Guidelines for treatment of chronic primary angle-closure glaucoma☆

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A R T I C L E   I N F O

Article history:
Received 8 September 2014
Accepted 30 September 2014
Available online 14 April 2015

Keywords:
Glaucoma
Closed-angle
Guideline
Glaucoma treatment

A B S T R A C T

Objective: To present a clinical practice guideline update on the medical, laser, and surgical treatment of primary angle closure glaucoma (PACG) in adults.

Methods: Following the formulation of key questions using the PICO scheme (Patient/Problem, Intervention, Comparison, Outcome), a systematic review was performed on the literature published to date, including international clinical practice guidelines. The AMSTAR and Risk of Bias tools were used for evaluating the quality of the information. The level of evidence and grade of recommendation were established following the Scottish Intercollegiate Guidelines Network (SIGN) system.

Results: Following the above methodology, recommendations of medical, laser and surgical treatment in adult PACG and levels of evidence are presented.

Conclusions: Although the level of scientific evidence for many of the questions raised is not very high, a review is presented on updated treatment recommendations for adult PACG. The limitations for the implementation of these recommendations is include two criteria: (a) most studies have been conducted in Asian populations, and (b) the effectiveness is

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Scope and objectives

Clinical need for this clinical guide

Glaucoma is one of the main causes of blindness in the world. Data from Asia indicate that open angle primary glaucoma (OAPG) accounts for 75% of glaucoma cases and that primary angle closure glaucoma (PACG) would account for a fourth part. However the severity of the latter is greater, which means that the number of patients who lose their eyesight is similar in both types of glaucoma.1,2 The probability that a patient with PACG will become blind is 4% at 5 years,3 making early diagnostic and treatment an imperative need.

From the therapeutic viewpoint, we are faced with a broad range of options: isolated or combined topical and systemic antiglaucoma drugs for treating glaucoma generally and closed angle glaucoma particularly. In addition, a number of laser or surgical procedures can be applied including the suggestion of cataract surgery for reducing intraocular pressure (IOP), halting or slowing down vision loss or acting on etiopathogenic mechanisms.

However, the variability of this entity in clinical practice is very large as can be seen by the dissimilar conclusions and uncertainties expressed in publications. Most of our knowledge is based on information on IOP reduction but does not adequately cover other aspects such as preservation of vision or cost-effectiveness. In addition, a large part of published studies have been carried out on Asian populations, which means that the conclusions cannot be directly extrapolated to Caucasian populations.

Accordingly, the development of a therapeutic guide for PACG seems entirely justified and in both the Glaucoma Society of Spain [Sociedad Española de Glaucoma (SEG)] and the Glaucoma Research Group of RETICS RD12/0034 on ocular diseases "Prevention, early detection and treatment of degenerative and chronic prevalent ocular pathology" (OFTARED) have promoted and supported the development of this clinical practice guide (CPG), in which glaucoma experts of both organizations have taken part.

Population

Groups included in the guide

This guide comprises adults over 18 years of age with a diagnostic of chronic primary angle closure glaucoma (CPACG), associated or not to lens opacity. In order to comprise the entire range of the disease, the study has also included subjects with suspected primary angle closure (SPAC) and primary angle closure (PAC).
Medical treatment
- First-line therapeutic group. The guide will assess scientific evidence for recommending a pharmacological group as the first line of treatment and any differences in said group between active products.
- Combined treatment. The guide will assess available scientific evidence on combined therapy, including fixed combinations.

Laser treatment
The guide will also assess scientific evidence for recommending laser treatment for CPACG, including iridotomy or surgical laser, iridoplasty and cyclophotocoagulation.

Surgical treatment
In addition, the guide will assess scientific evidence for recommending surgical treatment for CPACG including trabeculectomy, nonperforating glaucoma surgery, drainage implants, cataract surgery and combined cataract and glaucoma surgery.

Objectives of the guide
The purpose of this guide is to present general guidelines to assist CPACG treatment. Lines of action will be suggested without aiming to establish obligatory criteria to exempt ophthalmologists or primary health care physicians of their responsibility to ponder a specific case and take action on the basis of their sound professional criterion. In addition, it places no restrictions whatsoever on professional freedom for taking decisions for treating a specific patient. Accordingly, physicians may opt for a different treatment within required habitual techniques if they understand that, according to their experience, a desired result requires a different therapy. The fact that any option may not be considered in this document as a recommended action guideline cannot be construed at all as a poor professional practice or an infringement of lex artis ad hoc.

Validity and update
Prior to planning this CPG, all participants signed a conflict of interest statement indicating that none of the signatories had any interest which could bias their participation herein.
Although it is not feasible to determine the time of appearance of relevant information which may modify the recommendations of this guide, it is estimated that half of the CPG will be outdated in a mean period of 5.8 years, and therefore it is estimated that this CPG should be reviewed 5 years after its preparation unless team members or users detect significant and relevant changes in scientific knowledge which would make an earlier review advisable.

Methodology
In order to establish the guidelines, a broader review of the literature and existing protocols has been carried out to by a Committee of Experts of the SEG, the RETICS glaucoma research group of ocular diseases “Prevention, early detection
and treatment of degenerative and chronic prevalent ocular pathology” (OFTARED) and advisors on research methodology.

The guidelines set forth in the Methodological Manual for Preparing Clinical Practice Guide in the National Health System have been applied, together with a combined methodology comprising adapting–preparing–updating.

The first step was designing the key questions of the guide. This was done utilizing the PICO scheme (Patient/Problem, Intervention, Comparison, Outcome) and the study type. Subsequently, CPG search and selection was carried out, as well as Cochrane reviews on CPACG. After assessing these with the AGREE application, the CPG of the American Ophthalmology Academy and of the European Glaucoma Society were accepted.

The second step was to analyze whether the selected CPGs and Cochrane reviews adequately addressed each question, on the basis of the following seven criteria: the question addressed in the guides, the existence of a Cochrane review, consistency, updating requirement, grade of recommendation, clarity and applicability.

In the event that the CPG did not address the question, Cochrane reviews or meta-analysis were sought. The quality of the latter was assisted with the criteria of the Assessment of Multiple Systematic Reviews (AMSTAR) tool, after which the article was rated in one of three scores (−, +, ++) by two group evaluators.

In the absence of meta-analysis or Cochrane reviews, clinical trials or other types of articles of lesser relevance were sought and analyzed with the “Risk of Bias” tool, similarly rating the article in three scores (−, +, ++) by two evaluators.

On the basis of the above criteria, the strategy to be followed with each question was selected: de novo preparation, partial preparation or adoption of recommendations based on CPG and/or Cochrane reviews.

The steps followed for the questions prepared de novo were as follows: search and evaluation of evidence, formal evaluation, synthesis of evidence and preparation of recommendations based on the Scottish Intercollegiate Guidelines Network (SIGN) system. In this classification, the scientific level of evidences range from 1++ (high-quality meta-analysis, systematic reviews of clinical trials or high-quality clinical trials with very low risk of bias) to 4 (expert opinion) (Table 1), while grade of recommendation ranges from A (maximum recommendation) to D (lowest level) (Table 2). An additional category is added in the recommendations, i.e., “good clinical practice” (GCP), which is a recommended practice based on clinical experience and consensus amongst the evaluation team and, although lacking supporting evidence, nobody would question in routine daily practice.

### Table 1 – SIGN scientific level of evidences.

<table>
<thead>
<tr>
<th>Scientific level of evidences</th>
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<tbody>
<tr>
<td>1+ High-quality meta-analysis, systematic reviews of clinical trials or high-quality clinical trials with very low risk of bias</td>
</tr>
<tr>
<td>1 Adequately performed meta-analysis, systematic reviews of clinical trials or adequately performed clinical trials with low risk of bias</td>
</tr>
<tr>
<td>1 Meta-analysis, systematic reviews of clinical trials or clinical trials with high risk of bias</td>
</tr>
<tr>
<td>2++ High-quality systematic reviews of cohort or case and control studies. Cohort or case and control studies with very low risk of bias and high probability of establishing a causal relationship</td>
</tr>
<tr>
<td>2+ Adequately performed cohort or case and control studies with low risk of bias and moderate probability of establishing a causal relationship</td>
</tr>
<tr>
<td>2 Cohort or case and control studies with high risk of bias and significant risk of a non-causal relationship</td>
</tr>
<tr>
<td>3 Non-analytic studies, such as case reports and case series</td>
</tr>
<tr>
<td>4 Expert opinion</td>
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### Table 2 – SIGN grades of recommendation.

