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ORIGINAL ARTICLE

Early beta-blocker-carbonic anhydrase inhibitor fixed combination use after Ahmed glaucoma valve implantation

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Abstract

Purpose: Ahmed glaucoma valve (AGV) implantation is an effective surgical option for glaucoma. However, subconjunctival fibrosis is a limiting factor that decreases surgical success. It has been proposed that introducing aqueous suppressants (AS) in the early post-operative period may reduce subconjunctival inflammatory mediators and fibrotic reactions. Starting AS early, before intraocular pressure (IOP) rises, may reduce plate fibrosis and improve post-operative surgical outcomes.

The objective of this study was to evaluate the effect of the early introduction of a timolol and carbonic anhydrase inhibitor (TCAI) fixed combination, a commonly used AS drug, on the outcomes of AGV implantation.

Methods: This study included all eyes that underwent AGV implant surgery between 2017 and 2022. Eyes that received TCAI within the first 2 post-operative weeks to reduce IOP or control subconjunctival fibrosis around the plate were included in Group 1. Group 2 consisted of eyes in which antiglaucoma medications were introduced stepwise only when IOP increased during follow-up visits after the first 2 post-operative weeks. Patients who received antiglaucomatous drugs other than TCAI within the first 2 post-operative weeks were excluded. Follow-up data were analyzed and compared between the two groups in terms of IOP control and surgical success.

Results: IOP decreased from 36.8±10.3 mmHg and 37.5±12.0 mmHg to 13.5±5.49 mmHg and 14.5±6.47 mmHg at the last visit in Groups 1 and 2, respectively ($p<0.001$ for both). Surgical success at the last visit was 86.1% in Group 1 and 78.2% in Group 2 ($p>0.05$). The median number of needling procedures showed a significant difference between the groups: 0 (range, 0–2) in Group 1 and 1 in Group 2 (range, 0–4) ($p<0.05$). Although TCAI therapy was initiated when IOP was >10 mmHg in Group 1, no hypotony-related complications were observed in this group.

Conclusion: Initiating TCAI in the early post-operative period after AGV implantation has a beneficial effect in reducing the need for needling procedures.

Keywords: Ahmed glaucoma valve; brinzolamide-timolol; dorzolamide-timolol; timolol-carbonic anhydrase inhibitor fixed combination.

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Ahmed glaucoma valve (AGV) (New World Medical, Rancho Cucamonga, California, USA) is a glaucoma drainage device used worldwide. They are primarily indicated for refractory or advanced glaucomatous eyes or eyes unresponsive to other medical or surgical treatment options.[1] The AGV is an explant that provides aqueous drainage from the anterior chamber to the subconjunctival space through its tube.[2] The AGV FP7 model has a plate with a 184-mm2 draining surface area.[2] It has a valve mechanism that prevents over-filtration and ensures one-way aqueous drainage through the tube when intraocular pressure (IOP) exceeds 6 mmHg.[2] This valve mechanism allows for immediate post-operative controlled drainage, aiding physicians in achieving early IOP control after tube surgery. Despite its efficacy, certain factors limit surgical success.[3] The most important of these is the early conjunctival fibrous tissue reaction around the plate, which limits drainage.[4] Some researchers have suggested that early post-operative intraocular inflammation and the subconjunctival access of inflammatory mediators through aqueous drainage are important causes of the fibrous subconjunctival reaction.[5] Another proposed mechanism is the early establishment of intra-bleb hydrostatic pressure, which may trigger bleb fibrosis.[6]

Reducing aqueous humor (AH) production in the early post-operative period may lower IOP and decrease the rate of drainage through the tube, thereby reducing the transport of inflammatory mediators to the subconjunctival space.[7] This reduction in AH access may help prevent the development of bleb fibrosis. Timolol-carbonic anhydrase inhibitor (TCAI) fixed combination drugs decrease AH production synergistically through non-selective β-adrenergic receptor blockade and inhibition of carbonic anhydrase enzyme activity in the ciliary pigment epithelium. Two forms of TCAI fixed combinations are commercially available: dorzolamide 2% + timolol 0.5% (DT) and brinzolamide 1% + timolol 0.5% (BT), both of which are applied twice daily.

