Pattern of Long-Term Intraocular Pressure Variation Following Gonioscopy-Assisted Transluminal Trabeculotomy: Two-Year Outcomes

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Précis: Patients with clinically uncontrolled open angle glaucoma submitted to isolated gonioscopy-assisted transluminal trabeculotomy or combined with phacoemulsification not only achieved low mean IOPs, but also demonstrated stable IOP patterns during a 24-month follow-up.

Purpose: To assess the impact of gonioscopy-assisted transluminal trabeculotomy (GATT) on long-term intraocular pressure (IOP) variation.

Patients and Methods: An unicentric retrospective study including 169 consecutive patients who had undergone standalone GATT or combined with phacoemulsification (PHACOGATT) due to clinically uncontrolled open angle glaucoma, with at least 12 months of follow-up was conducted. Long-term mean IOP, long-term IOP peak, long-term IOP fluctuation, coefficient of variation, mean-positive IOP variation, sustained clinically significant positive IOP variation, and number of follow-up visits with IOP $\geq$15 mm Hg were investigated.

Results: One hundred sixty-nine eyes from 169 patients were included (GATT group = 101 patients; PHACOGATT group = 68 patients). Mean long term IOP (12.0 ± 1.8 vs. 11.2 ± 2.0 mm Hg), mean long-term IOP peak (12.9 ± 2.6 vs. 11.8 ± 3.5 mm Hg), and mean coefficient of variation (0.07 ± 0.08 vs. 0.05 ± 0.09) were lower in the PHACOGATT group, while mean IOP fluctuation (1.0 ± 3.7 vs. 1.2 ± 1.8 mm Hg) was lower in the GATT group. In addition, the overall mean-positive IOP variation was 0.79 ± 1.64 mm Hg. Finally, only 6.5% of the patients presented sustained clinically significant positive IOP variation and IOP was $\geq$15 mm Hg in 5.9% of the follow-up visits.

Conclusions: Patients with clinically uncontrolled open angle glaucoma submitted to GATT or PHACOGATT achieved low mean IOPs and demonstrated stable IOP patterns. Our results provide additional evidence supporting GATT and PHACOGATT as viable options for the treatment of medically uncontrolled glaucoma patients requiring low and stable IOPs.

Key Words: gonioscopy-assisted transluminal trabeculotomy, long term intraocular pressure variation, minimally invasive glaucoma surgery

(*J Glaucoma* 2025;34:630–636)

Elevated intraocular pressure (IOP) is the major risk factor for glaucoma development and progression.[1–3] Incisional surgeries are often used in clinically uncontrolled cases, which did not respond to maximum tolerated topical therapy and laser surgery.[4,5] In this context, gonioscopy-assisted transluminal trabeculotomy (GATT) is a relatively new micro-invasive glaucoma surgery that improves aqueous humor flow through Schlemm canal, using a microcatheter or a polypropylene suture, consequently reducing IOP.[6,7]

It is well-established that IOP is a dynamic parameter that fluctuates over time. Long-term IOP variation, which can be obtained from single IOP measurements repeated during serial office visits, refers to the IOP variation that occurs over months to years. In this context, previous studies,[8–10] including large clinical trials,[11–14] have shown a significant association between long-term IOP variation and glaucoma progression. Therefore, evidence suggests that, in clinical practice, not only low IOPs but also stable IOPs may be important to reduce disease progression, especially in moderate to advanced glaucoma cases.[15,16]

Effectiveness of standalone GATT and phacoemulsification with intraocular lens implantation combined with GATT (PHACOGATT) on mean IOP reduction has been demonstrated in previous studies[6,7,17–19] and reports provide evidence that GATT is a viable option even in advanced glaucoma.[19–21] Nonetheless, these studies focused on the evaluation of mean IOP reduction in different timepoints, with special attention to success rates in the last follow-up visit and the impact on medication burden. Therefore, there is scant data when it comes to the effects of GATT and PHACOGATT on IOP variation, especially on long-term variation. The purpose of this study was to assess the impact of standalone GATT and PHACOGATT, as primary treatment options, on long-term IOP variation parameters in eyes with uncontrolled glaucoma.

