Review Article

Clinical implication of recent randomized control trial in primary angle-closure disease management

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Blindness due to primary angle-closure glaucoma (PACG) can be reduced significantly if the ongoing angle-closure process is arrested at an early stage. Various treatments such as laser peripheral iridotomy (LPI), iridoplasty, and clear lens extraction (CLE) have been advocated as first-line therapy for primary angle-closure (PAC), PACG, and high-risk cases of primary angle-closure suspect (PACS). EAGLE study, propagated the effectiveness of CLE over LPI for the management of primary angle closure and have sparked controversy regarding the role of LPI as a first line procedure. Randomized controlled trials (RCT), systematic reviews, and meta-analyses of RCTs done on the same question provide us with a solid base for creating guidelines/modules for our day-to-day clinical practice. A systematic review was conducted, searching several databases, including PubMed, Cochrane Library, EMBASE, and ClinicalTrials.gov, for the last 16 years (January 2005–December 2021) for RCTs with data published related to primary angle-closure disease (PACD). The search strategy included the following terms: "Primary Angle Closure disease," "Primary Angle Closure Glaucoma," "Primary Angle Closure," "Primary Angle Closure Suspect," "clear lens extraction," "laser iridotomy," "laser peripheral iridotomy," "argon laser peripheral iridoplasty," "selective laser trabeculoplasty," "trabeculectomy," "randomized control trial," and "meta-analysis of randomized control trial." In this review, we will discuss recently published RCTs (within the last 16 years) for the management of PACD and their clinical implications in day-to-day practice.

Key words: Acute angle closure, clear lens extraction, laser iridotomy, primary angle-closure disease (PACD), randomized control trial

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Blindness due to primary angle-closure glaucoma (PACG) is nearly 2.5 times more than that due to primary open-angle disease (POAG). However, it can be reduced if the ongoing angle-closure process is arrested at an early stage.[1] Various treatments such as laser peripheral iridotomy (LPI) and iridoplasty have been advocated as first-line therapy for primary angle closure (PAC), PACG, and high-risk cases of primary angle-closure suspect (PACS).[1] Recently, the randomized control trial (RCT) known as Effectiveness in Angle-Closure Glaucoma of Lens Extraction (EAGLE) study propagated the effectiveness of clear lens extraction (CLE) over LPI for the management of PACD and sparked controversy regarding the role of LPI as a first-line procedure.[2] Several other studies have also demonstrated the effectiveness of clear lens extraction, even in acute angle-closure glaucoma.[3-5] As CLE improves the visual outcome and thereby the quality of life of a patient, it is becoming a reasonable choice for surgeons as well. However, a dilemma arises whether to choose between LPI, a safe, cost-effective, and non-invasive out-patient department (OPD) procedure, versus CLE, which is costly, carries an inherent risk of surgery, and has a steep learning curve.

Randomized controlled trials, systematic reviews, and meta-analyses of RCTs done on the same question provide us with a solid base for creating guidelines/modules for our day-to-day clinical practice.[6,7] In this review, we will discuss recently (last 16 years) published RCTs for the management of PACD and their clinical implications in day-to-day practice. Independent systemic literature search was conducted by two authors in PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov for the last 16 years (January 2005–December 2021). The search strategy included the following terms: "Primary Angle Closure disease," "Primary Angle Closure Glaucoma," "Primary Angle Closure," Primary Angle Closure Suspect," "clear lens extraction," "laser iridotomy," "laser peripheral iridotomy," "argon laser peripheral iridoplasty," "selective laser trabeculoplasty," "trabeculectomy," "randomized control trial," and "meta-analysis of randomized control trial."

Table 1a and b show an outline of all RCTs related to PACD published in the last 16 years. The figure shows details of authors' names, study aim, primary endpoint, number of subjects enrolled with follow-up duration, and important study results.

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Table 1a: Shows details of authors names, study aim, primary endpoint, number of subjects enrolled with follow up duration