Early studies have reported better IOP control after AGV implantation with the use of early aqueous suppressant (AS) drugs.[6,8,9] We propose that the early introduction of a TCAI fixed combination may improve surgical outcomes by reducing subconjunctival fibrosis following AGV implantation. In this retrospective study, we aimed to evaluate the effect of the early introduction of TCAI fixed combination drops in eyes that underwent AGV implantation in terms of IOP control, surgical success, needling rates, and hypertensive phase (HP) development.

Materials and Methods

This retrospective study was conducted at a single tertiary eye center and adhered to the principles of the Declaration of Helsinki and its recent revisions. Approval was obtained from the Local Ethics Committee (registration code: HNEAH-KAEK 2023/12-4060).

Patient files from those who underwent AGV implantation for advanced and refractory glaucoma between January 2017 and December 2022 were reviewed. Patients of any age and with any etiology of glaucoma who had undergone AGV implantation to manage glaucoma were included, which provided that they had at least 6 months of post-operative follow-up and complete patient records. Patients with previous glaucoma implants, those with <6 months of follow-up, and those with incomplete records were excluded from the analysis.

All surgeries were performed by experienced glaucoma surgeons using a modified long scleral tunnel technique with a fornix-based approach, as described by Kugu et al.[10] Three scleral incisions were made at 10–12 mm, 6–8 mm, and 1.5–2 mm from the limbus using a 60° bevel-up 2.0-mm crescent knife, creating two scleral tunnels. After priming, the AGV plate was secured to the sclera with two absorbable 7/0 Vicryl sutures, 8–10 mm from the limbus. The silicone tube was advanced through the scleral tunnel, and the tip of the tube was implanted into the anterior chamber through a scleral incision made with a 20-gauge microvitreoretinal knife. At the end of the procedure, subconjunctival gentamicin and dexamethasone injections were administered. Post-operative drug therapy included topical antibiotic drops 4 times daily for 1 week and prednisolone acetate every 2 h until bedtime for 2 weeks, followed by 4 times daily for 6 additional weeks with a tapering schedule.

Patient records were reviewed to determine the use of post-operative antiglaucomatous drugs, including the molecules introduced and the timing of their initiation. Cases in which TCAI fixed combination drugs (both DT and BT) were initiated within the first 2 post-operative weeks formed Group 1, while patients who did not receive any TCAI fixed combination or other antiglaucomatous drugs within the first 2 post-operative weeks were assigned to Group 2.

TCAI fixed combination therapy was in the early post-operative period when IOP exceeded 15 mmHg to reduce IOP or when signs of subconjunctival fibrosis were observed, which provided that IOP was not below 10 mmHg. To prevent hypotony and related complications, early IOP

control visits were scheduled within a week after initiating TCAI therapy. The patients in Group 1 continued using TCAI fixed combination drugs for at least 3 months. After 3 months, the treatment was either discontinued, continued with the same regimen, or adjusted based on IOP levels. The patients in Group 2 received antiglaucomatous drugs only if IOP increased after the first 2 post-operative weeks. Patients who received IOP-reducing therapies other than TCAI fixed combination within the first 2 post-operative weeks were excluded from the analysis.

Data collected including patient age, sex, glaucoma type, lens status, visual acuity in logMAR, past intraocular surgeries (including intravitreal anti-vascular endothelial growth factor injections, pan-retinal photocoagulation, and transscleral cyclophotocoagulation), the number of active glaucoma medication molecules preoperatively and at the last visit, IOP preoperatively and postoperatively (1st day, 1st week, 2nd week, 1st month, 3rd month, 6th month, 1st year, and last visit), follow-up duration, early post-operative TCAI fixed combination use, HP development, needling procedures, additional revisional procedures, other surgical interventions, and changes in visual acuity. In this paper, the term "number of glaucoma medications" refers to the number of active anti-glaucomatous molecules used.

Surgical success was defined as achieving a ≥20% reduction in IOP and IOP ≤21 mmHg without additional glaucoma surgery for IOP control or serious complications (e.g., phthisis bulbi, and loss of light perception). Failure was defined as IOP >21 mmHg on two consecutive visits, additional surgery for glaucoma control, or AGV explantation due to hypotony or anatomic reasons. HP was defined as an increase in IOP above 21 mmHg within 6 post-operative months, not attributable to mechanical complications, such as tube obstruction by the iris or vitreous.