Received for publication October 12, 2024; accepted March 9, 2025.
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Disclosure: The authors declare no conflict of interest.
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DOI: 10.1097/IJG.0000000000002565

MATERIALS AND METHODS

This was an unicentric, retrospective study, designed to assess the pattern of long-term IOP variation following standalone GATT and PHACOGATT surgeries in medically uncontrolled open angle glaucoma patients. This protocol adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committee and the institutional review board of the Onofre Lopes University Hospital. Due to the retrospective nature of the study, the requirement for written informed consent was waived.

Participants

We reviewed the charts of consecutive patients that had undergone GATT or PHACOGATT due to clinically uncontrolled open angle glaucoma, between January 2017 and May 2022, at the Glaucoma Sector of Onofre Lopes University Hospital (Natal, Brazil). In order to be included, participants had to have at least 5 postoperative IOP follow-up measurements and a minimum of 12 months of follow-up. Data were collected up to 24 months of follow-up, whenever available. When both eyes of the same patient were eligible for the study, only the right eye was arbitrarily chosen for analysis.

Glaucoma was defined as the presence of glaucomatous optic neuropathy (GON) associated with a characteristic visual field (VF) defect. We defined GON as cup-to-disc ratio >0.6, the asymmetry between eyes ≥ 0.2, the presence of localized defects of the retinal nerve fiber layer, and/ or neuroretinal rim in the absence of any other anomalies that could explain such findings. In addition, a patient was considered to be clinically uncontrolled based on anatomic and/or functional progression, or if IOP values were above the target range defined by the attending physician based on VF, optic nerve evaluation, age and risk factors, in accordance with the European Glaucoma Society guidelines.[22] Eyes that presented with angle closure glaucoma, any corneal disease or ocular trauma, or that had undergone any intraocular surgery or laser procedure within 6 months before GATT were excluded.

Procedures and Surgical Technique

All participants had undergone a comprehensive ophthalmological evaluation, including best-corrected visual acuity, slit-lamp biomicroscopy, tonometry, gonioscopy, dilated fundoscopy, VF testing (24-2 Swedish interactive threshold algorithm—Standard protocol, Humphrey Field Analyzer II; Carl Zeiss Meditec Inc., Dublin, CA), optic disc stereophotographs, and color/red-free fundus imaging. At each office visit, a single reliable IOP measurement was performed under topical anesthesia with a Goldmann applanation tonometer, before pupil dilation. Clinical and ocular data collected included age, race, sex, IOP, central corneal thickness (CCT), VF mean deviation (MD), previous intraocular surgery, and type of glaucoma were assessed at the baseline visit. Follow-up visits were scheduled at 1, 3, 6, 12, and 24 months postoperatively and additional follow-up visits were performed according to the clinician's discretion. Long-term IOP variation parameters were derived from the single IOP measurements repeated during serial office visits collected between months 3 and 24, in order to avoid the influence of possible confusion factors on IOP (such as corticosteroid effect, hyphema, and inflammation), that are usually observed during the initial postoperative period.

All surgeries were performed by a single surgeon (B.M.F), following a standard technique. Briefly, after superior nasal and temporal corneal paracentesis, a solution containing lidocaine and carbachol was injected in the anterior chamber. Afterwards, the anterior chamber was filled with methylcellulose 2% and a nasal goniotomy was created with a 26-gauge needle. A thermally blunted 5-0 polypropylene suture was then inserted through the goniotomy and circumferentially advanced with the aid of a 23-gauge serrated-tip microsurgical forceps. The distal tip of the suture was advanced by 360 degrees and was retrieved at the nasal goniotomy site and

