The ROYAL COLLEGE of
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REVIEW ARTICLE

Surgical and laser interventions for pseudoexfoliation glaucoma systematic review of randomized controlled trials

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Abstract
To assess the comparative effectiveness and safety of different surgical and laser techniques in people with pseudoexfoliation glaucoma (PXFG). We conducted a systematic review including randomized controlled trials (RCT) that compared any pair of surgical or laser treatment versus other type of intervention in PXFG. RCT were identified by a highly sensitive search of electronic databases and two individuals independently assessed trial eligibility, abstracted data and assessed risk of bias. We performed Bayesian Meta-Analysis when outcomes were comparable. The search strategy identified 6171 records. Six studies (262 subjects) were included. Two trials analyzed the same pair of surgical interventions comparing phacoemulsification as solo procedure or combined with trabecular aspiration and we performed meta-analysis. Other RCTs compared the following interventions: trabecular aspiration associated with phacoemulsification versus phacotrabeculectomy, non-penetrating deep sclerectomy associated or not with phacoemulsification, selective versus argon laser trabeculoplasty and one-site versus two-site phacotrabeculectomy. For IOP data, none of the trials reported a difference between pairs of surgical techniques, nor changes in visual acuity or number of post-operative medications. The overall risk of bias is moderate to high. There are no apparent differences in efficacy and safety, although with large uncertainty, between surgical or laser techniques for PXFG. Based on the low-quality evidence from the six studies included in this review, it is not possible to justify the preferential use of non-penetrating surgery, MIGS or trabecular aspiration (with or without cataract surgery) in PXFG. Further research is needed to determine the optimal management of this condition.

Introduction

Pseudoexfoliation (PXF) is an age-related systemic pathology characterized by the accumulation of extracellular microfibrillar material in the eye and many other tissues as blood vessels, skin, kidneys, heart, lungs, or meninges, among others [1]. It is the most common identifiable cause of glaucoma [2].

The exact pathophysiological process remains unclear but it is considered a multifactorial disease that involves genetic and environmental factors and whose pathogenesis is based on the theory of microfibrillar elastosis, creating an excessive amount of abnormal cross-linked fibrils that aggregates, deposits, and increases resistance in the trabecular meshwork, with the consequent increase of intraocular pressure (IOP) [3–6]. Other non-genetic factors such as an increased natural exposure to ultraviolet ambient [7] have been also associated with PXF syndrome.

PXF can cause open-angle glaucoma or, less frequently, angle-closure glaucoma, and it is also a major risk factor for serious complications at the time of cataract extraction [8]. Compared with primary open-angle glaucoma (POAG), pseudoexfoliation glaucoma (PXFG) has worse prognosis due to higher IOP and is often associated with severe optic nerve damage [9] and faster VF progression [10]. Medical treatment, laser, and surgical procedures for managing PXFG are the same as POAG but filtering surgery is more

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frequently required [11]. At present, we do not know precisely which treatment offers us the greatest effectiveness in terms of good IOP control and a better long-term safety profile. A systematic review comparing the success and complication rates of any intervention is crucial to answer this question.

The goal of this study was to systematically assess the comparative effectiveness and safety of different surgical and laser techniques in people with PXFG.

Methods

The review protocol was registered at PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero, registration no. CRD42019127051). This article adheres to the PRISMA statement checklist for the preferred reporting of systematic reviews and meta-analysis.

Eligibility criteria for considering studies for this review

This systematic review included randomized controlled trials that evaluated laser or surgical interventions for patients with PXF. Non-randomized studies were excluded.

We looked for any surgical and laser intervention on patients with PXF, not only those specific to PXF. Studies evaluating different open-angle glaucoma populations including POAG and PXF were included, but analyzed only if they reported data separately on the PXF subgroup. We included participants with PXFG and those with PXF and high IOP (i.e., above 21 mmHg). There were no restrictions based on participant age, gender, ethnicity, or co-morbidity.

Interventions

We included trials that compared any pair of surgical or laser interventions and any surgical or laser procedure versus other type of intervention. These include: laser trabeculoplasty, trabeculectomy, non-penetrating filtering surgery such as deep sclerectomy, phacoemulsification, glaucoma drainage devices, minimal invasive glaucoma surgeries, cyclodiode procedures, combined surgeries including cataract extraction and other type of intervention. We accepted any comparator, including different surgical techniques and medical treatment.

Outcome measures

Our primary outcome was mean change in IOP 2 years after the intervention. However, we planned to report IOP outcomes at any other times, if and when available.

Secondary outcomes

- Visual acuity: mean change in best-corrected visual acuity (BCVA),
- Visual field (VF) progression: change in mean deviation (MD) measured by automated perimetry or as reported by the primary study,
- Structural progression: as reported,
- Mean number of glaucoma medications and proportion of participants who are drop-free post-intervention,
- Additional surgical or laser intervention for glaucoma,
- Adverse effects and complications, including corneal edema, hyphema, cataract, inflammation or hypotony, among others.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (latest issue), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLD-MEDLINE (January 1946 to present), EMBASE (January 1980 to present), PubMed (1948 to present), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to present), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not have any date or language restrictions. We used Science Citation Index to search the reference lists of included studies in order to identify additional eligible studies.