Groups 1 and 2 were compared for IOP changes, HP occurrence, needling procedures, and surgical success.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User, version 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics were presented as the number of units, percentage, mean±standard deviation, median, minimum, maximum, and interquartile range values. The normality of the data distribution of numerical variables was evaluated using the Shapiro-Wilk test of normality. The homogeneity of variances was evaluated using Levene's test. First and last-visit IOP and logMAR values were compared using the paired t-test, and the number of glaucoma medications was compared using the Wilcoxon test. In the comparison of two-category groups and numerical variables, the independent-samples t-test was used if the data were normally distributed, and the Mann–Whitney U-test was used otherwise. The Chi-square test was conducted to compare categorical variables with each other. Survival probabilities for failure status were calculated using Kaplan–Meier analysis, and survival times were compared between Groups 1 and 2 using log-rank (Mantel-Cox) analysis. $P<0.05$ was considered statistically significant.

Results

The medical records of all patients who underwent AGV implantation between 2017 and 2022 were reviewed. A total of 36 eyes from 36 patients who received early TCAI therapy were included in Group 1, while 133 eyes from 133 patients who did not receive any early glaucoma medication were included in Group 2. Among these, 25 (69.4%) patients in Group 1 and 91 (68.6%) in Group 2 were male ($p>0.05$). The median age was 54.9±23.7 years in Group 1 and 58.2±17.5 years in Group 2 ($p>0.05$). The median follow-up period was 17.9 months in Group 1 and 23.6 months in Group 2 ($p=0.001$). Glaucoma-type distribution, lens status, and other characteristics of the groups are shown in Table 1. A statistically significant difference was observed in glaucoma-type distribution, with primary open-angle glaucoma and secondary glaucoma being more frequent in Group 2 ($p=0.023$).

As shown in Table 2, the mean preoperative IOP was 36.8±10.3 mmHg in Group 1 and 37.5±12.0 mmHg in Group 2. Postoperatively, IOP decreased to 14.4±11.1 mmHg and 12.4±8.7 mmHg on the 1st post-operative day and 13.5±5.49 mmHg and 14.5±6.47 mmHg at the last visit in Groups 1 and 2, respectively ($p<0.001$ for both). The IOP change curve over time for both groups is shown in Figure 1.

Preoperatively, the median number of glaucoma medications was 3 in Group 1 and 4 in Group 4. At the last visit, this number was reduced to a median of 2 in both groups ($p=0.02$ for Group 1 and $p<0.001$ for Group 2). The mean logMAR visual acuity values of Groups 1 and 2 were 2.3±0.8 and 1.9±1.0, respectively, in the pre-operative period. At the last visit, these values were 2.4±0.8 ($p=0.507$) and 2.1±1.0 ($p=0.011$) for Groups 1 and 2, respectively.

HP was detected in 19 eyes (54.3%) in Group 1 and 73 eyes (55.3%) in Group 2 ($p>0.05$) (Chi-square test). The median number of needling procedures with antimetabolite for encapsulated blebs was 0 (0–2) in Group 1 and 1 (0–4) in

Table 1. Descriptive characteristics of the groups

Variables	Group 1 n=36	Group 2 n=133	Statistics (P-value)
Age (SD)	54.9 (23.7)	58.2 (17.5)	0.806*
Sex (%)			
Male	25 (69.4)	91 (68.6)	>0.999†
Female	11 (30.6)	42 (31.6)	
Laterality (%)			
Right	19 (52.8)	67 (50.4)	0.852†
Left	17 (47.2)	66 (49.6)	
Visual acuity (logMAR), mean (SD)	2.27 (0.86)	1.90 (1.04)	0.064‡
Lens status, n (%)			0.503†
Aphakic	5 (13.9)	12 (9)	
Phakic	11 (30.6)	51 (38.3)	
PCIOL	20 (55.6)	66 (49.6)	
SFIOL	0	4 (3)	
Glaucoma type, n (%)			0.023†
Aphakic glaucoma	4 (11.2)	1 (0.8)	
Congenital glaucoma	1 (2.8)	1 (0.8)	
NVG	17 (47.2)	53 (39.8)	
POAG	1 (2.8)	17 (12.8)	
PACG	1 (2.8)	3 (2.3)	
PEXG	7 (19.4)	22 (16.5)	
Secondary	5 (13.9)	33 (24.8)	
Uveitic	0	3 (2.3)	
Number of pre-operative surgeries, median (min–max)	2.5 (1–5)	2 (0–5)	0.093*
Number of pre-operative glaucoma medications, median (min–max)	3 (1–4)	4 (0–4)	0.079*
Pre-operative IOP (mmHg), mean (SD)	36.8 (10.3)	37.5 (12.0)	0.757‡
Follow-up duration (months), mean (min–max)	17.9 (6–69)	23.6 (7–55)	0.001*
Number of needling procedures, median (min–max)	0 (0–2)	1 (0–4)	0.037*