Authors	Diagnosis	Study objective	Primary endpoints	Average follow-up (months)	No. of patients/eyes
Lam *et al*.[29]	Acute PAC	Compare primary phacoemulsification/IOL versus LPI in the prevention of IOP rise in patients soon after APACs were aborted	IOP reduction, Degree of PAS formation visual acuity, VCDR, MD and PSD on the visual field	18	31 31
Hussain *et al*.[30]	Acute PAC	Compare primary phacoemulsification/IOL versus LPI in the prevention of IOP rise in patients soon after APACs were aborted	IOP reduction, Degree of PAS formation visual acuity, VCDR, MD and PSD on the visual field	24	19 18
ZAP Trial[8-10]	PACS	To assess the efficacy and safety of LPI in preventing the development of PAC as well as acute AAC in eyes with PACS	conversion of PACS to PAC	72	889 eyes 889 eyes
ANA-LIS Trial[17]	PACS	To assess the efficacy and safety of LPI in preventing the development	conversion of PACS to PAC	60	476 eyes 476 eyes
Cai *et al*.[21]	Acute PAC	assess the IOP reduction after ALPI between systemic medical therapy in patients with APAC	IOPR, IOPR% from baseline to the endpoint and PAS formation	12	51 eyes in 4 RCT 55 eyes in 4 RCT
Narayanswamy *et al*.[23]	Chronic PACG	To assess the IOP lowering efficacy of SLT versus Travoprost (0.004%) in eyes with PAC and PACG with patent LPI and oat least 180 degrees open	IOP ≤21 mmHg with/ without medication /Without medication	6	50 50
Narayanswamy *et al*.[18]	Chronic PACG	of PAC as well as acute AAC in eyes with PACS PAC & PACG with patent LPI and at least 180-degree appositional closure	IOP ≤21 mmHg with/ without medication /Without medication	6	92 91
Li *et al*.[25]	PACG	Assess the efficacy and safety of latanoprost compared with other glaucoma medications in the treatment of PACG	absolute changes in IOP incidence of ocular adverse events	minimum 3 month	1096 patients from 10 RCT
Cheng JW *et al*.[26]	PACG	Assess IOP lowering efficacy of PG Analogues in patients with PACG	absolute and relative reduction in IOP from baseline,	minimum 3 month	1090 from 9 RCT
EAGLE Trial[2,33,34]	PAC with clear lens	assess the efficacy, safety, and cost-effectiveness of clear lens extraction versus LPI for the first-line treatment of PACG and PAC	patient-reported health status, IOPR, incremental cost-effectiveness ratio	36	208 211
Deng BL *et al*.[40]	PACG	efficacy and safety of trabeculectomy, phacotrab+IOL group and phaco-IOL PACG	IOP Reduction, Surgical complications	not mentioned	1495 EYES from5 RCT and 11 CCT
Wang F *et al*.[38]	PACG with coexisting cataract	compared the efficacy and safety of Phaco against Phacotrab in PACG with coexisting cataract	IOP Reduction, WMD OF IOP REDUCTION Surgical complications	2-13.2	468 patient from 5 RCT

Role of Laser Iridotomy in PACS

ZAP trial

Randomly chosen eyes of 889 patients received LPI, while the fellow eyes of all these patients served as a control. The primary outcome was the incidence of PAC at 72 months based on either (I) raised IOP (>24 mm Hg on two occasions); (II) PAS ≥ 1 clock hour; or (III) an episode of acute angle-closure (AAC).[8-10]

The primary endpoint occurred in 19 eyes (4.19 per 1,000 eyes/year) in LPI-treated eyes versus 36 eyes (7.97/1,000 eyes per year) in control eyes. The authors reported 47% reduction in the rate of development of primary outcome (hazard ratio: 0.53) in the LPI group compared to the control group and increased probability of primary outcome with age and shallower AC depth (limbal and central). They could not find any correlation with high IOP, narrow angles according

Table 1b: Shows details of authors names, mode of intervention, and important study results