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
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<tr>
<td>A At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guide; or a volume of scientific evidence comprised by studies rated as 1+ and with high consistency between them</td>
</tr>
<tr>
<td>B A volume of scientific evidence comprised by studies rated as 2++, directly applicable to the target population of the guide and exhibiting high consistency between each other; or scientific evidence extrapolated from studies rated as 1++ or 1+</td>
</tr>
<tr>
<td>C A volume of scientific evidence comprised by studies rated as 2+ directly applicable to the target population of the guide and which exhibit high consistency between each other; or scientific evidence extrapolated from studies rated as 2++</td>
</tr>
<tr>
<td>D Level 3 or 4 scientific evidence; or scientific evidence extrapolated from studies rated as 2+</td>
</tr>
</tbody>
</table>

Studies rated as 1– and 2– should not be used in the process of preparing recommendations due to high bias potential.

- Suspected primary angle closure (SPAC), with at least 180° of iridotrabecular contact, normal IOP, no evidence of peripheral anterior synchiae (PAS) (Fig. 3) or glaucomatous optic neuropathy (Figs. 1–3).
- Primary angle closure (PAC), iridotrabecular contact with presence of synchiae and/or increased IOP, but without glaucomatous optic neuropathy.
- Primary angle closure glaucoma (PACG), iridotrabecular contact with glaucomatous optic neuropathy, usually associated with PAS and increased IOP although sometimes not found in the initial exploration.

### Classification of primary angle closure

Angle closure comprises a range of clinical conditions based on anatomic risk and glaucomatous damage (Table 3). Following the guidelines of the European Glaucoma Society, based on Foster’s postulates (2002), PAC is classified in the following stages:

- Suspected primary angle closure (SPAC), with at least 180° of iridotrabecular contact, normal IOP, no evidence of peripheral anterior synchiae (PAS) (Fig. 3) or glaucomatous optic neuropathy (Figs. 1–3).
- Primary angle closure (PAC), iridotrabecular contact with presence of synchiae and/or increased IOP, but without glaucomatous optic neuropathy.
- Primary angle closure glaucoma (PACG), iridotrabecular contact with glaucomatous optic neuropathy, usually associated with PAS and increased IOP although sometimes not found in the initial exploration.

### Prevalence

Angle closure prevalence (with or without glaucomatous optic neuropathy) varies in different demographic areas of studies, for instance 0.4% in the Baltimore Eye Study, 0.6% in the north of Italy, approximately 1.5% in Asian populations and reaching...
3.8% in Alaskan indigenous populations and Eskimos over 40 years of age.6

There are very clear demographic risk factors for PAC, with important clinical implications. Nearly 25% of elderly Chinese women exhibit PAC, to the point that it has been stated that in clinical practice every elderly woman in China has angle closure unless otherwise proven.2 Prevalence varies considerably in Asia, with lower rates in some subpopulations such as the Japanese and much higher in others such as those mentioned in Myanmar,13 where PACG accounts for 84% of blindness due to glaucoma, most of them secondary to acute glaucoma episodes. It is estimated that the prevalence of PACG in China is 10–15 times higher than in the white population.14

In what concerns the European population, a recent systematic review has estimated that 0.4% of the population over 40 years of age exhibit PACG, with 75% of these being female.15 Prevalence increases with age, reaching nearly 1% (0.94%) in patients over 70 years. Taking into account the progressive aging of the European population, it can be foreseen that this prevalence will increase 9% in Europe in the next decade.15

<table>
<thead>
<tr>
<th>Table 3 – Angle closure rating classification.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iridotrabecular contact &gt;180°</td>
</tr>
<tr>
<td>SPAC</td>
</tr>
<tr>
<td>PAC</td>
</tr>
<tr>
<td>PACG</td>
</tr>
<tr>
<td>PAC: primary angle closure; PACG: primary angle closure glaucoma; IOP: intraocular pressure; PAS: peripheral anterior synechiae; SPAC: suspected primary angle closure.</td>
</tr>
</tbody>
</table>

**Risk factors**

Besides the demographic risk factors discussed above, PAC is more frequent in patients with family history and elderly females. Ocular risk factors include hypermetropia, central or peripheral anterior chamber reduction (Figs. 4 and 5), increased corner curvature, lens thickening and short axial length.6

Considering the anatomic base that determines narrow angle, angle closure is more frequently a bilateral disease.11

**Fig. 3 – Peripheral anterior synechia.**

**Fig. 4 – Narrow peripheral anterior chamber with iridoendothelial contact.**

**Fig. 5 – Narrow central anterior chamber and cataract.**

**Treatment of glaucoma by primary angle closure**

**Overview**

The decision to treat eyes with SPAC or PAC depends on the relative risk of developing glaucoma or exhibiting an acute angle closure episode.11 Unfortunately there is very little literature on this topic, particularly in relation to the Caucasian population. Published acute glaucoma development rates vary
between 6% and 10%, while the chronic glaucoma development rates are between 17% and 35%.11,16

**Suspected primary angle closure**

Due to the lack of data, particularly for the European population, the preferred treatment for SPAC is ophthalmological examination, including regular gonioscopy as a requirement (GCP).11 The approach must be individual and accordingly the indication for peripheral iridotomy in patients with SPAC is based on special considerations such as symptoms suggestive of intermittent angle closure, use of systemic drugs predisposing to pupil blockage or difficulty to obtain immediate access to an ophthalmological consultation for reasons of health, occupation or place of residence.5,11

It is essential that all patients with SPAC without iridotomy must be warned of the risk of acute glaucoma and that some pharmaceutical products including nasal decongesting agents, drugs for dizziness, anticholinergics, etc., which produce miosis could induce an acute glaucoma crisis. In addition, said patients should be informed about acute glaucoma symptoms and reminded to immediately visit an ophthalmologist if said condition is suspected.5

**Primary angle closure and glaucoma due to primary angle closure**

Patients with PAC should be treated for preventing conversion to glaucoma, while patients with PACG should be treated to avoid the progression of glaucomatos damage. In both cases, the algorithm includes laser iridotomy and added medical or surgical treatment in the presence of persistent high IOP.11

Treatment of PACG is considerably different to that of OAPG due to its mechanism of action. The pathogenesis of PACG begins with anatomic alteration of the anterior segment (narrowing of chamber angle) followed by trabecular mesh structural and functional damage due to PAS or perhaps other mechanisms related to contact with iridian tissue, intermittent or sustained increased IOP and subsequent glaucomatous optic neuropathy.2

Treatment of SPAC and PAC is focused on modifying the configuration of the anterior segment before irreversible glaucomatos damage occurs. For this reason, the typical approach consists in laser iridotomy (LI) or surgery, which is usually indicated in PAC as well as in PACG. However, most frequently this procedure does not enable IOP control, requiring the application of antiglaucomatos treatment.

Once glaucomatos damage has occurred, the purpose of treatment (just like in OAPG) is to diminish IOP. In these cases, modifying the iris anterior configuration does not appear to be as effective as in the earlier pre-glaucomatos phase.17

**Medical treatment**

The guide of the European Glaucoma Society indicates that medical treatment is rarely efficient in PACG,19 with the main approach being mainly surgical either with laser, filtrating procedures or lens surgery in isolation or associated to filtrating surgery. Medical treatment is regarded as a preparation for laser-surgery treatment or as a supplement in the event of poor response.

In general, the pharmacological treatment guidelines are similar to those for OAPG. Thus, for the American Ophthalmology Academy, once iridotomy has been performed OAPG treatment does not change and accordingly patients with residual open angle or any combination of open and closed angle should be followed up and treated following the same guidelines for OAPG (level of evidence 4, grade of recommendation D)5,18,19 (Table 4).

When analyzing the efficacy of medical treatment in PACG its must be pointed out that there are very few medical treatment studies specifically designed for PACG. Many included patients had previously submitted to LI and the majority refer to the Asian population, which means that the data thereof cannot be directly extrapolated to Caucasian patients. Table 4 summarizes the level of evidence and grade of recommendation of the various medical treatment options.

