/26
38. Rodriguez-Una I, Azuara-Blanco A, King AJ. Survey of glaucoma surgical preferences and post-operative care in the United Kingdom. Clin Exp Ophthalmol. 2017;45:232–40. Epub 2016/10/12
39. Vinod K, Gedde SJ, Feuer WJ, Panarelli JF, Chang TC, Chen PP, et al. Practice Preferences for Glaucoma Surgery: A Survey of the American Glaucoma Society. J Glaucoma. 2017;26:687–93. Epub 2017/07/12

AUTHOR CONTRIBUTIONS

SPB, MJLP, and AAB conceived and designed the study, SPB and MJLP conducted the trial, ILU performed the analytical calculations, SPB drafted the paper, MJLP, AAB, and ILU reviewed the paper and edited it, AAB supervised the Project.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Sara Pose-Bazarra.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.