TABLE 1. Baseline Clinical and Demographic Data of Study Patients

	GATT group (n = 101), (%)	PHACOGATT group (n = 68), (%)	*P*
Age (y)	69 (55; 76.2)	61 (57; 69.5)	0.02
Sex (M/F)	67.3/32.7	68.5/31.5	0.99
Race (White/Others)	79.2/20.8	60/40	0.01
Diagnosis			
POAG	68.3	80.8	0.11
Corticoid-induced glaucoma	8.9	2.9	0.09
Juvenile glaucoma	8.9	0	0.16
SOAG	8.9	0	0.16
Others	5.0	16.3	0.06
Baseline IOP (mm Hg)	23.5 ± 7.9	22.8 ± 8.9	0.32
Glaucoma severity			
Mild glaucoma	20.2	32.7	0.12
Moderate glaucoma	36.9	29.1	0.07
Advanced glaucoma	42.9	38.2	0.03
MD index (dB)	−11.0 (−18.1; −6.8)	−8.2 (−18.3; −3.4)	0.12
Previous glaucoma surgery (n)	31	5	<0.01
SLT	10	1	0.06
TRAB	17	4	0.06
MP-TSCP	4	0	0.09
Lens status (Phakic/Pseudophakic)	23.8/77.2	100/0	

Data is given as mean ± SD or median and interquartile intervals, whenever appropriate.

F indicates female; IOP, intraocular pressure; M, male; MD, mean deviation; MP-TSCP, micropulse transscleral cyclophotocoagulation; POAG, primary open angle glaucoma; SLT, selective laser trabeculoplasty; SOAG, secondary open angle glaucoma; TRAB, trabeculectomy.

TABLE 2. Long-Term IOP Variation Parameters

	Overall (n = 169), mm Hg	GATT Group (n = 101), mm Hg	PHACOGATT Group (n = 68), mm Hg	*P*
Long-term mean IOP	11.7 ± 1.9	12.0 ± 1.8	11.2 ± 2.0	0.01
Mean long-term IOP fluctuation	1.1 ± 3.2	1.0 ± 3.7	1.2 ± 1.8	0.01
Mean long-term IOP peak	12.5 ± 3.0	12.9 ± 2.6	11.8 ± 3.5	0.03
Mean-positive IOP variation	0.79 ± 1.64	0.62 ± 1.93	0.89 ± 1.40	0.01
Sustained clinically significant positive IOP variation (%)	11 (6.5%)	8 (7.9%)	3 (4.4%)	0.52

Data is given as mean ± SD, whenever appropriate.
IOP indicates intraocular pressure.

extracted from the anterior chamber, creating a circumferential trabeculotomy. In some cases where anatomic resistance was detected while advancing the suture, a new goniotomy was created to retrieve the distal tip, creating a partial trabeculotomy that ranged from 90 to 360 degrees. The viscoelastic substance was then removed from the anterior chamber by anterior chamber irrigation with a balanced saline solution. Acute hypotony and hyphema were controlled using an anterior chamber viscoelastic injection. The amount of viscoelastic substance left in the eye was determined based on the degree of blood reflux and the presence and degree of episcleral venous fluid wave.

In the PHACOGATT group, phacoemulsification with intraocular lens implantation was performed first, then, the trabecular meshwork was accessed with nasal goniotomy, followed by the ab interno trabeculotomy. The same paracentesis was used for goniotomy and phacoemulsification, without any difference from the ordinary phacoemulsification surgical technique.

The postoperative eyedrop regimen followed the same protocol for both groups. All patients were treated postoperatively with topical moxifloxacin (4 times daily for 1 wk) and corticosteroids (prednisolone 1%). The topical corticosteroids were initially applied every 4 hours, and this dose was then gradually tapered over the first month of treatment.