Authors	Mode of intervention	Results	IOP Reduction (mmHg)	Comments
Lam *et al.*[29]	Phaco-IOL	↑IOP 1/30* (3.3)	59.7±8.71 to 12.6±1.9	High presenting IOP of>55 mmHg is an added risk factor for subsequent IOP rise
	LPI	↑IOP 14/30* (46.7)	57.9±11.8 to 15.0±3.4	4 (12.9%) repeat LPI
Hussain *et al.*[30]	Phaco-IOL	2 (10.5%) treatment failure, 4 (21.1%) control by medication	57.4±16.9 to 15.4±7.7	1 (5.3%) patient had re-surgery on day one
	LPI	7 (38.9%) treatment failure, 2 (11.1%) control by medication	55.8±13.2 to 13.7±6.1	6 (33.3%) patients had Cataract surgery, 1 (5.6%) repeated LPI
ZAP Trial[8-10]	LPI	19 eyes converted to PAC (4.19/1,000 eyes/year)		10% in LPI group complained of glare
	Observation	36 eyes converted to PAC (7.97/1,000 eyes/year)		49% with patent LPI had occludable angle after 2 weeks of LPI
ANA-LIS Trial[17]	LPI	23 eyes converted to PAC (4.8/1000/year)		Older subjects and eyes with higher baseline IOP were more likely to reach an endpoint
	Observation	46 eyes converted to PAC (9.8/1000/year)		
Cai *et al.*[21]	ALPI	WMDs of the IOPR% 12.91 at 2 hours in favour of ALPI		ALPI was more effective in lowering the IOP within the first two hours
Narayanswamy *et al.*[23]	SLT	60.0% eyes had complete success	4.0 (95% CI, 3.2-4.8)	Additional medications were required in 22.0% of patients
	Medical Rx (travoprost)	84.0% eyes had complete success	4.2 (95% CI, 3.5-4.9)	Additional medications were required in 8.0% OF patients
Narayanswamy *et al.*[18]	ALPI	35.0% eyes had complete success	4.9 (95% CI, 3.5–6.3)	30% failure rate
	Medical Rx (travoprost)	85% complete success	6.1 (95% CI, 5.1–7.1)	7.5% failure rate
Li *et al.*[25]	systemic medical therapy Various RCT involving medication	latanoprost was superior to Timolol but higher hyeremia latanoprost was marginally inferior to travoprost and bimatoprost but lowert hyperemia		Travoprost and bimatoprost are superior in IOP control than latanoprost, Latanoprost is better tolerated in patients with PACG
Cheng JW *et al.*[26]	Various RCT involving medication	Bimatoprost and Tavoporst had beeter IOP control than Latonoprost		Travoprost and bimatoprost are superior in IOP control than latanoprost,
EAGLE Trial [2,33,34]	Clear Lens Extraction	mean health status score (0·87), mean IOP (16·6 [SD 3·5] mm Hg)		CLE group had better health status score, lower mean IOP
	LPI	mean health status score (0·818), mean IOP (16·78 [SD 3·5] mm Hg)		
Deng BL *et al.*[40]	Trab vs Phaco-Trab vs phaco	phacotrab + IOL group was superior to Trabeculectomy group which was superior than phaco + IOL group in decreasing IOP.		BCVA was similar in all three group, number of Post-operative glaucoma medication was least in phaco-IOL-trab group
Wang F *et al.*[38]	Phaco Phaco-Trab	Lower no of post-operative glaucoma medication but higher risk of complication	WMD OF IOPR 1.37 mm Hg	higher risk of complications [odds ratio (OR)=0.04, compared with Phaco

to Shaffer grading, lens thickness, provocative tests, and gender.[9]

At 72 months follow-up, no significant adverse events were observed in the LPI group; 10% of the patients reported glare which was unrelated to the site of the iridotomy. Two weeks after LPI, angles remained closed in nearly 49% of patients which corroborated in the ANA-LIS trial.[11] ZAP trial also confirmed the current practice of placement of superior LPI locations to optimize anatomic changes after LPI.[12]

Author's conclusion

LPI had a modest, albeit significant, prophylactic effect in preventing the progression of PACS to PAC. However, in view

of the low incidence rate of conversion and no immediate threat to vision, the benefit of prophylactic LPI in PACS is limited and hence not recommended.

Our remarks

The reported rate of progression of 4% (36/889) from PACS to PAC at the end of 6 years follow-up in the control group is much less compared to 22% reported in the Vellore eye survey over 5 years without LPI and 12.4% despite patent LPI in the Chennai glaucoma study.[13,14] Under-estimation of progression in the ZAP trial may have been due to the lenient definition used for progression compared to that in the Vellore eye survey and Chennai glaucoma study. ZAP trial defined progression if either IOP was more than 24 mm Hg or there was development of minimum 1-clock hour (30°) of synechiae, while the Vellore eye survey and the Chennai glaucoma study reported progression even if one-point synechia developed in the angle.[13,14] The authors also excluded patients with positive dark room provocative tests and patients having post dilated IOP spike of more than 15 mm Hg; these subsets of patients were at high risk of progressing to PAC. Further, the IOP was measured with NCT during enrollment and follow-up, and IOP measurements were confirmed with applanation only if IOP was greater than 24 mm Hg, thereby potentially missing cases in which IOP was erroneously measured below 24 mm Hg on NCT.[15,16] Additionally, information on post-mid dilated gonioscopic changes would have helped to identify a high-risk group that could benefit from early LPI.

The number of needed to treat (NNT) for primary outcome (development of PAC/PACG) is 52.4. It means we need to treat at least 52 PACS eyes with LPI to prevent one eye from progressing to PAC. The exclusion of patients based on positive provocative tests was one of the limitations. Taking this into consideration, we calculated NNT for the hypothetical worst-case scenario (i.e., considering that all high-risk patients who were excluded in the ZAP trial would have progressed). If calculated for high-risk groups (subset of patients excluded from the study), NNT is again 52 as ZAP data shows that only one patient out of a total of 11,911 screened patients had an IOP rise of 16 mm Hg and was excluded. This again reiterates the fact that all PACS patients do not require LPI.

Our Recommendations

In view of the lower rate of conversion (4% over 6 years) and no potential threat to loss of vision, we recommend continuing the current practice of observation in PACS patients and to consider LPI only in high-risk groups.