Two review authors independently reviewed the titles and abstracts of all records identified. Each review author classified titles and abstracts as "relevant", "possibly relevant", or "not relevant". We retrieved the full-text reports of all records classified as "relevant" or "possibly relevant". Each review authors will assess every full-text article and classify the studies as "include" or "exclude". We resolved discrepancies through discussion, and if needed, a third review author was consulted. We contacted investigators of studies whose eligibility was unclear to request clarification. Two review authors independently extracted data, using internet-based data abstraction forms. We resolved discrepancies through discussion and consulted a third review author when necessary.

Risk of bias assessment

The Cochrane Handbook for Systematic reviews methods was used to assess the risk of bias. Two review authors independently assessed each included trial for potential sources of bias as being at low, high, or unclear risk of bias. Disagreements were resolved by discussion and a third

author arbitrated unresolved disagreements. We assessed the following potential risk of bias: selection bias (sequence generation, allocation concealment); performance bias (masking of participants and study personnel); detection bias (masking of outcome assessors); attrition bias (incomplete outcome data); and reporting bias (selective outcome reporting). We contacted study authors to request for not reported or unclear data. We graded the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and presented it in a summary table.

Data analysis and synthesis

The primary unit of analysis was the eye. For each study, treatment effects for numeric outcomes were estimated by computing raw or standardized mean differences (IOP and visual acuity, respectively). For binary outcomes (medication and adverse effects), relative risks were computed, making a continuity correction if no events were observed in a group (by substituting 0 events with 0.5). Standard errors of the treatment effects were also estimated.

An inverse variance-weighted random-effects meta-analysis of the treatment effects on the outcomes was performed. To this end, the Bayesian methodology proposed by Friede et al. [12] was used and this decision was made post-hoc due to the scarce number of studies found. This methodology is specially advocated when only a few studies are included in the meta-analysis, in which case standard frequentist techniques meet with difficulties in getting correct heterogeneity estimates. Non-informative uniform and DuMouchel priors are used for the pooled effect and the heterogeneity parameter (τ), respectively. Bayesian confidence intervals for the pooled effect were constructed as 95% shortest credible intervals. Bayesian confidence intervals for τ were obtained in a similar way

Besides estimating τ, the heterogeneity was also assessed by computing the I^2 index and conducting significance tests based on the Q statistic.

Analyses were carried out making use of the following packages for R (R Core Team) [13]: *bayesmeta* [14] for the Bayesian meta-analysis itself, *forestplot* [15] for constructing the forest plots, and *metafor* [16] for computing the effect-size estimates.

For medication need (yes/no), we used risk ratios (RRs) that refers to the relative risk of a patient being treated with at least one medication.
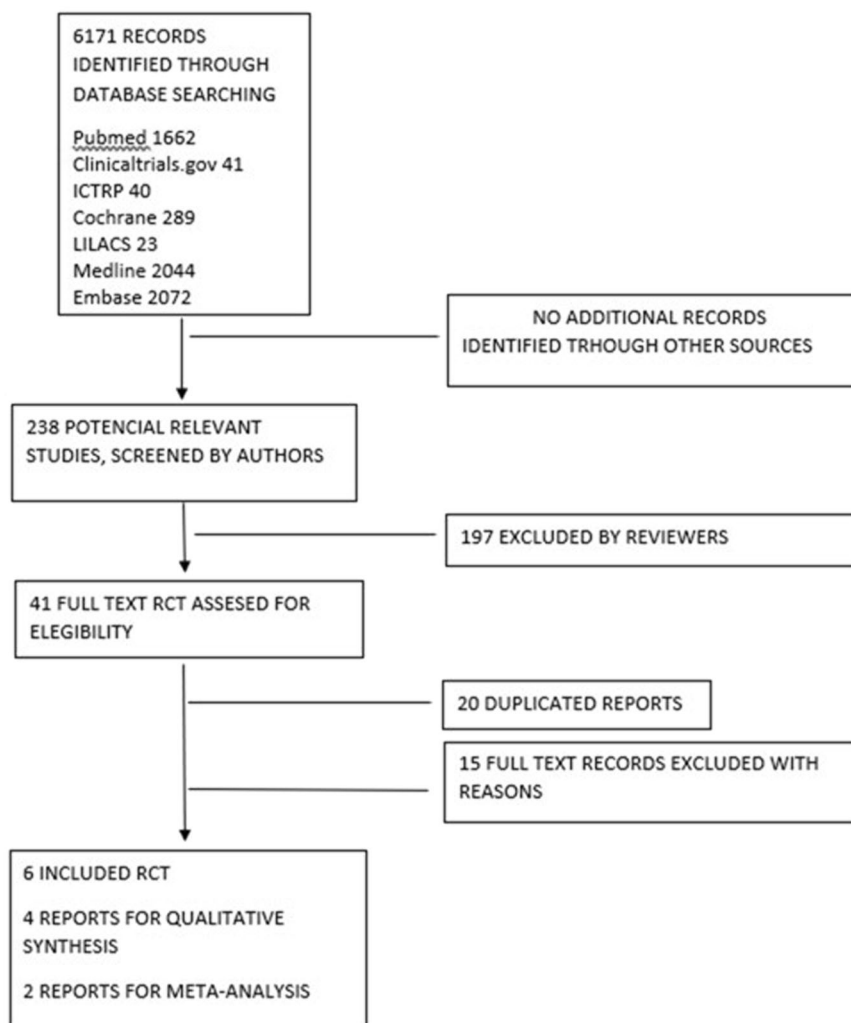
Results