Main Outcomes

The main outcomes of this study were parameters associated with long-term IOP variation in each group and the comparison of these parameters between groups (GATT vs. PHACOGATT). In this context, long-term mean IOP was assessed as a central tendency metric, while long-term IOP peak and long-term IOP fluctuation were assessed as variability metrics. Long-term IOP peak was defined as the maximum IOP measurement during the follow-up, while long-term IOP fluctuation was defined as the within subject SD of each patient's mean IOP during the follow-up. The within subject SD was used as a variation metric, instead of the IOP range, as it is less affected by outlier measurements and coefficient of variation (CoV) analysis was also performed to assess variability. In addition, 2 other IOP variation metrics were investigated: (1) mean-positive IOP variation, which was calculated as the difference between mean long-term IOP peak values and mean long-term IOP values; (2) sustained clinically significant positive IOP variation, which was calculated as the percentage of patients that presented with an IOP of 15 mm Hg or higher at 2 consecutive follow-up visits. Finally, the number of follow-up visits with an IOP of 15 mm Hg or higher was also calculated.

Sampling and Statistical Analysis

Descriptive analysis was used to present demographic and clinical data. D'Agostino-Pearson test was performed to determine whether data had a normal distribution. Normally distributed data were presented as mean and SD, whereas non-normally distributed data were presented as median and interquartile intervals. Regarding the comparison between groups, normally distributed data were compared using ANOVA, whereas non-normally distributed data were compared using the Kruskal-Wallis test. The Fischer exact test or χ^2 test were performed to evaluate

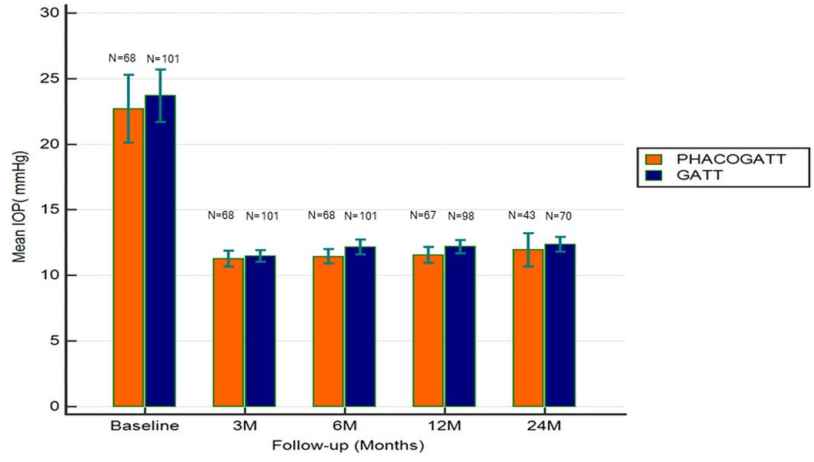

FIGURE 1. Long-term variation of mean IOP during follow-up. Figure 1 can be viewed in color online at www.glaucomajournal.com.

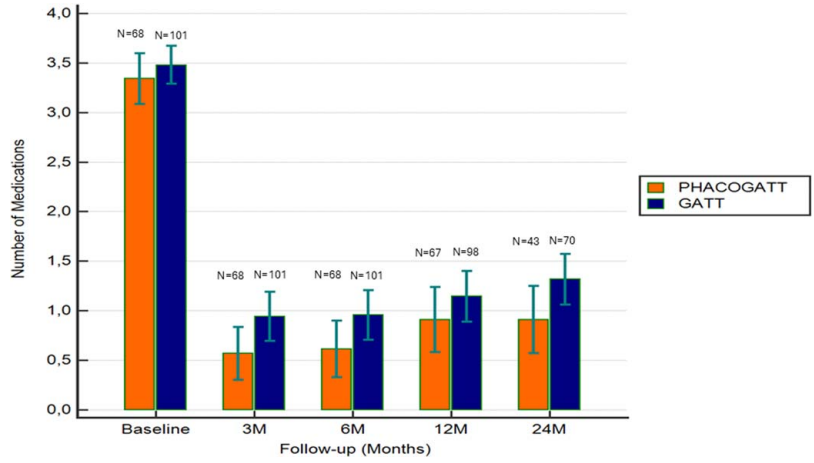

FIGURE 2. Long-term variation of the number of medications during follow-up. Figure 2 can be viewed in color online at www.glaucomajournal.com.

categorical variables whenever appropriate. Computerized analysis was performed using MedCalc software (MedCalc Inc., Mariakerke, Belgium) and statistical significance was set at $P < 0.05$.