ANA-LIS Trial

In a multi-centric, prospective, randomized controlled trial, 476 subjects over the age of 50 years were diagnosed as bilateral asymptomatic primary angle-closure suspects (PACS), with ≥2 quadrants of appositional angle closure on gonioscopy.[17] Each subject underwent prophylactic LPI in one randomly selected eye, while the fellow eye served as control. Subjects were followed up yearly for 5 years. The primary outcome measure was development of PAC (defined as the presence of peripheral anterior synechiae, and/or intraocular pressure >21 mm Hg or acute angle-closure [AAC]) or PACG over 5 years. At 5-year follow-up, the progression was significantly higher in the non-LPI eyes (46 [9.8%, 95%CI: 7.2–12.7] vs. 23 [4.8%, 95%CI: 3.1–7.2] LPI eyes, $P < 0.0001$). Older subjects (per year, HR = 1.06, 95%CI: 1.03–1.10, $P < 0.001$) and eyes with higher baseline IOP (per mm Hg, HR = 1.35, 95%CI: 1.22–1.50, $P < 0.0001$) were more likely to reach an endpoint. The NNT for preventing an endpoint was 22 (95%CI: 12.8–57.5).

Author's conclusion

LPI had a prophylactic effect in preventing the progression of PACS to PAC. However, in view of the low incidence rate of conversion and no immediate threat to vision, the benefit of prophylactic LPI is limited, and widespread prophylactic LPI for PACS is not recommended. The authors also concluded that their data supports ZAP trial findings.

Our remarks

In the ANA-LIS trial, the higher incidence of PAC and lower NNT (22) in the non-LPI group compared to the ZAP trial could be due to a difference in the definition used for PAC. In ANA-LIS, PAC was defined as the presence of more than half-clock hour of PAS formation compared to 1 clock hour in the ZAP trial. Even then the NNT in ANA-LIS is 22, which means that to prevent one eye from progressing to PAC over a period of 5 years, we need to treat at least 22 PACS eyes with LPI. Now the question arises as to whether 22 is a good NNT for PACS. Generally, 20 would be considered a good NNT for interventions with serious outcomes such as blindness or a very high probability of blindness. However, in PACS eyes, by doing LPI, we are only preventing progression to PAC (not blindness); these eyes can be easily followed-up and LPI can be reserved for a later date if the patient progresses to PAC.

NNT allows us to look for subgroups where the absolute risk is higher (and the NNT lower); therefore, costs of treatment (and its justification) are more acceptable. According to the ANA-LIS trial, we might want to treat those with a high IOP and old age group as the risk of progression is 30% higher and the effective NNT is lower.

Our Recommendations

Based on ANA-LIS, we recommend continuing the current standard practice of observation of PACS patients and consider LPI only for high-risk groups. The ANA-LIS trial identified older age and high baseline IOP as risk factors for progression (conversion to PAC).

Considering earlier publications, the results of the ZAP and ANA-LIS trials reinforce our current practice of observation in most PACS patients.

RCT on argon laser peripheral iridoplasty (ALPI) in PACD

Narayanaswamy *et al.*[18] compared ALPI with medical management in patients with patent iridotomy. They defined complete success as an IOP of 21 mm Hg or less without medication, and qualified success as an IOP of 21 mm Hg or less with medication. Failure was defined as an IOP of more than 21 mm Hg despite additional medications or an eye requiring glaucoma surgery. In the ALPI group, 35% and 70% achieved complete and qualified success, respectively; this was 85% and 92.5%, respectively, for the prostaglandin analog (PGA) group. The IOP decreased by 4.9 mm Hg in the ALPI group and by 6.1 mm Hg in the medication group. They reported a higher failure rate and lower IOP reduction in the ALPI group than PGA therapy in eyes with persistent appositional angle closure at the end of 1 year. The mean angle width increased significantly (1.6 vs. 2.0)

but PAS progressed from 1.7 to 2.6 clock hours from baseline to 1 year in the ALPI group compared to the PGA group.

Author's conclusion

The authors concluded that persistent appositional angle closure and raised IOP after LPI responds poorly to ALPI compared to PG analog. It also carries the risk of immediate pigment dispersion and a long-term increase in PAS formation.

Our remarks

This well-designed RCT showed better IOP control with PGA compared to ALPI, which is in concordance with previously randomized and non-randomized publications.[19,20] Increased incidence of PAS in the ALPI group can be attributed to the scarring of the iridocorneal angle secondary to argon laser. However, one of the most significant limitations of the study is its short duration. Additional long-term data on pre- and post-iridoplasty angle measurement, changes in angle width, and PAS progression would give better insight into ALPI's effects on the angle. A recently published Cochrane review also suggests that ALPI as an intervention may not be more effective than comparators in the management of chronic PAC/PAC despite a potential positive impact on anterior chamber morphology.[19]

Our Recommendations

As suggested by the authors and Cochrane review, we do not recommend ALPI in patients with persistent appositional angle closure and raised IOP.