The initial electronic search revealed 6171 references including articles and trial registry records. Two review authors independently screened the papers and 238 potentially relevant studies were identified and full copies were obtained. Of the 238 full-text reports reviewed, we identified 41 published RCT, and after removing 20 duplicate reports, we excluded other 15 studies [17–31] (Table 1). Finally, 6 RCT [32–37] met the inclusion criteria (Fig. 1). No additional records were identified when searching for other sources or results from records of ongoing or unpublished studies. Detailed description of each trial is presented in Supplementary material.

The trials randomized a total of 262 eyes of adult participants, with a sample size ranging from 25 to 76. Included trials were published between 1999 and 2015.

Table 1 Characteristics of excluded studies.

Study	Reason for exclusion
Ayala 2014 [17]	Participants: POAG and PXFG. There is no result subgroup for PXFG
Bergea 1994 [18]	Participants: POAG and PXFG. There is no result subgroup for PXFG
Carassa 2003 [19]	Participants: POAG and PXFG. There is no result subgroup for PXFG
Cillino 2004 [20]	Participants: POAG and PXFG. There is no result subgroup for PXFG
Cillino 2016 [21]	Participants: no PXFG patients
Chihara 2011 [22]	Allocation: Not a randomized trial
Fakharie 2016 [23]	Participants: POAG and PXFG. There is no result subgroup for PXFG
Gedde 2009 [24]	Participants: POAG and PXFG. There is no result subgroup for PXFG
Geffen 2017 [25]	Participants: POAG and PXFG. There is no result subgroup for PXFG
Hutnik 2018 [26]	Participants: POAG and PXFG. There is no result subgroup for PXFG
Jankowska-Szmul 2018 [27]	Participants: POAG and PXFG. There is no result subgroup for PXFG
Psilas 1989 [28]	Allocation: Not a randomized trial
Sanders 1999 [29]	Participants: POAG, PXFG and pigmentary glaucoma. There is no result subgroup for PXFG
Shingleton 1995 [30]	Allocation: Not a randomized trial
Vahedian 2017 [31]	Participants: POAG and PXFG. There is no result subgroup for PXFG

Fig. 1 Selection of studies.
Results from combining
searches for studies for inclusion
in this review.

Two studies enrolled POAG and PXFG patients [34–37] but results of PXFG were analyzed separately, while the other reports included only PXFG eyes. The studies were conducted in four countries: two in Greece [32, 37], two in Germany [33, 36], one in Turkey [34], and one in Canada [35]. Kent study [35] was a multicentre RCT, while the remaining trials were one-center trials.

The included studies compared a wide variety of interventions (see below). All trials had IOP as the primary outcome with a follow-up range from 6 to 30 months. Mean change in visual acuity, data about number of medications and complications was available (see below). No trial reported changes in VF, optic nerve progression or quality of life.

Risk of bias in included studies (Fig. 2)

Risk of bias for each individual trial is presented in Supplementary material. The overall risk of bias of the included RCTs is moderate to high. Five (83%) trials did not report the methods for random sequence generation and none of
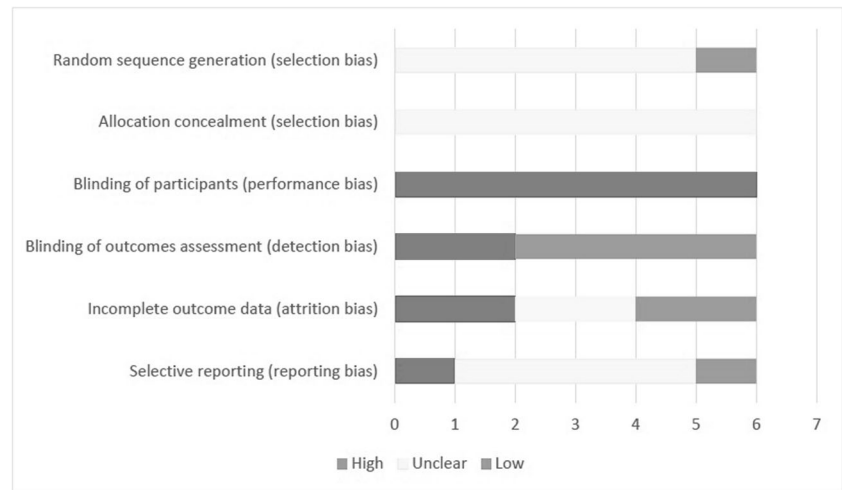
the trials reported on allocation concealment. No study has reported on masking of study participants. No trial protocol or register was available for four trials. Four out of six trials reported masking of outcome assessors for IOP. Sample size and power calculation were only performed in one of the studies [35]. No financial conflict of interests was reported in any trials.