*Mann–Whitney U-test; †Chi-square test; ‡t-test; SD: Standard deviation; PCIOL: Posterior chamber intraocular lens; SFIOL: Scleral fixation intraocular lens; NVG: Neovascular glaucoma; POAG: Primary open-angle glaucoma; PACG: Primary angle closure glaucoma; PEXG: Pseudoexfoliative glaucoma; IOP: Intraocular pressure.

Table 2. Pre-operative and last-visit IOP, glaucoma medication, and logMAR changes

	Pre-operative	Last visit	Test value	p
IOP				
Group 1	36.8±10.3	13.5±5.49	119.9	<0.001‡
Group 2	37.5±12.0	14.5±6.47	432.5	<0.001‡
Glaucoma medication				
Group 1	3 (1)	2 (3)	−3.03	0.02†
Group 2	4 (1)	2 (3)	−6.01	<0.001†
logMAR				
Group 1	2.3±0.8	2.4±0.8	0.44	0.507‡
Group 2	1.9±1.0	2.1±1.0	6.62	0.011‡

Data are given as mean±standard deviation or median (interquartile range) values; ‡Paired t-test; †Wilcoxon test; IOP: Intraocular pressure.

Group 2 (p=0.037) (Mann–Whitney U-test). At least, one needling procedure was performed in 8 (22.2%) eyes in Group 1 and 50 eyes (37.5%) in Group 2 during the follow-up period.

Surgical success at the last visit was achieved in 31 eyes (86.1%) in Group 1 and 104 eyes (78.2%) in Group 2. The cumulative survival probabilities of the groups according to failure time are shown in Figure 2. The estimated

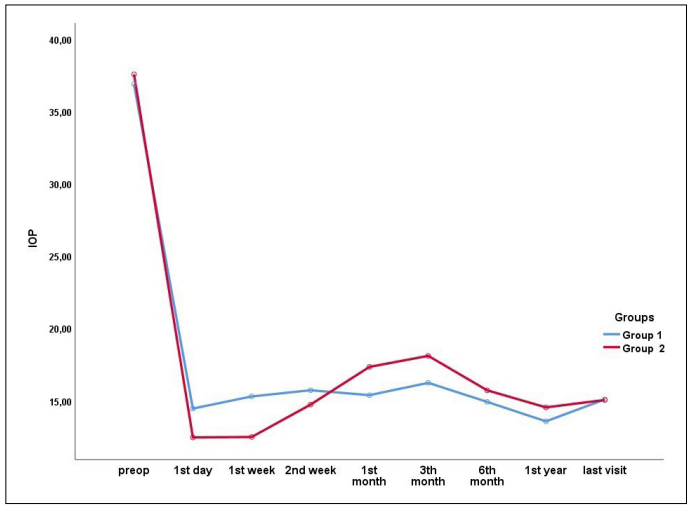

Fig. 1. Mean intraocular pressures before surgery and during the follow-up period. IOP: Intraocular pressure.

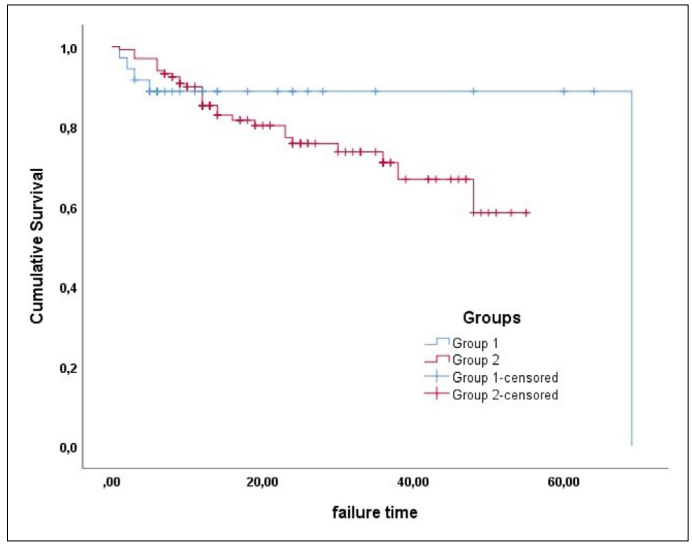

Fig. 2. Kaplan–Meier survival analysis of AGV implantation in Groups 1 and 2. Success rates were not significantly different between the groups (p=0.417, Mantel-Cox log-rank test). AGV: Ahmed glaucoma valve.

survival time using Kaplan–Meier analysis within the 95% confidence interval was 61.5 months for Group 1 and 42.3 months for Group 2. However, the survival estimates for the two groups showed no statistically significant difference according to the log-rank test (p>0.05).