Role of ALPI in Acute PAC

Four prospective, randomized, controlled trials were eligible for meta-analysis where patients presenting with acute PAC and high IOP were randomized into ALPI or standard medical treatment.[21] The acute PACG eye of both groups continued to receive topical pilocarpine (1%) until peripheral iridotomy could be performed. The authors compared the difference in IOP reduction between two groups for various time intervals. The baseline IOP, the IOP at 2 h, and the final IOP were 39.5, 26.4, and 18.3 mm Hg in the ALPI group, and 39.3, 32.5, and 20.1 mm Hg in the standard care group. The IOPR% (% IOP reduction) was significantly higher (30% at 15 min to 12.9% at 2 h) for the first 2 h in favor of the ALPI group; however, there was no statistically significant difference between the two groups in IOP reduction at 24 h and subsequent visit (up to 6 months) after therapy. The duration of attack had no impact on IOP reduction. In comparison, no significant difference in the degree of PAS, CDR, mean endothelial count, and percent of patients requiring topical glaucoma medication after treatment was noted. The authors concluded that both ALPI and systemic medications were equally effective to decrease the IOP but favored ALPI in lowering the IOP within the first 2 h. ALPI may be a better choice for rapidly lowering the IOP in patients with APAC within a short period.

Author's conclusion

The authors concluded that ALPI may be a better choice for rapidly lowering the IOP in patients with APAC within a short period.

Our remarks

Retrospective long-term follow-up data (33 ± 9 months) indicated that 30% of Chinese eyes with acute treatment with immediate ALPI followed by LPI developed less PAS and had IOP <21 mm Hg without medications. Also, there were minimal long-term complications on the cornea and the lens from the laser treatment.[22] From an Indian perspective, acute PAC is relatively uncommon, and if the option of iridoplasty is available, it can be considered in acute PAC, especially if the anterior chamber is too shallow to perform a laser iridotomy.

Our recommendation

As there is no significant long-term benefit of ALPI in acute PAC and considering the technical challenges in doing ALPI in acute attack with risk of corneal burn, we recommend ALPI in acute PAC only if LPI is not possible due to extremely shallow AC and the surgeon has enough experience of handling acute PAC patients with ALPI.

Role of SLT in PACG

Narayanaswamy *et al*.[23] randomized patients with a baseline IOP of >21 mm Hg to either SLT or PG analog (Travoprost, 0.004%). At 6months, there was no difference in the absolute mean reduction of IOP (4.0 vs. 4.2 mm Hg) or the IOPR% (16.9% vs. 18.5%) between the SLT and PGA groups. Complete success (IOP <21 mm Hg without medications) was achieved in 60.0% of the eyes in the SLT group compared with 84.0% of eyes in the PGA group. Additional medications were required in 22.0% of patients in the SLT group compared to 8.0% in the PGA group. The mean endothelial cell count showed a significant decrease from baseline in the SLT arm (4.8%). Eyes with PAC or PACG respond to SLT in the short term, but the overall long-term therapeutic effectiveness needs further evaluation.

One of the most significant limitations of the study is its short duration of only 6 months. Kurysheva, in a prospective cohort study, reported a 3.8-mm Hg IOP reduction and a decrease in the number of medications (1.19 pre-SLT vs. 0.48 post-SLT) at the end of 6 years.[24] They also reported the need for repeat SLT in nearly 35% of patients.

Author's conclusion

The authors concluded that patients with patent LPI and increased IOP show short-term response to SLT. They also concluded that SLT failed to show beneficial effects compared to PG analog.

Our remarks

In PACG, if laser PI is patent and IOP is borderline high, SLT can be considered. One needs to remember that like POAG, SLT has a limited role in controlling IOP that too only in the early stage of PACG. The decrease in the corneal endothelial count after SLT needs to be kept in mind.

Our Recommendations

As IOP reduction is minimal, we do not recommend SLT as a first-line option; however, in a situation where most ocular hypotensive medications are contra-indicated, SLT may be considered.

RCT on Medical Management

Li *et al*.[25] showed that the IOP reduction efficacy of latanoprost was slightly superior to that of timolol and marginally inferior to that of travoprost and bimatoprost. Incidence of conjunctival hyperemia was more in the latanoprost group compared to

timolol but lesser than that in the travoprost and bimatoprost groups.

In a meta-analysis involving nine RCTs enrolling a total of 1090 patients, Cheng *et al*.[26] evaluated the IOP-lowering efficacy of topical prostaglandin analogs (PGA) in patients with chronic angle-closure glaucoma (CACG). The difference in absolute IOP reduction between PGAs and timolol varied from 0.4 to 1.6 mm Hg at a diurnal curve, 0.9 to 2.3 mm Hg at a peak, and 1.3 to 2.4 mm Hg at a trough. The authors concluded that latanoprost, travoprost, and bimatoprost provide significant IOP-lowering efficacy in eyes with CACG, and the three PGAs were at least as effective as timolol.

