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The Effect of Trabeculectomy on Intraocular Pressure of the Untreated Fellow Eye in the Collaborative Initial Glaucoma Treatment Study

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Abstract

Purpose—To describe the intraocular pressure (IOP) of the untreated fellow eye following unilateral trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS).

Design—Data collected from a prospective, multicenter, randomized clinical trial

Participants—Three hundred patients with newly diagnosed open-angle glaucoma enrolled at 14 centers in the United States who were randomized to initial trabeculectomy.

Methods—After baseline evaluation and randomization to initial trabeculectomy in the study eye, patients were evaluated at 3 and 6 months, and at 6-month intervals thereafter. The IOP was measured by Goldmann applanation tonometry. All eyes included in the analysis were untreated fellow eyes, and the data were censored for potential IOP lowering events in the fellow eye including trabeculectomy, argon laser trabeculoplasty or cataract extraction. Predictive factors for IOP response in the fellow eye to initial trabeculectomy in the study eye were analyzed using a linear mixed model.

Main Outcome Measure—IOP in the untreated fellow eye during follow up.

Results—While the IOP in the fellow eye was lower than baseline at 3, 6, 12, 18 and 24 months after trabeculectomy in the study eye, this decrease was statistically significant only at month 12 (mean decrease from baseline, 0.73 ± 3.37 mm Hg; $P=0.0134$). Predictive associations with higher IOP in the fellow eye during follow-up included higher baseline IOP ($P<0.0001$), lower level of

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education ($P=0.0129$), time ($p=0.0005$) and the presence of other vascular disease ($p=0.0069$). Patients who ultimately required fellow eye trabeculectomy ($p<0.0001$) or argon laser trabeculoplasty ($p<0.0001$) but not cataract extraction ($p=0.4597$) in the fellow eye had lower IOPs during follow-up after these procedures.

Conclusion—There was no evidence of a substantial effect of trabeculectomy on the untreated fellow eye IOP during follow up. Trabeculectomy does not appear to decrease the mean IOP of the fellow eye, as suggested by some previous studies.

Keywords

glaucoma; intraocular pressure; trabeculectomy; fellow eye; contralateral eye

INTRODUCTION

A contralateral effect on intraocular pressure (IOP) has been well documented with unilateral use of topical antiglaucoma medications.^{1–10} In the largest of these investigations, the Ocular Hypertension Treatment Study, after over 700 patients were initiated on a monocular trial of unilateral topical beta-blocker therapy, the IOP reduction in the untreated fellow eye was approximately 1.5 mmHg.¹ Possible explanations for this effect include systemic absorption and transfer of the topical beta blocker to the fellow eye, or the “ophthalmotonic consensual reaction,” in which IOP reduction in one eye affects the other.¹¹ A similar IOP reduction in the fellow eye has been reported following laser trabeculoplasty, although this has also been hypothesized to be due to better compliance with medications following laser.^{12–14} Given that glaucoma often affects both eyes, determining whether IOP reduction in one eye can affect that in the contralateral eye would be informative and potentially valuable, both theoretically and practically.

There is conflicting evidence regarding a contralateral IOP lowering effect after unilateral incisional glaucoma surgery.^{15–17} Studies on this subject are limited in some cases by retrospective methodology^{16, 17} with the potential for selection bias, by limited sample size and follow up,^{15, 17} inadequate washout from medications or by inconsistent medical and/or surgical treatment of the operated or fellow eye either at baseline or during the follow up period.^{15–17} In addition, limited baseline IOP assessment raises the possibility of regression to the mean, a potential confounder.¹⁸

Conduct of the Collaborative Initial Glaucoma Treatment Study (CIGTS) presented an opportunity to study IOP response in the fellow eye of subjects who underwent unilateral trabeculectomy. In this clinical trial, 607 newly diagnosed, previously untreated, open angle glaucoma patients were randomized to either surgery or medical therapy. Patients with any significant or recent ocular hypotensive treatment were excluded, and those randomized to initial surgery did not receive IOP lowering medications in either eye at baseline or during follow up.¹⁹ Masked IOP measurements were obtained by a specified protocol with six baseline IOP values taken over two separate visits, thereby limiting regression to the mean. Inclusion was not based solely on elevated IOP but also on evidence of visual field loss and/or glaucomatous optic nerve damage. Because of these features, the data collected during the prospective CIGTS are well suited to use in evaluating the IOP response of the fellow eye after unilateral trabeculectomy.