**Table 4 – Level of evidence and recommendation in medical treatment of PACG.**

<table>
<thead>
<tr>
<th>Medical treatment in PACG</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>After iridotomy is performed, the medical treatment guideline does not differ from OAPG</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>PG are the first line of medical treatment</td>
<td>1−</td>
<td>B</td>
</tr>
<tr>
<td>Traroprost is more efficentia than carteolol. IOP reduction does not correlate with angle opening</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Timolol is nearly as effective as PG and can be a good therapeutic alternative</td>
<td>1+</td>
<td>B</td>
</tr>
<tr>
<td>Bimatoprost and latanoprost exhibit similar efficacy. Bimatoprost could be more effective in synechial closure &gt;3 h</td>
<td>1−</td>
<td>B</td>
</tr>
<tr>
<td>Bimatoprost produces hyperemia in a higher percentage of eyes</td>
<td>1−</td>
<td>B</td>
</tr>
<tr>
<td>Latanoprost and traroprost exhibit similar efficacy after iridotomy</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>In complete synechial closure, PG is the first choice medical treatment</td>
<td>1+</td>
<td>A</td>
</tr>
<tr>
<td>Traroprost is more efficentia and better tolerated than pilocarpin, in addition to easier posology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association of brimonidin with topical exhibits a similar additive effect as that found in OAPG</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>The rest of therapeutic groups and combined fixed and non-fixed therapy would have the same indications as in OAPG</td>
<td>4</td>
<td>D</td>
</tr>
</tbody>
</table>
First line monotherapy
In order to evaluate the first line monotherapy in PACG, the first question relates to the efficacy and safety of prostaglandin analogs (PG) as compared to betablockers. In addition, comparisons were proposed between the rest of the antiglaucoma therapeutic groups although hardly any information was obtained and therefore, for most of the remaining recommendations, the reference had to be based on expert recommendations.

Prostaglandin analogs vs topical betablockers. PG analogs are the most potent topical ocular hypotensors currently in the market. There is insufficient scientific evidence to confirm their efficacy in OAPG and ocular hypertension.20,21 However, data related to angle closure patients are scarce. In 2009, Cheng et al. published a meta-analysis which included nine randomized clinical trials with good methodological quality comprising 1090 patients, studying the efficacy of three PG analogs (latanoprost, bimatoprost and travoprost) in the treatment of PACG.18 Five of the nine trials assessed efficacy in monotherapy in comparison with timolol and the other four compared PG analogs with each other, reaching the conclusion that the three PG analogs were more efficient than timolol for reducing IOP in PACG. However, the differences with timolol are small and therefore said authors consider that timolol is nearly as effective as PG analogs and therefore a good option for treatment (level of evidence 1+, grade of recommendation B).

In said meta-analysis, the maximum IOP reduction in the day light curve was obtained by latanoprost (31%), followed by travoprost (28%), bimatoprost (26%) and timolol (23%), which obtained similar results in the daylight curve valley.

After the publication of said meta-analysis, an additional randomized clinical trial was published comparing 0.005% latanoprost with nighttime administration and 0.5% timolol every 12 h in patients with PAC and PACG with high IOP after LI in Chinese population,22 including 142 patients randomly allocated to one of the two treatments, with a follow-up of 8 weeks. These patients exhibited at least 90° of open angle and therefore the trial cannot be extrapolated to patients with broader synchia closure. In addition, 20% of patients of each group had previously undergone filtering surgery. Even though both treatments produced significant IOP reductions from the first week up to the end of the follow-up, treatment with latanoprost achieved the lowest IOP in all the visits of the study. At the end of the follow-up, the latanoprost treatment achieved an additional reduction of 1.8 mmHg vis-à-vis timolol. The most frequent adverse event in the latanoprost group was transient blurred vision 1–2 h after treatment administration (35.2% in the latanoprost group and 21.4% in the timolol group), followed by conjunctival hyperemia (14.1% vs 4.3%, respectively). Three timolol group patients abandoned the study due to systemic effects related to the betablocker action (arrhythmia, 5.7%). From this study it could be concluded that PG, specifically latanoprost, would be the first line of treatment for PACG patients who did not achieve sufficient IOP reduction after LI in the Chinese population. However, as the study involved patients having at least 90° of ciliary strip visible with gonioscopy, the data cannot be extrapolated to complete angle closure cases (level of evidence 1−, grade of recommendation B).

Travoprost-carteolol
After the meta-analysis discussed above, a case-control clinical trial was carried out comparing 0.004% travoprost and 2% carteolol in Asian patients with PAC or PACG after LI or trabeculectomy. The trial also reached the conclusion that travoprost produces a significantly higher tension reduction when compared to carteolol, and that the IOP reduction was not correlated with the angular open degree.23 The data of this trial support the above conclusions, although their methodological precision is lower (level of evidence 3, grade of recommendation C).

Comparison between prostaglandins
PG analogs latanoprost, travoprost and bimatoprost have demonstrated similar ocular hypotensive efficacy in patients with OAPG and ocular hypertension. In what concerns PACG, the following comparisons between PGs have been evaluated:

Latanoprost-bimatoprost. Two comparative studies have been found. Chen carried out a randomized and masked trial with 82 Asian patients with PACG comparing latanoprost and bimatoprost after iridotomy with a follow-up of 12 weeks.24 Both products achieved significant IOP reduction in all the follow-up periods, without statistically significant differences between the groups. The mean reduction in absolute values at the end of the follow-up period was of 5.2 mmHg. The ocular hypotensor effect was maintained throughout the day light curve. Efficacy could be slightly lower to that referred in other PACG with PG studies, probably because the baseline IOP of the study population was lower. The most common adverse effect was hyperemia, exhibited by 10% of the patients treated with latanoprost and 15% of those treated with bimatoprost.

A second randomized clinical trial25 included 60 patients with PACG after 6 weeks follow-up. It was also found that both products exhibit a statistically significant similar IOP reduction (absolute value reduction of 8.9 mmHg with bimatoprost and 8.4 mmHg with latanoprost), without finding differences in the daylight curve. An interesting finding was that in patients with PAT over 90°, bimatoprost achieved a greater reduction (an additional 1.2 mmHg) than latanoprost. The authors postulated that this effect could be dependent on the different absorption pathway of both drugs (predominantly scleral for bimatoprost and corneal for latanoprost) or to other self-regulation mechanisms of prostaglandin F receptors.

As in the Chen study, the bimatoprost group exhibited more local adverse effects, almost twice as many as the latanoprost group, notably hyperemia which occurred in 37.9% of patients treated with bimatoprost vis-à-vis 22.4% of those treated with latanoprost.

Both studies exhibit the limitation of a short follow-up period, particularly the latter. This excludes assessment on long-term efficacy and safety. In addition, they were carried out with Asian populations and therefore cannot be directly extrapolated to Caucasians.

From the above clinical trials, it was concluded that in Asian populations with PACG after iridotomy, bimatoprost and latanoprost are equally effective. Bimatoprost could be more
effective in patients with synechiae closure exceeding 3 h. The most common adverse effect was hyperemia, which occurred most frequently in patients treated with bimatoprost (level of evidence 1–, grade of recommendation B).

Latanoprost-travoprost. Chen carried out a randomized clinical trial comparing latanoprost and travoprost in patients with PACG after IL. The mean reduction in absolute value at the end of the follow-up was 5.3 mmHg in the latanoprost group and 5.1 mmHg in the travoprost group. The ocular hypertension effect was lower than that usually obtained with PG analogs, which is explained by the low baseline IOP of the study population. The most common adverse effect was hyperemia, present in 10% of patients treated with latanoprost and in 16% of those treated with travoprost.

From this study it can be concluded that latanoprost and travoprost can be considered as similar therapeutic options in efficacy and safety in the treatment of residual PACG after peripheral iridotomy (level of evidence 1–, grade of recommendation B).

Latanoprost vs combined therapy. Only one randomized clinical trial was found, comprising 18 Japanese patients after IL, comparing latanoprost with a non-fixed combination of timolol and 1% dorzolamide (instead of 2%, which is the usual concentration in our environment but was not available in Japan at the time of said study) with a duration of 12 weeks. The latanoprost group exhibited higher, statistically significant IOP reductions in all the visits (additional 2 mmHg with latanoprost, 33% against 24%). No changes were appreciated in the perimetry and the adverse effects were comparable with the exception of higher bradycardia incidence in the combined therapy group. As the formulation for this study was not the habitual formulation in our country, the conclusions of this study are not applicable in our routine clinical practice.

Action mechanism of prostaglandin analogs in primary angle closure and primary angle closure glaucoma. The action mechanism of PG analogs in PAC is not clear. It has been postulated that they may reach the ciliary body through the open portion of the chamber angle, increasing in this way exit through the uveoscleral pathway; alternatively, that they may access through other pathways such as the posterior chamber between the lens, the iris and the root of the iris or through the sclera. It has also been suggested that they facilitate aqueous humor exit through PAS to the ciliary body and that for this reason may be efficient even in the presence of complete synechiae closure. In this regard, Kook et al. studied 14 Korean patients with PACG and 360° synechiae closure, and found that latanoprost produced a statistically significant IOP reduction in all the follow-up visits, said reduction representing an absolute value of 8.8 mmHg in the final visit (3 months). As in the baseline IOP was very high (mean value of 30.3 mmHg), the effect is even higher to that obtained in other trials which lower baseline IOP values. It can be concluded that with complete synechiae closure, PG analogs and specifically latanoprost would be the initial medical treatment of choice (level of evidence 3, grade of recommendation C).