Author's conclusion

Both meta-analyses concluded that PG analogs provide significant IOP-lowering efficacy in eyes with CACG, and they are at least as effective as timolol.

Our Remarks

This meta-analysis did not report the effect of IOP reduction in relation to the degree of PAS; however, Aung *et al*., in RCT comparing latanoprost to timolol, reported that the degree of PAS does not have any impact on PG analog.[27]

Our Recommendation

The medical management in PACG is similar to POAG patients once LPI is patent. We recommend PG analog as the first line of drug. However, if cost is an issue and the patient does not have any systemic contraindication, topical beta-blocker is a good alternative.

Pilocarpine in Plateau Iris Syndrome (PIS)

We could not find any RCT/meta-analysis for the effect of pilocarpine in PIS. However, available literature suggests that in PIS, anteriorly located ciliary processes support the peripheral iris. Pilocarpine produces iris thinning and is an effective method of opening the angle and can be considered once LPI is patent.[28]

Role of Cataract Surgery in PACD

Acute Primary Angle Closure

Lam *et al*.,[29] in a prospective randomized trial, compared the effects of primary phacoemulsification-IOL versus LPI soon after an episode of APAC was aborted. At the end of 18 months, the early phaco-IOL group demonstrated better IOP control, fewer glaucoma medications to maintain IOP <21 mm Hg, and less extensive PAS compared to the LPI group. However, no statistically significant difference in visual acuity, vertical cup to disc ratio (VCDR), median mean deviation (MD), and pattern standard deviation (PSD) was noted between the two groups. None of these patients required further surgery to control IOP.

RCT by Husain *et al*.[30] compared the efficacy of primary Phaco-IOL with LPI in the early management of APAC and coexisting cataract. Patients with APAC that had IOP lowered to ≤30 mm Hg by medications within 24 h were randomized either to LPI (done 72 h after the medical treatment) or Phaco-IOL (5–7 days after lowering of IOP). At 2 years, there was significantly less treatment failure in the Phaco-IOL group (2/19, 10.5%) compared to the LPI group (7/18, 38.9%).

Author's conclusion

Both studies concluded that Phaco-IOL resulted in a better IOP control with a lower number of medications at 2 years compared to LPI if performed within the first week in patients with APAC and coexisting cataract.

Our remarks

RCTs results show that early Phaco-IOL is more effective in controlling IOP and preventing subsequent IOP rise compared to LPI as the first line of treatment. Various other small non-randomized studies have also reported good IOP control in patients undergoing Phaco/IOL performed even weeks to months after initial LPI.[31,32] However, phacoemulsification in acute PAC is technically challenging because of the cloudy cornea, shallow anterior chamber, poor mydriasis, and weakness of the zonular fibers. In RCTs, most of these surgeries were performed by experts. As the APAC eyes are acutely inflamed and may compromise the surgical success, it is advisable to perform cataract surgery after medically controlling the inflammation and corneal edema. In APAC eyes, visual prognosis and IOP control can be significantly improved if cataract surgery is performed after treating the acute attack by LPI, and after controlling, corneal edema, IOP, and inflammation.

Our Recommendation

Keeping in mind the technical challenges of performing cataract surgery and the good long-term outcome of non-randomized studies with delayed cataract surgery in eyes with acute PAC, we recommend continuing the current practice of performing LPI as the first line of treatment in such eyes. Cataract surgery can be performed at a later date after mitigation of corneal edema and inflammation is under control.

Clear Lens Extraction in PAC/PACG with mild damage (EAGLE Study)

Augusto Azuara-Blanco *et al.* published the first, large-scale prospective randomized study comparing LPI with clear-lens extraction as the initial treatment of PAC and PACG.[2,33,34] In total, 208 patients were assigned to the clear-lens extraction group, and 211 were in the LPI group. The study details are already published. The authors reported a small but significant advantage of primary CLE over LPI for all measured outcomes. The mean health status score (0.87 [SD: 0.12]) on the European Quality of Life-5 Dimensions (EQ-5D) questionnaire was 0.052% higher (95%CI: 0.015–0.088, P = 0.005) and mean IOP (16.6 [SD: 3.5] mm Hg) 1.18 mm Hg lower (95%CI: −1·99 to − 0·38, P = 0·004) after CLE compared to LPI.

Author's conclusion

The authors concluded that early CLE was more efficacious cost-effective than LPI and should be considered as an option for first-line treatment.