The five GRADE domains (Methodological limitations of the studies, inconsistency of effect, imprecision, indirectness, and publication bias) were used to assess the quality of the evidence obtained from the included studies (concerns were rated as 'not serious', 'serious' or 'very serious'). Certainty of the evidence was rated as low and very low and is presented in Tables 2 and 3.

Effects of interventions

Two trials [32, 33] compared the same interventions and were able to meta-analyze the reported outcomes. In addition, we provide summary data for each other pair of surgical or laser comparisons.

Fig. 2 Risk of bias. Summary of author's judgements on each risk of bias item for each included study.

Table 2 Quality of evidence summary.

GRADE domain	Judgment	Concerns about certainty domains
Methodological limitations of the studies	All trials had a high risk of bias concerning the lack of ability to mask (blind) participants and personnel to the intervention received, and the ability to mask the assessor to the outcomes measured. Other sources of bias include limitations due to loss to follow-up, withdrawal of patients after randomization, and undescribed random sequence generation.	Serious
Indirectness	The participants, intervention and comparators used by the studies all provide direct evidence to the clinical question at hand.	Not serious
Imprecision	The total number of participants included in all the trials was 246 participants (262 eyes). Some outcomes were only measured by a single trial and followed participants to 12 months. Studies included in the meta-analysis showed wide confidence intervals.	Not serious, borderline
Inconsistency	Studies used evaluated different interventions and used different comparators. Studies included in the meta-analysis showed moderate heterogeneity I2 27.5%.	Serious
Likelihood of publication bias	No unpublished data was available for analysis. Of the published studies, no financial conflicts of interest were declared. Published studies did not exclusively show positive findings.	Not serious

Clear cornea phacoemulsification versus phacoemulsification with trabecular aspiration [32, 33]

These two trials included a total of 76 eyes of 76 participants. Seventy-five eyes contributed on the primary analysis of IOP data. The pooled mean difference of IOP between phacoemulsification (PHACO) and phacoemulsification with trabecular aspiration (PHACO + ASP) was estimated to be 0.56 mmHg (95% CI: −1.35 to 2.58) (Fig. 3). Heterogeneity was moderate ($I^2 = 27.5\%$).

The pooled relative risk of using post-operative topical medication of PHACO versus PHACO + ASP was estimated to be 1.39 (95% CI: 0.61–3.49). Heterogeneity was assessed as moderate ($I^2 = 22.8\%$) (Fig. 4).

The pooled standardized mean difference of visual acuity between PHACO and PHACO + ASP was estimated to be −0.12 Snellen lines (95% CI: −1.22 to 0.96), and between-study heterogeneity was only moderate ($I^2 = 23.0\%$) (Fig. 5).

The relative risk of the most frequent ocular adverse events were as follows: zonulolysis RR = 1.61 (0.10–19.00), descemetolysis RR = 0.16 (0.005–5.31), anterior synechiae formation RR = 0.46 (0.01–16.23), capsule opacification RR = 0.53 (0.15–1.77), and anterior chamber bleeding RR = 0.11 (0.003–4.35). Although complications appeared more frequently in the PHACO + ASP than in the PHACO group, the 95% CIs for the pooled relative risks shown in the forest plots of Figs. 6–10 must be interpreted in the sense that there was insufficient evidence to conclude an increased risk of complications associated with trabecular aspiration.

Table 3 GRADE evaluation for PXFG trials comparing surgical interventions.

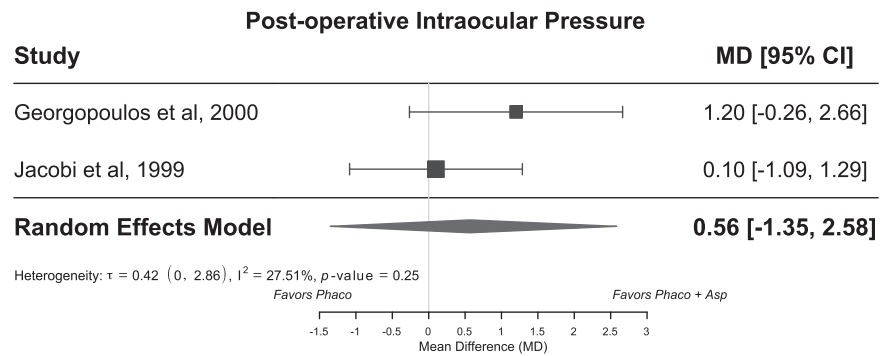| Outcome	Comparison (First author and year)	No of studies (participants)	RR (95% CI)	Methodological limitations	Consistency	Directness	Precision	Publication bias	Certainty of the evidence (GRADE) and score
Mean IOP (mmHg) 1 year after treatments	Phaco versus Phaco + trabecular aspiration (Georgopoulos 2000, Jacobi 1999)	2 (75)	RR 0.56 (−1.35 to 2.58)	−1[a]	−1[b]	0	0	0	Low (2)
	Phaco with trabecular aspiration versus phacotrabeculectomy (Jacobi 2000)	1 (40)	–	−1[a]	0	0	−1[c]	0	Low (2)
	NPDS with phacoemulsification versus NPDS alone (Bilgin 2014)	1 (25)	–	−1[a]	0	0	−1[c]	0	Low (2)
	SLT versus ALT (Kent 2015)	1 (76)	–	−1[a]	0	0	−1[c]	0	Low (2)
	One-site versus two-site phacotrabeculectomy (Bagli 2009)	1 (46)	–	−1[a]	0	0	−1[c]	0	Low (2)
Use of topical medication	Phaco versus Phaco + trabecular aspiration (Georgopoulos 2000, Jacobi 1999)	2 (75)	RR 1.39 (0.61–3.49)	−1[a]	−1[b]	0	0	0	Low (2)
Visual acuity after treatment	Phaco versus Phaco + trabecular aspiration (Georgopoulos 2000, Jacobi 1999)	2 (75)	RR −0.12 (−1.22 to 0.96)	−1[a]	−1[b]	0	−1[c]	0	Very low (1)
Adverse outcomes	Phaco versus Phaco + trabecular aspiration (Georgopoulos 2000, Jacobi 1999)	2 (75)	Zonulolysis RR 1.61 (0.10–19.00) Anterior synechiae formation RR 0.46 (0.01–16.23) Capsule opacification RR 0.53 (0.15–1.77) Descemetolysis RR 0.16 (0.005–5.31) Anterior chamber bleeding RR 0.11 (0.003–4.35)	−1[a]	−1[b]	0	−1[c]	0	Very low (1)