Pilocarpin
Miotics, specifically pilocarpin, have been broadly used in PACG and in acute angular closure (AAC). Their action mechanism is based on miosis and iris root traction, with ensuing chamber angle enlargement. However, in some types of angle closure glaucoma such as phacomorphic or malign glaucoma, miotics may aggravate the condition due to anterior iridocristalline displacement and aggravation of pupil blockage. Due to their adverse effects such as posterior synechiae, miosis, ciliary spasm and accomodative myopia, miotics are hardly used as chronic treatment in our environment, although 1% pilocarpin continues to be broadly used in Asian countries.

No recent studies have been found comparing pilocarpin with other antiglaucoma drugs with the exception of a comparative study with travoprost. Wor et al. performed a double blind randomized clinical trial with parallel groups comparing 0.004% travoprost applied during the night against 1% pilocarpin four times a day in Chinese patients with PACG or PAC after IL, during 12 weeks. Travoprost produced a greater tension reduction than pilocarpin in all the studied periods. The presence of peripheral anterior synechiae was not relevant for the obtained IOP results. In said 3-month period, it was observed that none of the two drugs had any influence on the PAS degree and its distribution vis-à-vis baseline.

In what concerns adverse effects, patients treated with pilocarpin exhibited more frequently periorcular pain, cephalgia, miosis and blurred vision whereas in the group treated with travoprost the most frequent effect was hyperemia.

From this study, it can be concluded that in Chinese patients with PACG or PAC, travoprost is more efficient and better tolerated than pilocarpin, in addition to having the advantage of a more comfortable posology (level of evidence 1+, grade of recommendation A).

Betablockers
The majority of recent studies on betablockers are referred above in the comparison with PG analogs. In addition, Metherlaird et al. carried out a randomized clinical trial comparing 0.5% timolol drops every 12 h with 0.1% timolol gel once a day in patients with PACG. The study involved 25 patients and although 0.5% timolol was more efficient at different times of the daytime curve, said differences were not significant, which could be attributable to the small size of the sample. The same can be said about the non-significant reduction of systolic arterial pressure after treatment with timolol gel and diastolic pressure with timolol 0.5%.

Accordingly, studies with larger sample size are required to reach conclusions about differences in efficacy and safety between said betablocker formulations in PACG.

Rest of antiglaucoma drugs
No randomized clinical trials comparing the usefulness of topical anhydride inhibitors and alpha-2 agonists as a first-line therapy in PACG have been found. In what concerns combined therapy, only one study was found with brimonidine. In PACG with Asian patients, the association of brimonidine with topical betablockers provides a mean additive effect of 4.5 mmHg, very similar to that obtained in patients with OAG (level of evidence 3, grade of recommendation C).
Table 5 – Level of evidence and recommendation in treatment laser del PACG.

<table>
<thead>
<tr>
<th>Treatment laser in PACG</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iridotomy is indicated for managing PACG, PAC and opposite eye after acute angle closure</td>
<td>4</td>
<td>GCP</td>
</tr>
<tr>
<td>In SPAC, iridotomy is indicated in special cases (drugs causing angle closure, previous clinic compatible with angle closure, difficulty of quick access to hospital)</td>
<td>1−</td>
<td>B</td>
</tr>
<tr>
<td>Iridotomy indicated in plateau iris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum recommended iridotomy size 150–200 μm</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>Argon laser iridotony exhibits a rate of closures superior to Nd:YAG laser</td>
<td>1−</td>
<td>B</td>
</tr>
<tr>
<td>Suppressing use of anti-aggregants or anticoagulants prior to iridotomy not required</td>
<td>1−</td>
<td>B</td>
</tr>
<tr>
<td>In PACG, trabeculeptomy is more efficient than LI</td>
<td>1−</td>
<td>B</td>
</tr>
<tr>
<td>After iridotomy, the posterior subcapsular component of the cataract may progress</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>LI in temporal location determines lower risk of de novo dysphotopsia than superior localization</td>
<td>1+</td>
<td>B</td>
</tr>
<tr>
<td>After AAC, cataract surgery provides greater tension control possibilities than LI, but has higher risk of complications then in eyes with open angle</td>
<td>1−</td>
<td>B</td>
</tr>
<tr>
<td>Argon laser iridoplasty is standard treatment for persistent apositional PAC after LI</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>In PAC or PACG, PIAL associated to LI does not provide significant advantages vis-à-vis LI on its own</td>
<td>1+</td>
<td>B</td>
</tr>
</tbody>
</table>

The consensus of the group of experts is that indications and use of topical carbonic anhydrase inhibitors and alpha-2 agonists in PACG are the same as in OAPG, their usefulness being mainly as second line drugs for combined therapy (level of evidence 4, grade of recommendation D).

**Treatment with laser**

Table 5 details the level of evidence and grade of recommendation for the various therapeutic options with laser in PACG.

**Iridotomy**

In 1856, Von Graefe observed that surgical iridectomy was able to heal an acute episode of glaucoma and improve other forms of the disease. However, many years had to pass before it was understood that the hypotensor effect of said technique was based on the removal of pupil blockage and to demonstrate that small peripheral iridectomy was equally efficient.

As from the fifties, technological developments enabled said technique based on laser. First, a xenon arch was used, followed by Ruby laser and subsequently argon laser. In the 80s, the Neodymium-doped Yttrium Aluminum Garnet (Nd:YAG laser) appeared, which has been considered as the standard for this procedure up to this date (Fig. 6).

Analyzing publications on this procedure gave rise to a number of practical problems due to the heterogeneous nature of diagnostic definitions and study populations. Many papers considered AAC, PAC and PACG jointly. Likewise, it is necessary to state that, due to the increased weight of publications on angular closure in Asian countries, most of the studies refer to said racial group and therefore the conclusions cannot be directly applied to our environment.

**Which is the risk of acute glaucoma due to angle closure in subjects with primary angle closure?** In a prospective study carried out in Singapore, the authors dilated 471 patients with narrow anterior chamber (AC) and only three developed acute glaucoma. The protocol of this study included administration of acetazolamide after iridotomy. Even so, incidence was in the range of 0.2% and accordingly the authors concluded that the risk was low.

Which is the indication? Is it recommended to perform iridotomy in all cases? There is consensus that iridotomy is indicated for management of PACG, PAC and in the opposite eye of patients who have suffered an acute episode of narrow angle glaucoma (GCP). Its usefulness in SPAC is not established. However, in the concurrence of specific circumstances such as the use of drugs which could produce angle closure, previous clinic compatible with AAC episodes, progressive angle narrowing or personal circumstances which impede quick access to hospital, it could be indicated (level of evidence 4, grade of recommendation D; GCP).

Although it is known that plateau iris configuration is associated to poor response to iridotomy, there is consensus that even in these cases a pupil blockage component could be associated, and therefore iridotomy would be indicated (GCP).

**Technique.** In what concerns the size of iridotomy, no published studies have been found and therefore an attempt to reply this question involved the development of biophysical...
models. Initially, it was believed that 50μ was sufficient to prevent pupil blockage. However, said calculations probably underestimated required dimensions because they were carried out taking into account an iris thickness of 50μ, well below actual values. Accordingly, the current tendency is to consider iridotomy as safe when it has a diameter of at least 150–200μ.38,39 (level of evidence 4, grade of recommendation D).

Two decades ago, LI demonstrated it was as efficient as a surgical iridectomy and even safer.40 Even so, when laser technology is not available, surgical iridectomy would be a valid alternative.37

There is significant geographical variability in the type of laser being used. In Europe, generally the Nd:YAG laser is used, with argon laser being used in Japan, while both types are combined in Singapore. Argon LI has demonstrated lower risk of bleeding because, being a heat-based laser, it coagulates vessels but exhibits a higher closure rate than with Nd:YAG laser41 (level of evidence 1−, grade of recommendation B). In dense iris it would be recommendable to pretreat with argon laser to reduce the amount of Nd:YAG energy required to perfo-rate the iris and complications.34,52 This sequential technique would be particularly indicated in very narrow chambers or with very low endothelial count (level of evidence 1−, grade of recommendation B).

The use of anticoagulants and anti-aggregants does not seem to increase the risk of bleeding and therefore interrupt- ing use of these drugs does not seem necessary (level of evidence 1−, grade of recommendation B).