MATERIALS AND METHODS

This investigation represents a post-hoc evaluation of data from 300 subjects enrolled in the CIGTS who were randomized to receive initial trabeculectomy from October 1993 through April 1997.¹⁹ Patients with prior ocular hypotensive treatment greater than 14 days or those

with any treatment within the preceding 3 weeks were excluded. Participants had newly diagnosed, previously untreated, phakic, open-angle (primary, pigmentary and exfoliative) glaucoma. All patients were required to have an IOP of at least 20 mmHg in addition to meeting optic disc and/or visual field criteria in the qualifying eye. Enrollment occurred at 14 clinical centers, where investigational review board approval was obtained for the study and where written, informed consent was obtained. The study adhered to the tenets of the Declaration of Helsinki and is HIPAA-compliant. A full description of the study's organization, criteria for entry, treatment sequences, outcome assessment methods, follow-up procedures and baseline characteristics of enrolled patients has been published.¹⁹

Because patients had either one or both eyes eligible for treatment, the treating ophthalmologist selected a study eye to receive initial treatment prior to randomization. For the purposes of this investigation, the eye contralateral to the eye designated to receive initial trabeculectomy is considered the fellow eye. If prior to randomization the decision was made to treat both eyes, trabeculectomy on the fellow eye took place no sooner than 4 weeks after surgery of the first eye but no later than 6 months after randomization. If further treatment after trabeculectomy was required in the surgical eye, argon laser trabeculoplasty (ALT) was the next treatment step, followed only then by a sequence of medications and other interventions. Follow-up data up to and including the 60-month visit are included in the present study. At months 3 and 6, and subsequently at 6-month intervals after baseline, patients underwent a comprehensive ophthalmologic examination that included measurement of IOP by Goldmann applanation tonometry.

IOP readings in both eyes were obtained in a masked fashion and followed recommended guidelines that involved a certified operator and a reader.²⁰ Two IOP measurements were recorded and the average became the final IOP value for data entry unless the two IOPs varied by more than 2 mmHg. If so, a third measurement was taken and the median of the 3 then was used as the IOP value of record. At the two baseline visits wherein eligibility was assessed, three IOP values were obtained as described above, separated by at least one hour. Thereby, six baseline IOP values (three per visit) were obtained during the baseline visits, and one value was obtained at each follow-up visit in both eyes. Tonometers were calibrated monthly.

Potential IOP lowering events in the fellow eye including trabeculectomy, argon laser trabeculoplasty or cataract extraction were identified so that the data could be censored to exclude IOP measurements from these patients at post-event time points. Paired Student t-tests were used to compare mean IOP between baseline and follow-up visits in the fellow eye, excluding censored data points. A linear mixed model was used to evaluate factors predictive of IOP change during follow-up.²¹ Variables entered into the mixed model included time, time squared, baseline fellow eye IOP, education, sex, race, marital status, hypertension, other vascular disease, diabetes, diagnosis, clinical center, treatment, smoking status, baseline fellow eye visual field mean deviation and the presence of a censoring event. Correlations between the IOP change from baseline in the study eye and the IOP change from baseline in the fellow eye were determined at 3, 6, 12, 18 and 24 months, excluding censored data points. SAS software version 9.1 (SAS, Cary, NC) was used for all analyses.

A last observation carry-forward (LOCF) analysis was performed in order to address possible bias from the number of missed observations due to censoring events or missing follow up visits. For this analysis, the last pre-censored IOP was carried forward for patients who underwent any censoring event (whether pre-planned at randomization or required during follow up) including trabeculectomy, ALT or cataract extraction in the fellow eye during the follow up period. The most recent IOP value was carried forward for patients lost to follow up. For missing visits, the IOP value prior to that visit was carried forward.

Participants who had had an IOP reducing event occur prior to the scheduled month 3 follow-up visit, who dropped out prior to the month 3 visit, or who missed their 3 month visit did not have any IOP values to carry forward and were excluded from the LOCF analysis.

RESULTS

Demographic data of patients undergoing trabeculectomy as well as operative details and perioperative complications have been reported.^{22, 23} Table 1 presents IOP statistics for the fellow eye at baseline and during the follow-up period, excluding censored data points. Note that the number of patients included in the analysis decreased at each visit; even so, at 5 years IOP data were available on 89 enrolled patients who had undergone unilateral trabeculectomy only and continued untreated in the fellow eye. Table 2 presents the numbers and types of censoring events at each time point. The majority (82.9%) of trabeculectomies occurred within the first 12 months (as expected due to the protocol), whereas most (96.9%) of the cataract extractions took place after one year of follow up. Figure 1 illustrates IOP values from baseline through year 5 for the study and fellow eyes, excluding censoring events.