SCORE: Type of evidence RCT = 4 (4 = High; 3 = Moderate; 2 = Low; 1 = Very Low).
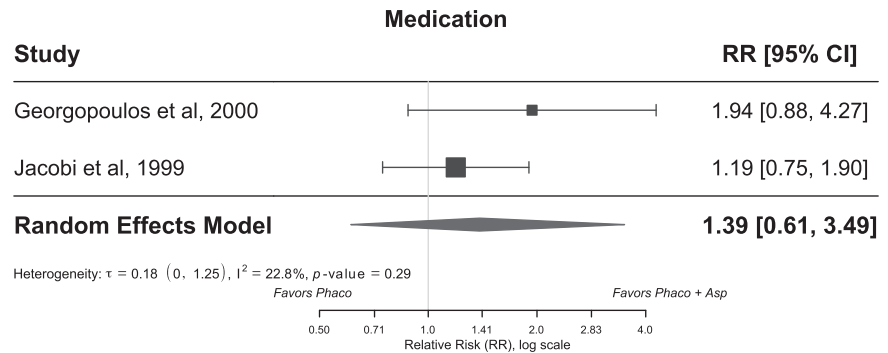
[a]Downgraded −1 due to high risk of bias.

[b]Downgraded −1 due to moderate heterogeneity.

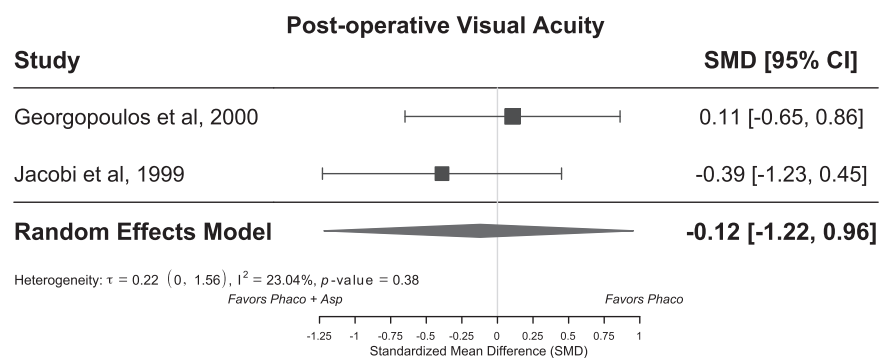[c]Downgraded −1 due to wide confidence intervals and small sample size.

Fig. 3 Primary outcome: Intraocular pressure. Forest plot of meta-analysis of studies comparing the effect of PHACO and PHACO + ASP on IOP. Values expressed in Mean Difference (MD).

Post-operative Intraocular Pressure

Study	MD [95% CI]
Georgopoulos et al, 2000	1.20 [-0.26, 2.66]
Jacobi et al, 1999	0.10 [-1.09, 1.29]
Random Effects Model	**0.56 [-1.35, 2.58]**

Heterogeneity: $\tau = 0.42$ $(0, 2.86)$, $I^2 = 27.51\%$, p-value $= 0.25$

Favors Phaco — Favors Phaco + Asp

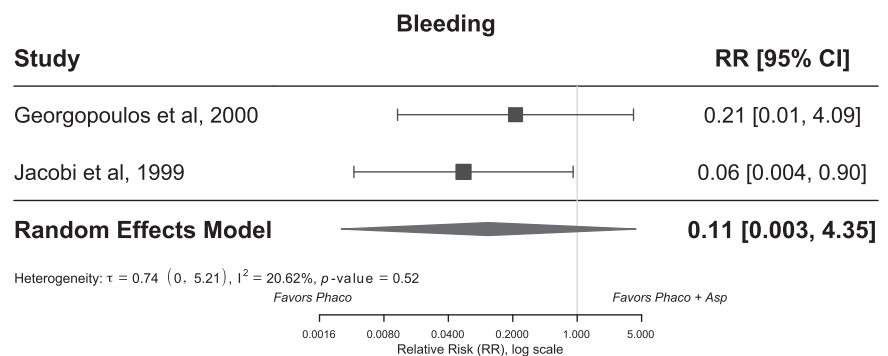-1.5 -1 -0.5 0 0.5 1 1.5 2 2.5 3
Mean Difference (MD)

Fig. 4 Secondary outcome: Medication. Forest plot of meta-analysis of studies comparing the effect of PHACO and PHACO + ASP on medication at 1 year after treatment. Values expressed in Relative Risk (RR).