RESULTS

A total of 169 eyes (169 patients) were included: 101 eyes in the standalone GATT group and 68 eyes in the PHACOGATT group. The mean follow-up duration was 19.8 ± 6.5 months in the standalone GATT group and 19.9 ± 6.1 months in the PHACOGATT group. The GATT group was older, had a higher percentage of white patients, had more advanced glaucoma patients and had a significant higher prevalence of previous glaucoma surgery than the PHACOGATT group. Baseline clinical and demographic characteristics data are presented at Table 1.

Considering IOP measurements at all timepoints in each group, no significant difference was found between IOPs at 3, 6, 12, and 24-month follow-up, within the standalone GATT group ($P \geq 0.09$), nor within the PHACOGATT group ($P \geq 0.16$).

When long-term IOP variation parameters were compared between groups (data presented as GATT vs. PHACOGATT, respectively), mean long-term IOP (12.0 ± 1.8 vs. 11.2 ± 2.0 mm Hg; $P = 0.01$), mean long-term IOP peak (12.9 ± 2.6 vs. 11.8 ± 3.5 mm Hg; $P = 0.03$) and mean coefficient of variation (0.07 ± 0.08 vs. 0.05 ± 0.09; $P = 0.01$) were lower in the PHACOGATT group, while mean IOP fluctuation (1.0 ± 3.7 vs. 1.2 ± 1.8 mm Hg; $P = 0.01$) was lower in the standalone GATT group. Nonetheless, although statistically significant, the differences found in mean long-term IOP (0.8 mm Hg) mean long-term IOP peak (1.1 mm Hg), mean IOP fluctuation (0.2 mm Hg), and mean coefficient of variation (0.02) were not clinically relevant.

Overall mean-positive IOP variation (difference between overall mean long-term IOP peak values and long-term mean IOP) was 0.79 ± 1.64 mm Hg and only 11 (6.5%) patients presented sustained clinically significant positive IOP variation. When the total of 615 follow-up visits was evaluated, IOP was 15 mm Hg or higher in only 40 visits, representing only 5.9% of the follow-up visits. When these 40 follow-up visits where IOP was 15 mm Hg or higher were assessed, change in the glaucoma treatment was indicated in 17 (42,5%) of them. Detailed data on long-term IOP variation parameters are presented at Table 2 and long-term variation of mean IOP and number of medications during follow-up are presented at Figure 1 and Figure 2, respectively.

Finally, comparing the differences in IOP measurements between groups at all timepoints, lower IOP values were observed in the PHACOGATT group at months 6 and 12 during follow-up, although no statistically significant difference was found between groups at the last follow-up visit (month 24). At 24-month follow-up, the mean IOP was 12.3 ± 2.3 mm Hg in the standalone GATT group and 11.9 ± 4.1mm Hg in the PHACOGATT group ($P = 0.07$), while the number of hypotensive medications was 1.3 ± 1.0 in the GATT group and 0.9 ± 1.1 in the PHACOGATT group ($P = 0.06$). Data regarding IOP and a number of medications at all timepoints are presented at Table 3.

TABLE 3. Comparison of IOP and Number of Medications at All Timepoints Between Groups

	GATT group (n = 101)	PHACOGATT group (n = 68)	*P*
IOP			
Baseline	23.5 ± 7.9	22.8 ± 8.9	0.32
3 mos	11.6 ± 1.8	11.1 ± 2.1	0.14
6 mos	12.1 ± 2.4	11.1 ± 1.7	< 0.01
12 mos	12.0 ± 2.0	11.2 ± 1.8	0.01
24 mos	12.3 ± 2.3	11.9 ± 4.1	0.07
No. medications			
Baseline	3.4 ± 0.8	3.1 ± 0.8	0.26
3 mos	0.9 ± 1.0	0.8 ± 1.4	0.14
6 mos	0.9 ± 1.0	0.6 ± 0.9	0.06
12 mos	1.1 ± 1.0	0.8 ± 1.0	0.08
24 mos	1.3 ± 1.0	0.9 ± 1.1	0.05

Data is given as mean and SD whenever appropriate.
IOP indicates intraocular pressure.