Post-operative complications included conjunctival dehiscence or exposure in five eyes in Group 2; hyphema in nine eyes in Group 1 and 36 eyes in Group 2; wipeout in one eye in Group 1 and two eyes in Group 2; and choroidal detachment in nine eyes in Group 2.

Discussion

There are two topical TCAI fixed combinations available on the market: DT and BT. Both dorzolamide and brinzolamide are carbonic anhydrase inhibitors that decrease AH production by inhibiting carbonic anhydrase. Timolol, a non-selective beta-blocker, inhibits beta-receptor stimulation on the ciliary epithelium, further reducing AH production and IOP. The combination of these two molecules acts synergistically and has been used extensively in the treatment of glaucoma.[11,12]

Akçay et al.[13] reported a 26.09–37.46% IOP reduction with a BT fixed combination and a 31.19–41.44% IOP reduction with a DT fixed combination (p>0.05). Cheng et al.[14] determined the IOP-reducing power of BT and DT to be 33% and 30%, respectively (p>0.05). In the present study, we analyzed the effect of the drugs when used within the first 2 post-operative weeks of AGV implant surgery when IOP was >15 mmHg or >10 mmHg with any sign of plate fibrosis. We did not analyze the effect of both drugs separately nor the IOP changes associated with the drugs. Instead, we focused on whether early initiation of both drugs affected the surgical outcomes of AGV implantation. None of the eyes showed hypotony (IOP <6 mmHg) or hypotony-related complications such as hypotony maculopathy or choroidal detachment. Notably, only 8 eyes (22%) in Group 1 that received early TCAI fixed combinations developed plate fibrosis and required needling, whereas 50 eyes (37.5%) in Group 2 underwent needling at least once. When we compared success ratios between the groups, it was 86% for Group 1 and 78% for Group 2 (p>0.05). Although the eyes receiving early TCAI therapy showed a higher success rate, the difference was not statistically significant.

In 2003, Ayyala et al.[15] defined HP as an IOP rise within the first 6 post-operative months of AGV implantation. Mahdavi and Caprioli[5] observed HP in 88 eyes (56%), noting resolution of HP in 19 of 68 eyes (28%). The authors concluded that eyes that developed HP had higher IOP levels, required more glaucoma medications, and experienced more surgical failures. In a prospective randomized clinical trial, Pakravan et al.[7] reported a 23.4% HP occurrence in the early initiation group of DT fixed combinations compared to 66.0% in the stepwise treatment group (p<0.001). In the same report, surgical success was higher in the early initiation group (63.2% vs. 33.3%; p=0.008). In our study, HP developed in 19 eyes (54.3%) in Group 1 and 73 eyes (55.3%) in Group 2 (p>0.05). However, we cannot conclude that early initiation of TCAI does not reduce HP occurrence, as we included some eyes that entered HP before TCAI was initiated. Accordingly, we cannot draw any definitive

conclusions regarding the positive or negative effect of early TCAI on HP occurrence.

Our study revealed significant results in the number of glaucoma medications and logMAR visual acuity values. AGV implantation resulted in a significant reduction in the median number of glaucoma medications in both groups. The mean visual acuity did not change significantly in Group 1 but decreased in Group 2 (increased logMAR value). In our cohort, various factors likely affected visual acuity, such as other intraocular pathologies and cataract development. Analysis of the IOP change curve after 2 weeks revealed lower mean IOP measurements in Group 1 than in Group 2. It is well known that preventing higher IOP spikes in advanced glaucomatous eyes helps preserve remaining visual function.[16] Early initiation of TCAI therapy likely helps prevent post-operative IOP spikes and preserve visual acuity.