Efficacy and safety of laser iridotomy. LI is a safe and noninvasive procedure with few complications. Its preventive effect on AAC episodes is established but its hypotensive efficacy is variable (described variable tension control of 0–80%).44 In fact, the majority of patients with PACG need to maintain or increase previous antiglaucoma treatment after LI.

In PACG, primary trabeculotomy involves several advantages in relation to primary LI such as greater IOP reduction with less fluctuations, diminished PAS progression and less associated complications in the antiglaucoma treatment (level of evidence 1−, grade of recommendation B).

Even though the complications rate of LI is low, potential complications must be fully taken into account.11,43,45–50

Complications of laser iridotomy. A range of complications have been reported during or after Nd:YAG LI, including increased IOP, injuries in corneal lens or retina, hyphema, iritis, development of posterior synechiae and visual alterations (such as the appearance of ghost images), endothelial loss and malign glaucoma.44 Fortunately these complications are infrequent and accordingly the risk-benefit ratio is deemed to be favorable.5,7,37

LI-induced endothelial loss is not significant. A recent prospective cohort study reported that cell loss after 1 and 3 years was slightly higher in eyes submitted to LI. In said reports, one of the eyes was submitted to LI with the contralateral eye acting as control. The percentage of loss vis-à-vis baseline in the group that received iridotomy was 3.6% after 1 year and 2.1% after 3 years, whereas in the contralateral eye group which did not undergo said procedure the loss was slightly lower, 3.2% and 0.9% after 1 and 3 years, respectively.51 It is noteworthy that the count is lower after 1 year than after 3 years, which suggests some recovery of the endothelium. A significant limitation in the assessment of these changes is derived from the fact that LI is performed on the periph- ery while the endothelial count is measured in the central cornea, and this does not reliably reflect the changes suffered by endothelial cells adjacent to the iridotomy.51

The cataractogenic effect of Nd:YAG LI, is an infrequent complication. Isolated reports have been published referring acute progression of cataract after iridotomy, in which inexpe- rienced surgeons applied excessive amounts of energy.47,48,52 At least one prospective series with Chinese patients, mostly females, has demonstrated cataract progression (mainly the posterior subcapsular component) after 1-year follow-up, although said study did not include a control group47 (level of evidence 3, grade of recommendation C).

A potential side effect are hypertensive peaks. Presurgery use of miotics and apraclonidine significantly reduces the probability and magnitude of said hypertensive peaks.54

As the use of pilocarpin during this procedure has been related with the development of malignant glaucoma,55–57 some authors propose avoiding the use of this miotic. Even though the references to malignant glaucoma brought about by the practice of iridotomy are very few, it has been demon- strated that iridotomy can induce localized choroidal effusion. This risk appears to be greater when YAG laser is com- bined with argon laser than using only Nd:YAG laser.53 Even so, the use of miotics prior to LI is recommendable as it stretches the iris and facilitates the procedure with less energy, in addition to the associated ocular hypotensor effect.7,34

Visual artifacts related to glare have been reported after LI.54 Said artifacts are hardly invalidating and their intensity diminishes with time. Even so, they could have some impli- cations in the selection of the most favorable location for iridotomy.34,45

A cohort study carried out with Chinese population, with 230 treated subjects compared to 268 untreated subjects, found no association between iridotomy and increased glare symptoms or signs. As this study was focused on Asian popu- lation it is possible that the dense pigmentation in this racial group’s eyes enables a more efficient compensation of the light dispersion induced by exposed iridotomy. The authors recom- mend selecting a crypt which enables executing the procedure with less energy, preferably in an area that will remain cov- ered by the eyelid,49 avoiding iridotomies in inferior location or exposed areas which could induce monocular diplopia and glare artifacts.

However, recently a prospective trial with 208 patients randomized for undergoing superior LI and temporal in the opposite eye. The group included 50.3% of Caucasian patients and 41% of Asian patients. It was observed that the appearance of new linear dysphotopsias was greater in eyes submitted to superior LI (10.7%) vs temporal LI (2.4%) (P = 0.002). The inci- dence of this complication in eyes with superior LI which was completely covered by the upper eyelid was of 6.5%, which means that said complication is not entirely avoided, while only 2.8% of eyes with nasal or temporal exposed LI exhibited new dysphotopsiae.50
The authors explained this surprising finding because in the cornea, which is in close contact with the superior eyelid, surface tension of the tear would form a triangular section tear deposit which would act as a prism with superior base, deviating light toward the most peripheral superior retina. In consequence, a beam of light with very little dispersion would stimulate the superior retina and produce linear dysphotopsia in the inferior hemifield. When iridotomy is carried out in the temporal iris, as said prism effect does not occur, light would impact the posterior pole after traversing the entire vitreous cavity, forming a circle with greater surface for dispersion, which would be less perceptible for the patient.

On the other hand, said authors found that temporal LI was significantly more painful than superior LI (mean score of 2.8 versus 2.2). They recommend taking into account the morphology and position of the eyelid when selecting the LI location. In case the temporal iris remains completely exposed, this could be the perfect location but patients having the temporal part of the eyelid partially covering the iris could give rise to dysphotopsia, making its recommendable to select a different location.50

At least in part, the discrepancies between the above referred articles could be due to ethnic reasons, because the study by Congdon et al. involved Asian populations while the study by Vera et al. included a group with mixed racial origin.55,56 From the latter study it can be deduced that temporal LI determines lower risk of de novo dysphotopsiae than superior LI (level of evidence 1+, grade of recommendation B). However, as the study did not separate patients by ethnicity, it cannot be known whether the conclusion can be extrapolated to the Caucasian population.50

Which parameters predict good response to iridotomy? Advanced age, smaller iridial area and a more curved iris correlate with good response.55,56 These three characteristics would be more prominent in eyes in which pupil blockage is the most important mechanism. On the contrary, the plateau iris configuration and the presence of peripheral anterior synechiae correlate to higher failure rates.37

Phacoemulsification vs peripheral laser iridotomy. Nd:YAG laser iridotomy has demonstrated its effectiveness in the prophylaxis of AAC episodes, although its effect on PAC and PACG is more relative because on many occasions it does not achieve chamber angle opening and/or IOP reduction.54,55 Azuara-Blanco et al.58 are carrying out a clinical trial titled EAGLE (Effectiveness of early lens extraction with intraocular lens implantation for the treatment of primary angle-closure glaucoma) that will include patients over 50, phakic without cataract with PACG or PAC, IOP > 30 mmHg without history of AAC episodes, randomized for extraction of transparent lens or for peripheral LI followed on not by iridoplasty. The results will be assessed from the clinical viewpoint (IOP after 3 years follow-up) as well as from the economic and quality of life viewpoints.

Lam et al.59 demonstrated that early cataract surgery can be considered after an AAC episode. In this randomized clinical trial, a group of Asian patients over 50 with clinically significant cataract and who had suffered an AAC were randomized for phacoemulsification (performed within 5.7 ± 3.3 days after the AAC) or LI (performed 4.3 ± 2.7 days after the AAC). After peripheral LI, 46.7% of patients exhibited high IOP at 18 months against 3.3% of patients submitted to phacoemulsification.

Likewise, Husain et al.60 demonstrated that phacoemulsification with IOL implant (in this case accompanied with goniosynechialysis) performed a week after an AAC episode improved IOP control at 2 years follow-up compared with peripheral LI.

Accordingly, it can be concluded that in cataract patients who suffer an AAC episode early phacoemulsification significantly reduces the risk of IOP elevation at 18–24 months with respect to LI. However, it must be taken into account that cataract surgery in eyes after AAC involves higher risk of surgery complications due to the narrowed anterior chamber and the tendency to choroidal diffusion. Therefore, said surgery should be performed by an experienced surgeon (level of evidence 1--, grade of recommendation B).