DISCUSSION

Elevated IOP and larger long-term IOP variation represent important risk factors for glaucoma progression. In this context, glaucoma treatment relies on sustained IOP

reduction focusing on stable and low IOP levels to avoid glaucoma progression. In this study, evaluating almost 170 patients with clinically uncontrolled glaucoma, we found that long-term IOP variation parameters following GATT and PHACOGATT surgeries not only demonstrated low mean IOPs over time but also provided highly stable IOP patterns. The authors are unaware of previous studies reporting such findings.

The impact of long-term IOP variation on glaucoma progression has been investigated in previous studies. On one hand, in the advanced glaucoma intervention study (AGIS)[13,14] and in the Collaborative Initial Glaucoma Treatment Study (CIGTS),[11,12] IOP fluctuation (range or SD) and IOP peak were independent and even stronger predictors than mean IOP for VF progression. In contrast, other studies, such as the ocular hypertension treatment study (OHTS), Early Manifest Glaucoma Trial (EMGT), and Ocular Hypertension Treatment in Diagnostic Innovations in Glaucoma Study (DIGS), found no influence of IOP variation parameters on VF progression.[23–25] A careful look reveals significant differences between these studies' populations, mainly related to baseline disease stages and treated IOP levels during follow-up. Even though these studies' results appear contradictory at first glance, they can be, in fact, complementary. Overall, when combined, their findings suggest that although IOP variation/fluctuation is not a significant risk factor for eyes with ocular hypertension or mild/moderate glaucomatous damage, it significantly impacts eyes with more advanced glaucoma, in which target IOP is usually set at low teens.[15]

The pattern of long-term IOP variation following glaucoma surgeries has been investigated in a few previous studies. In the AGIS study, in which the chosen surgical procedure for IOP reduction was trabeculectomy, the authors reported that IOP fluctuation was an independent and stronger predictor of VF progression than mean IOP, and the odds for VF progression increased by ~40% for each 1 mm Hg increase (of SD) in IOP fluctuation compared with 12% for each 1 mm Hg increase (of SD) in mean IOP.[13] In addition, Hong et al,[9] observed that, in patients undergoing combined phacoemulsification and trabeculectomy and IOPs consistently below 18 mm Hg, those with larger fluctuation (>2 mm Hg) had greater VF deterioration. These findings reinforce that patients with advanced glaucoma, often undergoing surgery during the course of the disease to achieve glaucoma control, need not only low, but also stable IOPs. When GATT is considered, there is growing evidence on GATT and PHACOGATT regarding their effectiveness on mean IOP reduction and reports provide evidence that GATT is a viable option even in advanced glaucoma.[19–21] Nonetheless, these studies have focused on the evaluation of mean IOP reduction in different timepoints, with special attention to success rates in the last follow-up visit and impact on medication burden without any long-term IOP fluctuation analysis. We understand that, since this surgical technique has been proposed for the treatment of moderate to advanced glaucoma patients and evidence suggest that IOP fluctuation impacts more eyes with advanced glaucoma than eyes with less damage,[15] studies assessing IOP fluctuation in the context of GATT surgery are necessary. In our study, even though VF progression was not evaluated, patients submitted to GATT and PHACOGATT achieved low mean IOP values (overall mean IOP of 11.7 mm Hg), in conjunction with stable IOP patterns [overall mean IOP fluctuation (within subject SD) of 1.1 mm Hg and mean IOP peak of 12.8 mm Hg] during 24 months of follow-up. These new and positive findings, related to how GATT and PHACOGATT, as primary surgical procedures, impact long-term IOP variation parameters, reinforce their role as an additional surgical alternative for managing eyes with clinically uncontrolled glaucoma.