Our remarks

This trial addresses the clinically relevant role of the lens in the management of PACD. It assumes significance in a country like ours where PACD is a significant health issue. The study reported improvement in patient-reported outcome questionnaires in the CLE group, which may be due to significant improvement in uncorrected visual acuity (for distance and near vision) post-surgery in this group. The CLE group required a lower number of medications (mean: 0.4 [SD:

Table 2: Summary of the existing evidence and the important clinical implications of various RCTs in different categories of PACD

	PACS	ACUTE PAC	PAC	PACG
Role of LPI	Indicated in the high-risk group.	Indicated in all patients as soon as possible.	Indicated in all patients	Indicated in all patients
Role of Laser Iridoplasty	Not Indicated	Not recommended as first-line Rx. Indicated in eyes where LPI is not possible due to extremely shallow AC.	Not recommended as first-line Rx, as IOP control is inferior to medical management in patients with patent LPI.	ALPI is inferior to medical management in patients with patent LPI. Start medical management after LPI if needed
Role of SLT	Not Indicated	Not Indicated	Has a limited role in managing PAC. Can be considered if patient has drug intolerance/ adherence issue with topical medications	Like POAG, SLT has a limited role in managing PACG
Role of medical management	Not indicated	Immediate topical pilocarpine/ Oral Acetazolamide/IV mannitol to reduce IOP and to plan for early YAG PI	Once LPI is patent, the medical management is similar to POAG. Pilocarpine has a role in PIS.	Once LPI is patent, medical management and its efficacy is similar to POAG.
Role of cataract surgery alone	In patients with visually significant cataract, only cataract surgery should suffice	Surgery is technically more demanding, however, if needed it is advisable to wait till mitigation of inflammation and corneal edema. It should be performed by experienced surgeons only.	In patients with visually significant cataract, only cataract surgery should suffice.	In early to moderate PACG, with IOP control on minimal medications (up to 2), only Phacoemulsification can be considered. May need to continue ocular hypotensive medications after surgery must be explained.
Role of clear lens extraction	Not Indicated	Not indicated as the first line of management	Not indicated as the first line of management in all patients. EAGLE study showed that CLE does have merit in selected patients. However, we need more studies to evaluate the role of ocular biometry and lens parameters to get the specific high-risk group where CLE may help	Not indicated as the first line of management in all patients.
Role of cataract surgery versus trab	Trabeculectomy not indicated. In patients with visually significant cataract, only cataract surgery should suffice	We recommend trabeculectomy if IOP remains high after patent LPI. Cataract surgery can be advised at a later date once the eye is quiet and the patient has a visually significant cataract.	Only cataract surgery should suffice. If IOP remains high/intolerance to medications, trabeculectomy can be advised.	In eyes where the primary objective is IOP reduction, we should prefer Trabeculectomy as the first choice of surgery.
Role of combined surgery vs. trab	Not indicated	We recommend trabeculectomy if IOP remains high after patent LPI. Combined surgery can be advised at a later date once the eye is quiet and the patient has a visually significant cataract with high IOP	Usually not required	In eyes where primary objective is IOP reduction, we should prefer Trabeculectomy as the first choice of surgery. We recommend combining surgery in patients with advanced damage/ more than 2 medications/ adherence issues with significant cataract

PACD: Primary Angle-Closure Disease, PACS: Primary Angle-Closure Suspect, PAC: Primary Angle Closure, Acute PAC: Acute Primary Angle Closure, PACG: Primary Angle-Closure Glaucoma

0.8] vs. 1.3 [1.0]), and only one patient underwent additional surgery to control IOP compared to 24 in the LPI group. Of these 24 patients in the LPI group, 16 (67%) underwent cataract surgery. However, the need for some cataract operations within 3 years may be due to age-related cataractous changes, and it should not be interpreted as an increased occurrence of an unfavorable outcome in the LPI group.

As patients with advanced damage were excluded from the study, the reported IOP difference of 1.18 mm Hg between the groups becomes clinically insignificant, especially in early to

moderate glaucoma patients. While various publications have shown mean corneal endothelial cell loss to be as high as 19% in PACD eyes,[35,36] this study has not reported corneal endothelial cell loss after phacoemulsification. One of the other limitations is that the results of this study can be applied only to patients of PAC with IOP >30 mm Hg, which represents a minority of patients and cannot be extrapolated to advanced PACG eyes. Also, the missing gonioscopy findings in nearly 50% of eyes at 3 years follow-up could have given proper insight into the dynamic change in angle status between both the groups, especially in the LPI group. Moreover, the information on lens parameters such as lens vault and lens volume would have helped to identify the high-risk group where CLE could benefit.

Our Recommendation

Considering the several limitations of this study and modest benefit in IOP reduction after CLE, we recommend continuing with the current practice of doing LPI as the first choice for PAC/early PACG patients. However, we need more RCTs studying the role of lens (lens vault/lens thickness) to identify the high-risk patients who can benefit from CLE.