Medication

Study	RR [95% CI]
Georgopoulos et al, 2000	1.94 [0.88, 4.27]
Jacobi et al, 1999	1.19 [0.75, 1.90]
Random Effects Model	**1.39 [0.61, 3.49]**

Heterogeneity: $\tau = 0.18$ $(0, 1.25)$, $I^2 = 22.8\%$, p-value $= 0.29$

Favors Phaco — Favors Phaco + Asp

0.50 0.71 1.0 1.41 2.0 2.83 4.0
Relative Risk (RR), log scale

Fig. 5 Secondary outcome: Visual Acuity. Forest plot of meta-analysis of studies comparing the effect of PHACO and PHACO + ASP on BCVA at 1 year after treatment. Values expressed in Standardized Mean Difference (SMD).

Post-operative Visual Acuity

Study	SMD [95% CI]
Georgopoulos et al, 2000	0.11 [-0.65, 0.86]
Jacobi et al, 1999	-0.39 [-1.23, 0.45]
Random Effects Model	**-0.12 [-1.22, 0.96]**

Heterogeneity: $\tau = 0.22$ $(0, 1.56)$, $I^2 = 23.04\%$, p-value $= 0.38$

Favors Phaco + Asp — Favors Phaco

-1.25 -1 -0.75 -0.5 -0.25 0 0.25 0.5 0.75 1
Standardized Mean Difference (SMD)

Fig. 6 Secondary outcome: Bleeding. Forest plot of meta-analysis of studies comparing the effect of PHACO and PHACO + ASP on twelve months post-operative complications: Bleeding. Values expressed in Relative Risk (RR).
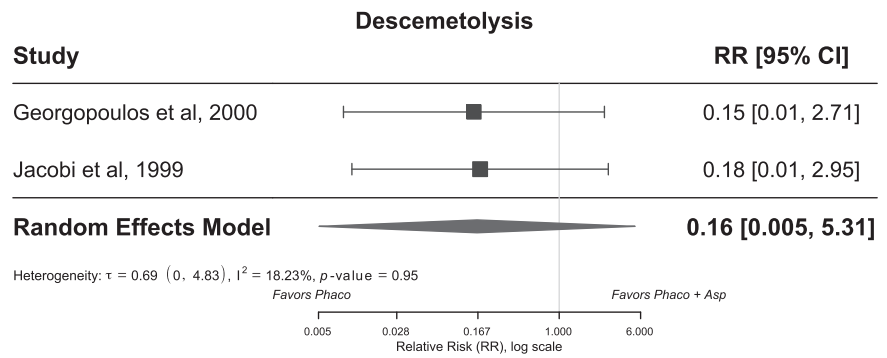
Bleeding

Study	RR [95% CI]
Georgopoulos et al, 2000	0.21 [0.01, 4.09]
Jacobi et al, 1999	0.06 [0.004, 0.90]
Random Effects Model	**0.11 [0.003, 4.35]**

Heterogeneity: $\tau = 0.74$ $(0, 5.21)$, $I^2 = 20.62\%$, p-value $= 0.52$

Favors Phaco — Favors Phaco + Asp

0.0016 0.0080 0.0400 0.2000 1.000 5.000
Relative Risk (RR), log scale

Phacoemulsification with trabecular aspiration versus phacotrabeculectomy [36]