As shown in Table 3, while the IOP (censored data) in the fellow eye was lower than baseline at 3, 6, 12, 18 and 24 months after trabeculectomy, this decrease was statistically significant only at month 12 (0.73 ± 3.37 mm Hg; $P = 0.0134$). Correlations between the fellow eye IOP change from baseline and the study eye change from baseline throughout the follow up period were determined (Table 4). There was a small but significant correlation between the magnitude of the IOP decrease in the study eye and the fellow eye at month 3 ($r = 0.27$; $p < 0.0001$), however this relationship was not present at months 6, 12, 18 and 24 and the IOP decrease compared to baseline at month 3 was not significant.

Table 5 presents a mixed model of predictive factors of IOP change in the fellow eye between follow up month 3 and year 5, adjusted for baseline IOP. Predictive associations with higher IOP in the fellow eye during follow-up included higher baseline IOP ($P < 0.0001$), lower level of education ($P = 0.0129$), time ($p = 0.0005$) and the presence of other vascular disease ($p = 0.0069$). The fellow eye had reduced IOP after trabeculectomy (10.67 mm Hg reduction, on average; $p < 0.0001$) or after ALT (3.59 mm Hg reduction; $p < 0.0001$) but not after cataract extraction (0.45 mm Hg reduction; $p = 0.4597$).

Descriptive IOP statistics for the last observation carry-forward (LOCF) analysis are presented in Table 6. After 18 months, 263 patients could be included in the LOCF analysis. Patients were excluded from the analysis due to an IOP-lowering event within the first three months ($n = 34$) and due to loss of follow-up after randomization ($n = 3$). The carry-forward analysis could not be performed on one patient with a missing fellow eye baseline IOP ($n = 1$) and on several patients ($n = 8$) who were absent from the month 3 visit. While the LOCF analysis allowed a greater number of patients to be included in the analysis, at no point during follow up was the IOP significantly lower than at baseline (Table 7).

DISCUSSION

The present study represents the largest evaluation to date of the untreated fellow eye response after unilateral trabeculectomy. In this prospective investigation, 300 patients were randomized to trabeculectomy and comparative pressures for untreated fellow eyes were available for post-hoc analysis for 254 patients at 3 months and for 114 patients at 2 years. The CIGTS study therefore provided a unique opportunity for long-term investigation of the effect of trabeculectomy on the fellow eye. Long-term IOP data were available for 89

patients at 60 months; these subjects had not undergone fellow eye trabeculectomy (or another IOP reducing event) for five years. The CIGTS follow-up provided sufficient power to address what would be considered a clinically relevant change in IOP in the fellow, untreated eye after trabeculectomy of the study eye at all time points through 60 months. For example, even a mean change of IOP in the fellow eye of 1.0 mmHg from baseline (which might be of borderline relevance clinically) would still have resulted in a highly statistically significant finding at all time points. In addition, the prospective nature and standardized protocols employed by the study avoided some other methodological problems encountered in the literature such as retrospective design, inadequate baseline IOP assessment, non-masked IOP measurement, and confounders involving hypotensive medication washout, compliance and crossover effects.

The fellow eyes of patients who underwent unilateral trabeculectomy demonstrated a small decrease in IOP over time; however, this decrease was modest, with only the 12-month time point showing a statistically significant decrease. Because a sizable number of patients underwent protocol-dictated trabeculectomy in the fellow eye, data points for these patients as well as patients who underwent cataract extraction and ALT in the fellow eye were censored at the time of the procedure. Censored patients had a higher baseline IOP and might have exhibited a greater fellow eye response on that basis.¹ To address possible effects of censoring and drop out on follow up IOP, a last visit carry forward analysis was performed. This analysis confirmed that there was on average no significant change compared to baseline in the IOP of the fellow eye following trabeculectomy.

In order to investigate which other factors influenced fellow eye pressures over the follow up period, a mixed model regression analysis was performed, similar to that described by Musch et al for the operated study eyes in CIGTS.²¹ Educational level was identified as a predictor of fellow eye IOP during follow up, reinforcing the concept that socioeconomic factors are associated with IOP.^{21, 24} Other vascular diseases (not including cardiovascular disease) were predictive of a lower IOP in the fellow eye during follow up, a new finding that warrants verification. Other variables associated with a higher IOP during follow up were time and a higher baseline IOP. Confirming the necessity of censoring, fellow eye ALT and trabeculectomy were significantly associated with an IOP decrease during follow up.

This study is limited by absence of fellow eye IOP data in the early postoperative period (e.g., post operative month one) and by a significant number of censoring events in the fellow eyes. Censoring was necessary, however, as >50% of fellow eyes underwent trabeculectomy. As confirmed by the mixed model, fellow eyes which underwent trabeculectomy or ALT did exhibit a significant IOP decrease following these events.