Role of Phacoemulsification versus Trabeculectomty in PACG

Tham *et al*.,[37] in a prospective randomized control trial, compared phacoemulsification versus trabeculectomy with adjunctive mitomycin C in medically uncontrolled chronic angle-closure glaucoma (CACG) without cataract. Over 24 months, trabeculectomy resulted in an 8.9-mm Hg IOP reduction compared to 8.4 mm Hg in the phacoemulsification group; however, on average, the trabeculectomy group required significantly less ocular hypotensive medications compared to the phacoemulsification group but was associated with more complications (46% vs. 4%). Eight (33%) of 24 trabeculectomy eyes demonstrated cataract during follow-up. The authors concluded that both phacoemulsification and trabeculectomy effectively reduce IOP in medically uncontrolled CACG eyes without cataract. Trabeculectomy is more effective than phacoemulsification in reducing dependence on glaucoma drugs but is associated with more complications.

Author's conclusion

The authors concluded that both phacoemulsification and trabeculectomy effectively reduce IOP in medically uncontrolled CACG eyes without cataract; however, trabeculectomy is more effective than phacoemulsification in reducing dependence on glaucoma medications.

Our remarks

Phacoemulsification in PAC eyes can be technically challenging. The surgeons involved in both studies were highly experienced. Training for routine cataract surgery might not provide the skills needed to reach consistently excellent results for phacoemulsification in clear lens/early cataract in primary angle-closure cases that would achieve the safety margin. Less-experienced surgeons might incur more difficulties and potentially severe intraoperative complications, which may compromise the post-surgical outcome.

Our Recommendation

In eyes where the primary objective is IOP reduction, we should prefer Trabeculectomy as the first-choice surgery.

Role of Phacoemulsification versus Trabeculectomty or combined Phacoemulsification and Trabeculectomy versus Phacoemulsification in PACG

Wang *et al*.[38] compared the efficacy and safety of phacoemulsification (Phaco) and combined phaco-trabeculectomy (Phaco-trab) in primary angle-closure glaucoma (PACG) with coexisting cataract. Five randomized controlled trials were included in the meta-analysis with a total of 468 patients (468 eyes) with coexisting PACG and cataract. Phaco-trab had a more significant IOP-lowering effect, a need for a lower number of antiglaucoma medications postoperatively, and less severe damage of optic nerve, but a higher risk of complications than Phaco. The studies indicated no significant difference between the two surgical methods for postoperative best-corrected visual acuity (BCVA) and loss of visual field. The authors concluded that Phaco-trab had a consistently more significant IOP-lowering effect and a lower number of antiglaucomatous medications needed postoperatively than Phaco but was associated with a high risk of complications.

Tham *et al*.[39] published combined complications of the RCTs involving trabeculectomy, phaco-trabeculectomy versus only phacoemulsification. In the phacoemulsification group, 5 of the 62 CACG eyes (5 events, 8.1%) and 16 of 61 CACG eyes (19 events, 26.2%) in the combined phaco-trabeculectomy group had surgical complications. This data converts into a number needed to harm (NNH) of 5.5, which means for nearly six glaucoma surgeries (either trabeculectomy/phaco-trabeculectomy), we get one more complication; however, the visual outcome was similar in both groups.

Author's conclusion

Phaco-trab had a consistently more significant IOP-lowering effect and a lower number of anti-glaucomatous medications needed postoperatively than the phacoemulsification group, but was associated with a high risk of complications.

Our remarks

Compared to phacoemulsification, trabeculectomy and phaco-trabeculectomy have a more significant IOP-lowering effect, lower number of antiglaucoma medications, and less damage to the optic nerve, but a higher risk of surgical complications. A NNH of 5.5; means the risk of surgical complications was higher in the glaucoma surgery group (either trabeculectomy/phaco-trabeculectomy); however, the visual outcome was similar in both groups.

Our Recommendation

We suggest to go ahead with cataract surgery only in early and moderate glaucoma where IOP is well under control with 1–2 medications. In advanced damage or in patients where adherence is an issue, we can consider combining cataract and glaucoma surgery.

Table 2 summarizes the existing evidence and the important clinical implications of various RCTs in different categories of PACD.

Conclusion

Excellent internal validity is the strength of RCTs. Randomization minimizes the risk of bias by confounding; however, the

generalizability (or external validity) of RCTs is an issue as the general population is not defined as the case in RCT. We have provided clinical implications and its usefulness in the day-to-day clinical practice of RCTs in PACD. Most of the RCTs available on PACD are with limited follow-up duration. The most extended follow-up was a study done by He *et al*.[9] was for 6 years; on the contrary, few RCTs had a follow-up duration of only 6 months. By definition, glaucoma is a chronic progressive disease, and any outcome we have observed in 6 months or even 2–3 years is inadequate to decide long-term management plans.

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Conflicts of interest

There are no conflicts of interest.

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