In this context, in order to provide more clinically meaningful information, we have proposed 2 different long-term IOP metrics in this study: mean-positive IOP variation and sustained clinically significant positive IOP variation. The first parameter, which aimed to provide an estimation of how IOP rises on average, across visits, compared with patients' mean IOP, revealed a small mean-positive IOP variation of <1 mm Hg. In addition, only 10% of the patients presented elevations of more than 2 mm Hg above their long-term mean IOP during the study follow-up period. The second parameter focused on a real clinical scenario that physicians frequently face after a glaucoma surgery: when an IOP peak is detected, how IOP behaves in the following visit? Can patients' IOP control be promptly restored with changes in the medication regimen? In our study, following GATT and PHACOGATT, an IOP of 15 mm Hg or higher was documented at 2 consecutive follow-up visits in <7% of the patients, reinforcing the stable pattern of sustained low IOPs presented by these patients during the 24-month follow-up.

In the face of our results, we believe it is important to discuss the main implications of our findings. In a review article about the importance of IOP fluctuation, Kim and Caprioli[16] proposed that, in order to prevent glaucoma progression, quality-based IOP control may be more important than quantity-based IOP reduction. This means that we should consider glaucoma treatment in terms of IOP modulation rather than simply IOP reduction. In other words, mean low IOPs are important, but sustained low IOPs and reduced peaks may be as important to control the disease, especially in patients with advanced disease and low IOP targets (often after surgery).[15] In this context, our findings that 93.5% of the patients did not present sustained clinically significant positive IOP variation and the observation that IOP was lower than 15 mm Hg in 94.1% of the follow-up appointments, also reinforce the low, sustained, and stable IOP profile following GATT and PHACOGATT. We believe these findings support the suggestion that both surgeries are viable options for the treatment of medically uncontrolled glaucoma patients requiring low and stable IOPs. It is worth noting that although the 15 mm Hg upper IOP limit for these parameters was arbitrarily chosen, it was defined according to previously published target IOP values and patients' disease severity (based on functional loss).[2,13,14] Almost 75% of the patients undergoing GATT and PHACOGATT in our study had moderate or advanced glaucoma. Having in mind a mean long-term IOP target between 12 and 13 mm Hg during the study follow-up, the chosen IOP value of 15 mm Hg appears an acceptable upper IOP limit based on the target IOP levels for patients with moderate to advanced glaucoma damage (which has been the profile of patients most often submitted to GATT surgery).

The comparison of long-term IOP parameters between groups revealed some differences that deserve further discussion. Mean long-term IOP, means long-term IOP peak, and mean coefficient of variation were lower, and there was a trend for less medication in the PHACOGATT group, while mean IOP fluctuation was lower in the

standalone GATT group. At first glance, these findings may suggest that phacoemulsification surgery improves GATT results, nonetheless a more detailed analysis is necessary. First, it is worth noting some differences between groups that may play an important role in those findings. The GATT group was older, had a higher percentage of white patients, had more advanced glaucoma patients and had a significant higher prevalence of previous glaucoma surgery than the PHACOGATT group. Even though previous reports present encouraging results in advanced-age patients,[26] advanced glaucoma[19–21] and eyes with previous glaucoma surgery,[27,28] studies have also demonstrated older age,[18,29] previous glaucoma surgeries,[27,28] and advanced glaucoma damage[30] to have a significant negative impact on surgical success rates. This finding may be related to the pathophysiological sequence implicated in aqueous outflow resistance. Trabecular meshwork malfunction appears to prompt a reduction in the dimension of the Schlemm canal and collector channel network.[31,32] In this context, a distal downstream pathway restriction to aqueous flow can be more pronounced in eyes with longer exposure to the disease.[32,33] Hence, younger individuals (age would be considered a surrogate measurement for the time of exposure to the disease), patients with milder disease and patients not previously submitted to glaucoma surgery would have less functional damage to the collector downstream system and would benefit the most from GATT. Regarding the impact of race on surgical outcomes, unlike the well-established impact of race on filtrating surgeries, there is no clear and consistent evidence about the influence of race in angle surgery. In contrast, it is worth noting that previous studies compared surgical success outcomes between GATT and PHACOGATT. Some studies found no difference between groups,[18,19] while Bozkurt et al[34] found a more pronounced reduction in IOP after standalone GATT, but the results might also have been influenced by older age in the PHACOGATT group. In the context of other minimally-invasive glaucoma surgeries, Guedes et al,[35] found better surgical outcomes by combining cataract surgery with a trabecular bypass procedure. The authors proposed that this finding might be related to the fact that fluidics during phacoemulsification surgery could open, wash, and "prime" the trabecular and post-trabecular outflow system, facilitating the exit of the aqueous humor from the anterior chamber. Nonetheless, they also suggest caution with that conclusion since surgery might have been indicated earlier in combined cases as patients were already being submitted to phacoemulsification and early-stage glaucoma is associated with better outcomes. Finally, we understand that although the differences found in mean long-term IOP (0.8 mm Hg) mean long-term IOP peak (1.1 mm Hg), mean IOP fluctuation (0.2 mm Hg), and mean coefficient of variation (0.02) were statistically significant, they were not clinically relevant. All these considered, we believe that our results are insufficient to support the assumption that phacoemulsification surgery improved GATT results.