Argon laser iridoplasty

Peripheral iridoplasty with argon laser (PIAL) is a useful procedure for eliminating the apositional angle closure caused by mechanisms other than pupil blockage. In angle closure cases originated in the posterior of the iris, such as plateau iris, lens-induced angle closure or due to posterior segment processes such as malignant glaucoma, iridotomy may not be enough to treat the underlying mechanism of the disease. PIAL can help to increase the angle opening. It has also been indicated as treatment for AAC or for opening the angle before laser trabeculoplasty.61

PIAL would be contraindicated in eyes with edema or severe corneal opacity, flat anterior chamber and extended angle closure.61

Action mechanism. Angle closure due to iris aposition is reversible but in the case of PAS it may be irreversible. Through PIAS a burn is induced in the periphery of the iris which pulls the latter, separating it from the trabecular mesh. Initial treatments were performed only in 90° of the angle and were frequently insufficient to produce sufficient retraction of the iris tissue. For this reason, Kimbrough et al. suggested expanding the treatment to cover 360°, using a gonioscopy lens which has become the cornerstone for the current technique.62

Technique. The technique is usually performed with argon laser through a contact lens (such as the Abraham lens) applying approximately six impacts per quadrant in the periphery of the iris, the most widely used parameters being 500 μ size, 0.5 s exposure time and low power (50–200 mW) with the aim of producing a burn that will induce iris retraction (Fig. 7). If the iris is not seen to contract, the power can be increased.61

Complications. PIAL is a long procedure and complications have been reported. Slight iritis is habitual in the first days after the procedure. As PIAL patients have a narrow anterior chamber, endothelial burns can occur which improved spontaneously in a few days without leaving sequel. However, some cases of corneal decompensation have been reported in patients with Fuchs’ endothelial dystrophy. Hemorrhage is a very infrequent complication. It has not been reported that PIAL accelerates the progression of cataracts. Some patients
Fig. 7 – Scars in the peripheral iris after peripheral iridoplasty with argon laser.

may develop slight anisocoria. Paradoxically, the pupil of eyes submitted to trabeculoplasty generally increase in size. This pupil diameter increase could be explained by the lesion of the small parasympathetic branches which innervate the sphincter muscle of the pupil.63

Usefulness of peripheral iridoplasty with argon laser in nonacute angle closure. In a recent meeting of international glaucoma experts, PIAL was considered as a standard treatment in patients with persistent apositional PAC after I.63 (level of evidence 4, grade of recommendation D).

A recent Cochrane review assessing the efficacy of PIAL in the treatment of SPAC, PAC or PACG in nonacute situations64 only found one clinical trial with 158 patients65 and two series of cases on which to base the review.

The only randomized clinical trial on the subject comprises 77 eyes randomized to an iridotomy group and 81 eyes to an iridotomy + PIAL group with a follow-up period of 1 year. The trial involved patients with synchial PAC or PACG. The addition of PIAL to iridotomy did not contribute significant advantages in what concerns IOP reduction, number of antiglaucoma drugs, need of surgery or campimetric progression.67 However, in the combined treatment group a greater anterior chamber amplitude was obtained as well as PAS reduction (level of evidence 1+, grade of recommendation B).

In addition to said clinical trial, two series of cases on the subject have been found. Ritch et al.66 carried out a retrospective study including 23 eyes of 14 patients with plateau iris submitted to treatment with PIAL and follow-up exceeding 6 years. In 87% of the eyes, the angle remained open throughout the follow-up period after the treatment. Three eyes exhibited gradual angle closure after 5–9 years but were reopened with a single retreatment. Accordingly, said authors suggest that said treatment is effective in the long-term.

In order to determine the efficacy and safety of iridoplasty after goniosynechialysis in patients with PACG and complete synchial angle closure, Lai et al.67 performed iridoplasty with diode laser in five eyes of five patients with PAS, 360° angle closure and IOP over 21 mmHg with maximum medical therapy, obtaining a success percentage of 80%. Post-surgery complications included the development of cataracts, hyphema and transient IOP increase.

At present there are two clinical trials on the subject which have not yet published their results. One assesses the efficacy of Pascal laser (ClinicalTrials.gov identifier: NCT01020071) and the other with argon laser (ClinicalTrials.gov Identifier: NCT009804739).

Therefore, even though expert consensus suggests the use of PIAL in persistent PAC after laser iridotomy, there is not enough sufficient evidence to support this recommendation. The only existent controlled clinical trial indicates that PIAL does not contribute advantages in the evolution of the disease when compared to isolated iridotomy, with the exception of reduction in the presence of PAS. Due to the lack of evidence in the literature for the prophylactic use of iridoplasty in these patients and considering that iridoplasty can be painful and may cause anterior chamber information, the decision to treat or not must be up to the glaucoma specialist in charge of treating the patient.

It would be recommendable to design randomized clinical trials with control groups to assess the efficacy and safety of PIAL in the various angle closure subtypes. In addition, taking into account that chamber angle evaluation in most available studies has been performed subjectively with gonioscopy, it would be advisable to include objective angle evaluation methods such as optic coherence tomography (OCT), ultrasound biomicroscopy or Scheimpflug cameras.

Trans-scleral cyclophotocoagulation
Trans-scleral cyclophotocoagulation with diode laser has been proposed as a therapeutic alternative in AAC cases due to its efficacy and the advantage of being a faster and simple technique which can be performed outside the operating theater.68 However, no information has been found on its potential usefulness for treating PACG.

Surgical treatment
Traditionally, the surgical treatment of PACG has included a range of techniques. Filtrating procedures, trabeculectomy with or without antimetabolites and drainage devices have been the most widely used surgery techniques. In addition, the isolated extraction of the lens with intraocular lens implant has been proposed69–78 associated or not to goniosynechialysis75–78 or viscoconjunctioplasty.79 Finally, it is also possible to perform surgery combining cataract extraction and filtering procedure.80,81 There is no evidence to indicate surgical treatment for SPAC or PAC cases, whereas in PACG the indication of various surgical treatment modes remains under discussion (Table 6).82,83

Isolated filtrating surgeries
Trabeculectomy. Trabeculectomy is the most widely used filtrating surgery for treating OAPG. No systematic reviews or randomized clinical trials have been found which study the efficacy and safety of trabeculectomy in PACG in comparison with other surgical techniques.

As commented above in relation to L1, primary trabeculectomy has demonstrated greater ocular hypotensor
Table 6 – Level of evidence and recommendation in surgical treatment of PACG.

<table>
<thead>
<tr>
<th>Surgical treatment in PACG</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabeculectomy is efficient to reduce IOP in PACG, but presents significant complications</td>
<td>2−</td>
<td>C</td>
</tr>
<tr>
<td>NPDS in isolation is not indicated in the presence of angle closure in the surgery intervention area</td>
<td>4</td>
<td>D, GCP</td>
</tr>
<tr>
<td>Molteno implants is an efficient surgery for PACG, that associates frequent post-surgery complications</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>In patients with transparent lens, hypotensor efficacy of phacoemulsification is similar to that of trabeculectomy with MMC, although with less reduction in post-surgery use of antiglaucoma drugs</td>
<td>1+</td>
<td>B</td>
</tr>
<tr>
<td>In patients with transparent lens, trabeculectomy determines more post-surgery complications than phacoemulsification</td>
<td>1+</td>
<td>B</td>
</tr>
<tr>
<td>In patients with cataract and PACG after iridotomy, phacoemulsification produces a significant IOP reduction and use of antiglaucoma drugs</td>
<td>2+</td>
<td>C</td>
</tr>
<tr>
<td>Viscogonioplasty or goniosynechialysis associated to phacoemulsification determines greater reduction of PAS extension but does not add ocular hypotensor efficacy to phacoemulsification. In addition, it could increase the risk of post-surgery complications</td>
<td>1–</td>
<td>B</td>
</tr>
<tr>
<td>Phacotrabeculectomy produces greater IOP reduction and antiglaucoma drug requirements than phacoemulsification on its own but determines greater frequency of post-surgery complications</td>
<td>1–</td>
<td>B</td>
</tr>
<tr>
<td>Combined phacoemulsification and NPDS surgery could be an efficient and safe alternative in some patients with PACG and cataract</td>
<td>3</td>
<td>D</td>
</tr>
</tbody>
</table>

Efficacy (IOP at 18 months follow-up of 15.1 ± 3.9 mmHg against 20 ± 6.9 mmHg with LI) and smaller IOP fluctuations (3.8 ± 2.1 mmHg against 5.44 ± 2.4 mmHg with LI).64

From non-comparative retrospective or prospective studies it can be deduced that trabeculectomy, either associated to antimetabolites64,65 or not66 produces a significant reduction in IOP, with results being poorer in medically not controlled primary acute angle closure cases64,67 which exhibit poor visual acuity and higher failure and complication rates.68

In relation with the use of releasable sutures in trabeculectomy of eyes with PACG, Liang et al. carried out a prospective and randomized study including 87 patients in the standard trabeculectomy group and 88 in the releasable suture group (two permanent and two releasable).89 Ocular hypotensor efficacy at 3 months was similar with both procedures. Transient hypotony was observed more frequently in the fixed suture group (20.4% vs 9.1%), without finding significant differences in the incidence of the rest of complications.89

In relation with patients with PACG and severe damage of the visual field (VF), Salmon et al. assessed the efficacy and safety of trabeculectomy in 46 eyes of 39 patients with advanced PACG. IOP < 21 mmHg was obtained in 91.1% of patients (66.7% without antiglaucoma drugs), with 8.9% of eyes requiring a second trabeculectomy in the three first years after the first intervention (re-intervened patients were younger). The most frequent complications were the appearance of cataract (19.6%), hyphema (13%) and athalamia (23.9%).90 However, at the present time lower IP values are required to consider surgical success in patients with severe glaucomatous damage.