The trial consisted in 40 PXFG patients who were randomized to either adjunctive trabecular aspiration (PHACO + ASP group, 20 eyes) or adjunctive trabeculectomy without the use of antimetabolites (PHACO-TRAB group, 20 eyes).
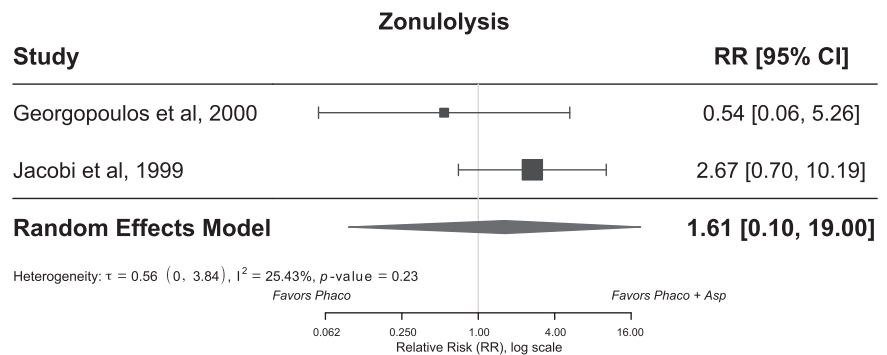
At 1 year the difference in mean IOP was not statistically significant (mean IOP was 19.5 ± 2.7 in the phaco-aspiration group and 17.5 ± 2.4 mmHg in the phaco-trab group. $p = 0.12$). However, mean number of glaucoma
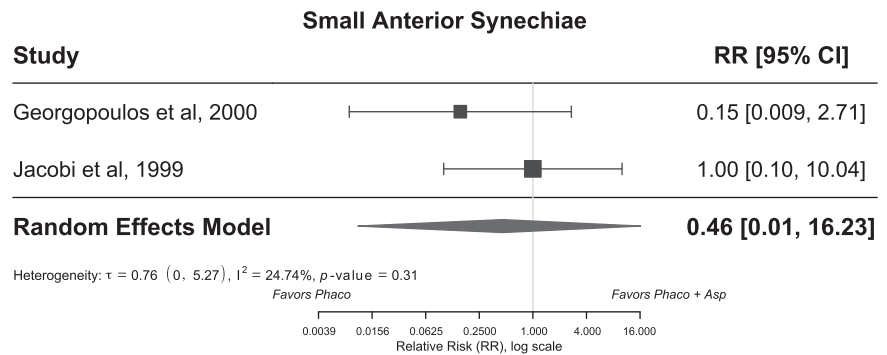
Fig. 7 Secondary outcome: Descemetolysis. Forest plot of meta-analysis of studies comparing the effect of PHACO and PHACO + ASP on twelve months post-operative complications: Descemetolysis. Values expressed in Relative Risk (RR).

Descemetolysis

Study	RR [95% CI]
Georgopoulos et al, 2000	0.15 [0.01, 2.71]
Jacobi et al, 1999	0.18 [0.01, 2.95]
Random Effects Model	**0.16 [0.005, 5.31]**

Heterogeneity: $\tau = 0.69$ $(0, 4.83)$, $I^2 = 18.23\%$, p-value $= 0.95$

Favors Phaco   Favors Phaco + Asp

0.005   0.028   0.167   1.000   6.000
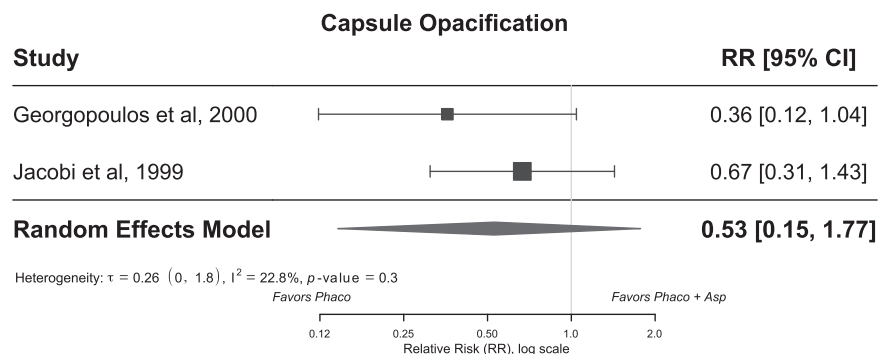Relative Risk (RR), log scale

Fig. 8 Secondary outcome: Zonulolysis. Forest plot of meta-analysis of studies comparing the effect of PHACO and PHACO + ASP on twelve months post-operative complications: Zonulolysis. Values expressed in Relative Risk (RR).

Zonulolysis

Study	RR [95% CI]
Georgopoulos et al, 2000	0.54 [0.06, 5.26]
Jacobi et al, 1999	2.67 [0.70, 10.19]
Random Effects Model	**1.61 [0.10, 19.00]**

Heterogeneity: $\tau = 0.56$ $(0, 3.84)$, $I^2 = 25.43\%$, p-value $= 0.23$

Favors Phaco   Favors Phaco + Asp

0.062   0.250   1.00   4.000   16.00
Relative Risk (RR), log scale

Fig. 9 Secondary outcome: Small anterior synechiae formation. Forest plot of meta-analysis of studies comparing the effect of PHACO and PHACO + ASP on twelve months post-operative complications: Small anterior synechiae formation. Values expressed in Relative Risk (RR).

Small Anterior Synechiae

Study	RR [95% CI]
Georgopoulos et al, 2000	0.15 [0.009, 2.71]
Jacobi et al, 1999	1.00 [0.10, 10.04]
Random Effects Model	**0.46 [0.01, 16.23]**

Heterogeneity: $\tau = 0.76$ $(0, 5.27)$, $I^2 = 24.74\%$, p-value $= 0.31$

Favors Phaco   Favors Phaco + Asp

0.0039   0.0156   0.0625   0.2500   1.000   4.000   16.000
Relative Risk (RR), log scale

Fig. 10 Secondary outcome: Capsule opacification. Forest plot of meta-analysis of studies comparing the effect of PHACO and PHACO + ASP on twelve months post-operative complications: Capsule opacification. Values expressed in Relative Risk (RR).