The present study has some limitations that should be addressed. First, due to the retrospective, nonrandomized design of the study, not only the selection of patients may have been influenced by the surgeon's decision to perform GATT instead of other surgical techniques, but also, the surgeon was inevitably not masked to the surgical intervention. Of note, this might have resulted at least in some degree of selection bias, since some patients at higher risk of failure were probably submitted to trabeculectomy (or any other filtering procedure) instead of GATT, which should be considered while interpreting our findings, as it might have influenced surgical outcomes. Second, also due to the retrospective design of the study, some follow-up loss was observed, especially in the 24-month follow-up. Nonetheless, we believe that the large initial sample included in the study at least mitigated this issue. Third, even though IOP fluctuation parameters are important risk factors for glaucoma progression, VF progression was not evaluated in our study. We believe that a longer follow-up period would be necessary for an adequate assessment of functional progression. Fourth, the behavior of long-term IOP variation before surgery might be considered important additional information. Nonetheless, patients included in this study were clinically uncontrolled glaucoma patients referred to surgical treatment in a reference hospital, therefore, in order to avoid glaucoma progression, these patients have not been followed without glaucoma surgical interventions and long-term fluctuation data are not available. Fifth, some might consider that short-term fluctuation data, such as diurnal IOP curves, could be useful for a more detailed IOP evaluation. We understand that although some parameters correlate significantly, they may not reflect the long-term IOP profile of stable open angle glaucoma patients, as their agreement is poor and many of these patients may experience test IOP peaks, despite long-standing stable disease and unchanged medical regimen.[36] Also, previous studies that demonstrated the association of glaucoma progression and long-term IOP fluctuation, such as the Advanced Glaucoma Intervention Study, used the same IOP measurement strategy performed in our study. Therefore, we believe that multiple IOP measurements during follow-up is the most adequate strategy to assess long-term fluctuation. Another limitation is that IOP variation parameters during the first 3 months of follow-up were not included in this analysis. We believe that IOP variations during this period are more influenced by transitory factors, such as bleeding, the use of topical corticosteroids, and intraocular inflammation, and, therefore, we chose not to include this period in the analysis. Subsequent studies assessing this specific postoperative period are suggested. In addition, since this is a retrospective, real-life scenario study, the time of the day when IOP was measured was not controlled in a standard manner and was variable between different patients, which we understand can influence IOP variation. Finally, due to the inherent limitations of retrospective studies, prospective and randomized comparative studies assessing long-term IOP parameters are also suggested.

In conclusion, while assessing long-term IOP variation in patients with clinically uncontrolled open angle glaucoma submitted to GATT and PHACOGATT, we found that these patients not only achieved low mean IOPs, but also demonstrated highly stable IOP patterns during a 24-month follow-up period. Our results provide additional evidence that supports GATT and PHACOGATT surgeries as viable options for the treatment of medically uncontrolled glaucoma patients requiring low and stable IOPs.

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