From all the above studies it can be concluded that trabeculectomy is an efficient treatment for reducing IOP and fluctuations thereof in patients with PACG, although it exhibits complications in the immediate and long-term post-surgery. It is more efficient than iridotomy but its efficacy and safety cannot be established in relation to other glaucoma surgery treatments (level of evidence 2−, grade of recommendation C).

Non-perforating deep sclerectomy. At the theoretical level, the presence of angle closure in the area in which filtering surgery is performed is a contraindication for nonperforating deep sclerectomy (NPDS). The majority of studies comparing trabeculectomy with NPDS have been performed in OAPG and exhibit similar success rates, with lower incidence of complications after NPDS.91-93 Eldaly et al.94 compared five studies comprising 311 eyes, 160 of which were submitted to trabeculectomy and 151 to nonperforating procedures (NPDS or viscoanalostomy), but none of said studies included eyes with angle closure and even so this review finds reduced evidence to conclude the superiority of one technique over another.

No studies have been found assessing the efficacy of isolated NPDS in PACG; it has only been proposed in surgery combined with phacoemulsification, as discussed below.95 The consensus of the working group is that NPDS on its own is not indicated in the presence of angle closure in the surgical intervention area (level of evidence 4, grade of recommendation D; GCP).

Drainage devices for glaucoma. No systematic reviews or randomized clinical trials have been found comparing exclusively drainage devices for glaucoma (DDG) and trabeculectomy in PACG. However, there is a prospective and noncomparative series of cases that studied the long-term results of Molteno DDG in patients with PACG. Said series comprised 21 eyes of 17 patients with a mean follow-up of 5.7 years. With a baseline mean IOP of 29.31 mmHg, said study obtained a mean IOP of 14.7 mmHg at the end of the follow-up. Early post-surgery complications arose (athalamia 24%, choroidal...
Accordingly, PACG, iridocorneal extraction, and trabeculectomy were used in this study. The results show that Molteno implants in PACG patients are an efficient option albeit not free of significant complications (level of evidence 3, grade of recommendation D).66

On the other hand, the TVT study (the Tube versus Trabeculectomy Study), designed for comparing the efficacy and safety of DDG surgery and trabeculectomy with mitomycin C (MMC) (0.4 mg/ml), 8% of the 212 eyes in the study exhibited PACG, 7% received Baerveldt’s DDG as primary treatment and 11% were treated with trabeculectomy with MMC.67 The results at 5 years did not reveal different behavior of patients with PACG in relation to the overall sample, both in terms of survival and complications.68 Accordingly, the overall conclusions could be partially extrapolated to the PACG group.

After 5 years follow-up a significantly higher failure rate was found in the trabeculectomy group (46.9%) compared to the DDG group (29.8%). Although the failure rate in trabeculectomy is similar to that of previous studies, that of DDG was lower than previously described,69 which could be explained by the fact that the patients were pseudophakic. As the inclusion criteria required previous failure of cataract or filtering surgery and that patients with PAC or secondary represented less than 10% of the sample, the data obtained from this study cannot be extrapolated to patients with PACG.

Isolated lens surgery in primary angle closure glaucoma
It has been stated in PACG and ocular hypertension that lens extraction reduces IOP and converts the anatomic predisposition to angle closure.71,99-101 The lens plays an important role in the mechanism leading to PACG. Eyes with PACG have thicker lenses which have a more anterior position than normal eyes,102 which determines anterior chamber and iridocorneal angle amplitude reductions. Cataract surgery may deepen the angle and enlarge the anterior chamber, thus improving the anatomic conditions which determine PACG.100,102,103 A 2008 Cochrane review concludes that there is not enough evidence to indicate superiority of lens extraction over other procedures for controlling IOP or the visual field loss in PACG, although it seems a plausible approach and therefore the decisions taken in clinical practice should be based on the judgment of the ophthalmologist.72 In addition to said review, a search for more recent literature has been made on the subject.

Transparent lens surgery. In the absence of cataracts, the lens extraction and the time of this operation remain in open debate. It has been estimated that up to 50% of patients with PACG will develop cataracts and require surgery due to age and the effect of the treatment.57,58 It has been proposed that early lens extraction will improve control of glaucoma due to increased chamber angle, thus reducing the need of medication and filtering surgery. In addition, it would improve uncorrected visual acuity in patients with hypermetropia (frequently associated to PACG) due to refractive error correction.58

Thomas et al.73 made a non-systematic review assessing the role played by transparent lens extraction (TLE) in the treatment of adult PAC, extrapolating the results of different studies published in the case of patients with cataracts because they consider that the size of the lens (with the exception of the intumescent lens) does not generally increase due to cataracts. They concluded that the indication of TLE as treatment for PAC or PACG should depend on the extension of the synechial closure and must not exclude the need of trabeculectomy, particularly in medically not controlled PACG.

Tham et al.104 made a prospective study on 50 eyes of 50 patients over 50 years of age with medically not controlled PACG and without the presence of cataracts. The patients were randomized in two treatment groups: phacoemulsification with intraocular lens implant (n = 26) or trabeculectomy with MMC (0.4 mg/ml during 3 min) (n = 24). After 2 years follow-up, a similar statistically significant reduction was achieved in both groups (34% with phacoemulsification and 36% with trabeculectomy). However, in the trabeculectomy group the number of antiglaucoma drugs was reduced to zero, whereas in the phacoemulsification group the mean number of drugs was of one. In addition, 19% of eyes (n = 5) in the phacoemulsification group exhibited poor tension control and three required trabeculectomy. Surgical complications were more numerous in the trabeculectomy group with MMC: 46% of intervened eyes exhibited some type of complication (cataract eight eyes, choroidal detachment two eyes, bleb leak two eyes, hyperfiltration requiring trabeculectomy revision one eye).

The results of this study suggest that isolated phacoemulsification in PACG reduces IOP in a efficient manner, comparable to trabeculectomy with MMC, although the latter is more likely to avoid the need of antiglaucoma drugs in the post-surgery period. This study cannot be extrapolated to patients with PACG and coexistence of cataracts, which is assessed in the next section. The authors conclude that isolated phacoemulsification could be an alternative to trabeculectomy in subjects 50 years old or more with PACG which is not medically controlled and without presence of cataracts, who have conditions making them more susceptible to complications or when the patient wishes to avoid possible risks associated
to filtrating surgery. However, trabeculectomy increases the possibilities of avoiding antiglaucoma treatment in the post-surgery and higher post-surgery complication rates (level of evidence 1+, grade of recommendation B).

Clinically significant cataract surgery. Numerous studies have been published demonstrating that phacoemulsification produces IOP reduction in patients with PAGC, although the majority have focused exclusively on patients with acute angle closure.52,105

In a prospective study including 79 eyes with PAGC submitted to phacoemulsification, Hayashi et al. demonstrated that cataract surgery in patients with PAGC significantly and consistently diminished IOP after 2 years follow-up.90 None of the eyes required additional glaucoma surgery. In addition, the number of antiglaucoma drugs also diminished, with 40% of patients not needing topical medication after surgery.

Lai et al.91 performed a non-comparative, prospective case series study in 21 eyes of 21 patients with PAGC and clinically significant cataract with pressures controlled with topical medication or not controlled (mean follow-up: 20.7 months). They found that isolated cataract extraction can significantly reduce IOP (mean reduction of 4.2 mmHg) as well as the need for topical medication (from 9.91 to 0.52 drugs).

For patients with medically controlled or not controlled PAGC and clinically significant cataract in which the pupil blockage component has been eliminated by means of iridotomy, phacoemulsification significantly diminishes IOP and the need of antiglaucoma medical treatment (level of evidence 2+, grade of recommendation C).