Most reports on HP follow AGV implantation.[5,15,17] However, some studies have also reported HP with the use of Baerveldt and Molteno tubes.[18,19] In a recent report, HP was detected after Baerveldt tube implantation at a rate of 48.6%, which is comparable to AGV.[18] Molteno et al.[20] described the histopathologic features of capsules surrounding Molteno implants. They reported that without aqueous flow, the episcleral plate of the implant stimulated encapsulation by a thin avascular collagenous layer. With aqueous flow, the inflammatory reaction changed to include both collagenous and vascular components developing in episcleral connective tissues. Freedman et al.[21] reported higher concentrations of transforming growth factor β and prostaglandin E_2 in the AH of patients with HP after Molteno implantation compared to those after trabeculotomy or in the control group. Similarly, Freedman et al.[22] observed high concentrations of cytokines, including transforming growth factor-beta 2 and interleukin-6, in the Molteno group. In addition to higher pro-inflammatory mediators, early construction of intra-bleb pressure may promote fibroblast activation and transformation into myofibroblasts, leading to both collagenous and vascular components developing in episcleral connective tissues. Reducing proinflammatory mediator exposure in the subconjunctival space and lowering intra-bleb pressure through decreased AH production have been proposed as potentially beneficial mechanisms for modifying the early wound healing process.

In previous studies, higher bleb fibrosis rates have been reported with the AGV S2 model than with the AGV FP7 model, attributed to the fibrogenic properties of polypropylene in the former versus silicon in the latter.[5,15,17,23] Plate fibrosis is expected to be less with the use of non-valved glaucoma drainage devices, as these tubes are sutured and early post-operative drainage is restricted, exposing subconjunctival tissues to fewer inflammatory mediators. Baerveldt and Molteno tubes have a wider drainage area, potentially exposing the conjunctiva to more diluted inflammatory mediators. Considering the changes in the environment following AGV implantation, AS during HP might act as an antifibrotic agent by reducing the secretion of AH and its inflammatory cytokines, as well as decreasing aqueous pressure in the bleb. An animal study involving rabbit eyes demonstrated that early treatment with AS after AGV implantation decreased bleb fibrosis following glaucoma shunt surgery and lowered IOP at 1 month.[24] Lee et al.[8] recently reported the results of their prospective study comparing the effects of AS and prostaglandin analogs during HP on IOP and surgical outcomes. They initiated either AS or prostaglandin analogs in cases where HP developed. The authors concluded that AS during HP resulted in better IOP control and a higher success rate compared to prostaglandin analog treatment. Finally, in clinical practice, when selecting glaucoma eye drops after tube surgery, the effects of glaucoma medication on the wound healing response should be considered. Although there is no definitive evidence on which AS has the best effect, choosing AS over prostaglandins as a first-line treatment appears to be more beneficial for modulating the wound healing process.

Although the small number of eyes that received TCAI within the first 2 post-operative weeks showed statistically non-significant success rates, survival times, and HP development, Group 1 required statistically significantly fewer needling procedures. None of the eyes that received early TCAI developed hypotony-related complications. A recent study investigating risk factors for HP found that younger age and higher pre-operative IOP were significant risk factors.[25] Many studies have reported that failure rates are higher in eyes that develop after AGV implantation. Therefore, effective treatment of HP is crucial to prevent further IOP-related damage.

Conclusion

Our study aimed to investigate the effect of early initiation of TCAI therapy on surgical success and the development of plate fibrosis after AGV implant surgery. The study was limited by its retrospective design and the small number

of patients who received early TCAI therapy. Nevertheless, we were able to demonstrate a beneficial effect of early initiation, such as fewer eyes requiring needling procedures during follow-up. Moreover, although IOP levels were not above 21 mmHg in most eyes when TCAI was started, none of the eyes showed hypotony after drug initiation.

Starting TCAI therapy within the first 2 post-operative weeks is beneficial for reducing the need for needling procedures for plate fibrosis.

Ethics Committee Approval: The Haydarpaşa Numune Training and Research Hospital Committee granted approval for this study (date: 06.02.2023, number: HNEAH-KAEK 2023/12-4060).

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Authorship Contributions: Concept: Y.U., S.I.; Design: Y.U., S.I.; Supervision: S.I.; Resource: Y.U., S.I.; Materials: Y.U., S.I.; Data Collection and/or Processing: Y.U., S.I.; Analysis and/or Interpretation: Y.U., S.I., O.A., R.B.; Literature Search: Y.U.; Writing: Y.U.; Critical Reviews: Y.U., S.I., E.T.V.

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