Capsule Opacification

Study	RR [95% CI]
Georgopoulos et al, 2000	0.36 [0.12, 1.04]
Jacobi et al, 1999	0.67 [0.31, 1.43]
Random Effects Model	**0.53 [0.15, 1.77]**

Heterogeneity: $\tau = 0.26$ $(0, 1.8)$, $I^2 = 22.8\%$, p-value $= 0.3$

Favors Phaco   Favors Phaco + Asp

0.12   0.25   0.50   1.0   2.0
Relative Risk (RR), log scale

medications was significantly lower in the PHACO-TRAB (decreased from 2.1 ± 1.1 to 0.3 ± 0.4) than in the PHACO + ASP group (dropped from 2.0 ± 0.9 to 0.6 ± 0.5) at 1 year after surgery ($p = 0.02$). The post-operative BCVA did not vary significantly between the treatment groups. Adverse effects associated with trabeculectomy such as hyphema, fibrinous reaction, anterior synechia formation, and ocular hypotony were more common in the PHACO-TRAB group.

Non-penetrating deep sclerectomy with phacoemulsification versus non-penetrating deep sclerectomy alone [34]

A total 52 eyes of 49 participants with POAG and PXFG were enrolled. Twenty-six eyes in the non-penetrating deep sclerectomy (NPDS) group of which 11 patients were classified as PXFG; and 26 eyes in the NPDS combined with phacoemulsification group (phaco-NPDS), of which 14 patients were classified as PXFG. The subgroup with PXFG was included.

There was no statistically significant difference in IOP between the two interventions at the end of the follow-up period (mean post-operative IOP in NPDS group 14.7 ± 0.4 and mean post-operative IOP in phaco-NPDS group $13.6 \pm 0.$ $p > 0.05$). BCVA was statistically better in phaco-NPDS patients, increasing from 0.16 ± 0.13 to 0.43 ± 0.3 and from 0.14 ± 0.24 to 0.27 ± 0.16 in the phaco-NPDS and NPDS groups, respectively ($p = 0.02$). Two complications were reported in the phaco-NPDS group (posterior capsule rapture and anterior capsule contraction), but the paper did not state whether they were on PXFG or POAG patients.

Selective laser trabeculoplasty versus argon laser trabeculoplasty [35]

The study enrolled 76 eyes from 60 PXF participants. Eyes were studied as independent variables although both eyes of the same patient were analyzed without any statistical adjustment. No paired method was used that could correct this bias. Forty five eyes received Selective Laser Trabeculoplasty (SLT) and 31 eyes received Argon Laser Trabeculoplasty (ALT). A total of 63 eyes completed 6 months of follow-up.

Differences in IOP were not statistically significant (mean IOP at 6 months of follow-up in ALT group was 18.2 ± 4.77 and 16.2 ± 4.77 in SLT group. $p = 0.12$). There was no statistically significant difference in the number of medications and adverse events. The trial did not report visual acuity outcomes.

One-site versus two-site phacotrabeculectomy [37]

Initially 100 patients were included in this RCT, 50 POAG eyes and 50 PXG eyes but patients with rupture of the posterior capsule were excluded. Finally, 46 patients in the PXG group were included in this review, 23 participants in the one-site group and 23 participants in the two-site group.

There were no statistically significant differences between the one- and two-site phacotrabeculectomy groups in terms of IOP (15 ± 1.8 mmHg in the one-site, 15.32 ± 1.31 mmHg in the two-site group. $p = 0.902$), number of antiglaucomatous drugs, nor in visual acuity after 36 months. One patient from each subgroup had a repeated trabeculectomy for uncontrolled IOP.

Discussion

Despite a systematic literature search about interventions in PXFG, only six relatively small RCTs were available to inform clinical decision-making. Most published studies involving several types of glaucoma patients did not provide separate results for this subgroup.

Available data on RCT in PXFG population are too scarce so, in future, we will need more research investigation to help us understand its optimal management

We could meta-analyse data from two trials. There was no evidence for any benefit of combined trabecular aspiration and phacoemulsification compared with phacoemulsification alone regarding IOP, visual acuity and number of post-operative medications. Few adverse effects were reported, but appeared more common in the trabecular aspiration arm. Regarding trials that were not meta-analyzed, there were no differences between interventions in terms of IOP, BVCA and number of post-surgical medications.

Methodological flaws were observed in all the six trials. Only one study [37] specified the random sequence generation but none reported allocation concealment. Two trials did not report any masking of investigators and four trials were not registered and had no published protocol. None of the six studies presented masked participants. Exclusions after randomization in Bagli study [37] also lead to high risk of bias.

Different types of approaches have been described for PXFG including laser procedures as well as surgical techniques. Insufficient information on comparative effectiveness is available at the present to help inform clinicians and patients. Studies are mostly retrospective, and the few clinical trials found have small sample size with large uncertainty in results, and relatively short follow-up. Given that the PXFG presents a different pathogenesis than POAG, but above all a more aggressive evolution, it would be necessary to know which treatments are more effective and safer when focusing on the management of this entity. This systematic review highlights the need for further research.

We found no other published systematic reviews on PXF glaucoma.

None of the studies reviewed included data on disease progression or quality of life.

In conclusion, this systematic review found several trials comparing laser and surgical interventions used for PXFG. However, there is still insufficient evidence to determine whether any particular surgical or laser technique is superior

to another. Small sample size and high risk of bias were common among the included RCT. Large and well-designed RCT are needed in PXFG.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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