Phacoemulsification combined with goniosynechiolysis or viscogonioplasty. Generally, in PAGC there are some iridocorneal angle areas that are permanently closed due to PAS. In these cases it has been proposed to associate goniosynechiolysis57,75,106 to phacoemulsification. This is performed injecting viscoelastic in the anterior chamber to give it supranormal depth. Subsequently, downward pressure is exerted with a blunt instrument in the most peripheral extreme of the iris adjacent to the insertion point in the angle so as to expose the trabecular mesh. The main complication is hemorrhage, which is more frequent in synechiae closure cases with long evolution periods.57,75,106,107

Teekhasanee and Ritch15 performed a noncomparative prospective study in 52 eyes of 48 Thai patients who exhibited AAC treated with iridotomy, IOP ≥ 21 mmHg with antiglaucoma treatment and presence of at least 180° of synechiae closure. They were submitted to phacoemulsification with IOL implant combined with goniosynechiolysis in the six first months after the AAC episode. In 90.4% of patients, IOP < 20 mmHg without medication was achieved (mean follow-up period: 20 months), with IOP reduction being correlated to the extension of recurring PAS. The most frequent complications were fibrin reaction in anterior chamber (more frequent when AAC was nearer surgery time), hypertensive peaks in the immediate post-surgery and limited hyphema. Said authors stated that the best time for surgery is 6 weeks after AAC.

Recently, Yor et al.108 have published a randomized clinical trial in 52 eyes of 39 patients with medically not controlled CPAGC and cataract, comparing goniosynechiolysis carried out before or after phacoemulsification. After surgery, anterior chamber depth was increased in both groups but in the group treated after phacoemulsification, the iris root was not sufficiently separated in some patients.

Another alternative is viscogonioplasty, utilizing high-density viscoelastic.109 After performing phacoemulsification, the high-density viscoelastic is injected first to increase anterior chamber depth and afterwards near the trabecular mesh but without touching it. As surgical instruments are not utilized to break PAS, the risk of complications such as hemorrhage or angle damage is reduced. In two prospective case series studies and a randomized clinical trial, Varma et al. have demonstrated its effectiveness in reducing IOP in patients with CPAGC with patent, medically not controlled iridotomy. However, they did not mention the amount of PAS before and after surgery and did not report details of gonioscopic findings.78,79,105,110

In a prospective study in 35 medically controlled eyes and 21 not controlled eyes with CPAGC, Razeghinejad and Rahat77 have demonstrated the effectiveness of this procedure, achieving absolute success rates of 40% and 38.1% respectively after 9 months of follow-up. In addition, the usefulness of this procedure has also been described for controlling IOP in two prospective case series studies of acute angle closure resistant to conventional treatment.78,111

Recently, in a controlled clinical trial comprising 65 eyes of 55 patients with medically not controlled PAGC and clinically significant cataract (follow-up of 6 weeks), Eslami et al.112 demonstrated that phacoemulsification, both isolated and combined with viscogonioplasty, produced chamber angle increases, greater anterior chamber depth, IOP reduction and PAS extension in patients. Even though it produced a greater reduction of PAS extension compared to isolated phacoemulsification, the addition of viscogonioplasty to phacoemulsification did not produce additional ocular hypotensor effect and caused a greater fibrin reaction in the anterior chamber during the immediate post-surgery.

In patients with clinically significant cataract and medically not controlled CPAGC, the addition of viscogonioplasty or goniosynechiolysis to phacoemulsification produced a greater reduction of PAS extension compared to isolated phacoemulsification but did not add greater effect for controlling short-term IOP and could increase the rate of immediate post-surgery complications (level of evidence 1–, grade of recommendation B).

Filtrating surgery combined with cataract

From a theoretical viewpoint, the combination of filtrating surgery and phacoemulsification is an attractive alternative for treating PACG with the coexistence of clinically significant cataract. However, no recommendations have been found in CPG or systematic reviews supporting the role of this technique for surgical treatment of PACG.

Tham et al.85 carried out a prospective and randomized clinical trial comparing phacoemulsification and phacotrabeculectomy (FT) with MMC in 72 patients with CPAGC...
adequately controlled with medical treatment. The results did not exhibit pressure differences between both groups neither in presurgery data nor after a minimum follow-up of 2 years. In the evaluations at months 1 and 3, IOP values were significantly lower in the FT group. Likewise, the number of antiglaucoma drugs was significantly lower in the FT group vis-à-vis the phacoemulsification group. No differences were found in optic disk changes or in perimetric progression between both groups. Visual acuity after surgery did not exhibit differences in the final follow-up. Intra-surgery complications exhibited similar rates in both procedures, while post-surgery rates were significantly more frequent in the FT group (14 complications, with seven cases of post-surgery hypotony) than in the phacoemulsification group (one complication).

Subsequently, in a similar study comprising 27 patients with cataract and pharmacologically not controlled CPACC, the same authors reached similar conclusions. On the basis of the joint results of the two previous publications, said authors presented a study aimed at assessing and comparing complication rates in the phacoemulsification and FT groups. No differences were found in the frequency of intra-surgery complications between both techniques (6.5% in the phacoemulsification group and 4.9% in the FT group). In contrast, post-surgery complications were significantly more prevalent in the combined surgery group. The group submitted to phacoemulsification on its own only exhibited one complication [posterior capsular fibrosis which required capsulotomy (1.6%)], whereas in the FT group 24.6% of the eyes exhibited post-surgery complications, the most frequent being hyphema (6.6%), anterior chamber flattening which required repositioning (4.9%) and bleb leak which required repair (3.3%).

In 2011, Deng et al. published a meta-analysis in order to compare the efficacy and safety of trabeculectomy, phacoemulsification and FT in PACG. Said study analyzed 5 randomized clinical trials and 11 controlled clinical trials, including 1495 eyes. In what concerns surgery success rates, the authors analyzed three controlled clinical trials comprising 274 eyes. The conclusions they obtained are as follows:

- The three procedures reduce IOP, with FT being superior to trabeculectomy and the latter superior to isolated phacoemulsification.
- The three procedures reduced the need of antiglaucoma drugs, with the reduction brought about by FT superior to that of phacoemulsification.
- No differences were appreciated in the surgical success rate between the three procedures.
- The three surgeries increased anterior chamber depth, with FT being superior to trabeculectomy and the latter to phacoemulsification.
- The three procedures similarly improved the exit ease coefficient.
- The three surgeries can improve visual acuity, although no differences were found between the FT and isolated phacoemulsification groups.
- Phacoemulsification was the technique which produced the lower amount of post-surgery complications.

Accordingly, it is concluded that FT achieves better ocular hypotensor effect and less need of antiglaucoma drugs when compared to phacoemulsification, with a comparable rate of intra-surgery complications but with higher post-surgery complication rate (level of evidence 1--, grade of recommendation B). These studies do not divide patients in relation to PAS extension and therefore the role this plays in the indication of isolated phacoemulsification or combined with trabeculectomy is not determined.

*Combined phacoemulsification and non-perforating deep sclerectomy surgery.* Only one study was found describing combined phacoemulsification and NPDS surgery for treating PACG, a retrospective study on 29 eyes of 26 patients with PACG who underwent combined phacoemulsification and NPDS procedure with hyaluronic acid implant and discretionary use of antinefobolites with a mean follow-up of 33.8 months. Mean presurgery IOP diminished from 20.3 to 15.9 mmHg and the mean number of topical drugs was reduced from 2.9 to 1. In addition, 14% of patients required post-surgery gonipuncture which produced efficient results. Overall, 52% of the eyes achieved complete success and 86% relative success, while 62% of eyes exhibited significant visual acuity improvement in the post-surgery. The complications described in the study include one choroidal effusion, three cases of external fistulization which required surgical repair and two punctate epitheliopathies. None of the cases exhibited anterior chamber flattening, hyphema, hypotonia or infection. Accordingly, in this retrospective case series, combined phacoemulsification and NPDS surgery proved efficient and safe in patients with PACG and cataract (level of evidence 3, grade of recommendation D).

**Limitations**

The limitations of the present CPG comprise that the majority of studies were carried out in Asian populations and therefore are not directly applicable to other ethnic groups.

Efficacy is measured in IOP reduction although most of the studies did not include functional parameters assessing glaucoma progression, which are the parameters which actually influence the visual capacity of patients.

There are no studies available on cost-effectiveness of the various treatments and procedures.

Finally, due to the scarcity of recent literature, in many sections the authors were obliged to extend their search further back in time in order to obtain sufficient information.

**Conflict of interests**

No conflict of interests has been declared by the authors.

**Acknowledgments**

Methodological support: Javier Zamora, Clinical Biostatistics Unit, Cochrane Collaborator Center, University Hospital Ramón y Cajal, IRYCIS, Madrid. Nieves Plana, Biostatistics Unit, Cochrane Collaborator Center, University Hospital Ramón y Cajal, IRYCIS, Madrid.
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