The fellow eye response to trabeculectomy is difficult to study methodologically and the literature on this topic is limited and inconsistent.^{15–17} Diestelhorst and Kriegelstein¹⁵ prospectively evaluated aqueous flow by fluorophotometry in 14 patients undergoing trabeculectomy. They reported a significant increase in aqueous flow but no significant change in IOP of the fellow eye 5 days after trabeculectomy. In a retrospective review, Yarangümeli et al¹⁶ found an increase in the IOP of the non-operated fellow eye 3 months after trabeculectomy, though the majority of their patients were on topical hypotensive medications in the fellow eye, complicating the analysis. Vysniauskiene et al¹⁷ reported an IOP decrease at postoperative day one and month one in the fellow eye of 24 patients reviewed retrospectively who underwent trabeculectomy. However, 11 of these patients were on ocular hypotensive medications in the fellow eye, and the IOP decrease was less robust in the remaining 13 patients not on ocular hypotensive medications, 12 of whom had

undergone prior trabeculectomy. Simmons reported an IOP increase in 10% of fellow eyes after trabeculectomy, however this result might be explained by chance alone.^{25, 26}

There are several possible explanations for these conflicting findings. A contralateral rebound IOP elevation caused by the preoperative withdrawal of glaucoma medication could possibly contribute to IOP elevations seen in fellow eyes. Schwartz²⁷ ascribed the IOP drop in the fellow eye to increased compliance, having observed a fellow eye IOP reduction in patients who were continued on bilateral topical therapy after having unilateral ALT. Regression to the mean (the tendency for high or low values to be closer to the sample mean on repeated measurement) could occur as the result of inadequate baseline IOP assessment and could mimic a fellow eye pressure reduction.²⁷ Regression to the mean would also explain a finding common to medical and laser fellow eye investigations that higher baseline IOP and greater treatment effect in the treated eye are often associated with greater fellow eye pressure reduction.

If the fellow eye response exists, several physiologic mechanisms are plausible. An IOP increase in the fellow eye could be due to a reflex increase in aqueous humor production, an effort of the eyes to compensate for the low IOP of the operated eye.^{28–30} Decreased aqueous perfusion of the trabecular meshwork of the operated eye after trabeculectomy can result in increased extracellular meshwork material, a response that could potentially be bilateral.³¹ Laser trabeculoplasty has been suggested to lower IOP in the fellow eye by a mechanism involving bilateral macrophage recruitment to the trabecular meshwork has been proposed.^{12–14} However, these speculations remain unproven and untested. Zimmerman and Kaufman proposed that unilateral timolol application, shown in several investigations to reduce IOP in the fellow eye, could do so via systemic absorption and delivery.^{1–4, 7–9, 31, 32}

A central nervous system-mediated reflex whereby alteration of the IOP in one eye is accompanied by a corresponding change in the contralateral eye has been named “ophthalmotonic consensual reaction.”¹¹ However its existence remains speculative.²⁹ Perkins found that ablation of the trigeminal nerve decreased the ophthalmotonic consensual reaction and other work suggests that the autonomic nervous system could be involved.^{10, 33} Tamm et al.³⁴ have described myelinated axons in the scleral spur of humans that terminate in bulb shaped structures similar to mechanoreceptors found in skin, tendons and joint capsules that could serve as specialized sensory receptors for IOP regulation. The efferent limb of such a reflex might involve a change in either the resistance in the meshwork or the production of aqueous humor of both eyes.

This report is largest study to date of the fellow eye response after trabeculectomy. Our investigation does not provide any strong evidence of the ophthalmotonic consensual reaction and suggests that any effect, if present, is transient and would be unlikely to influence clinical management. Finally, trabeculectomy does not appear to increase the mean IOP of the fellow eye as suggested by several earlier studies on this topic.

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References

1. Piltz J, Gross R, Shin DH, et al. Ocular Hypertension Treatment Study Group. Contralateral effect of topical beta-adrenergic antagonists in initial one-eyed trials in the Ocular Hypertension Treatment Study. *Am J Ophthalmol.* 2000; 130:441–453. [PubMed: 11024416]

2. Zimmerman TJ, Kaufman HE. Timolol: a beta-adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol.* 1977; 95:601–604. [PubMed: 322648]
3. Kwitko GM, Shin DH, Ahn BH, Hong YJ. Bilateral effects of long-term monocular timolol therapy. *Am J Ophthalmol.* 1987; 104:591–594. [PubMed: 3688100]
4. GLT Research Group. The Glaucoma Laser Trial: 4. Contralateral effects of timolol on the intraocular pressure of eyes treated with ALT. *Ophthalmic Surg.* 1991; 22:324–329. [PubMed: 1896168]
5. Drance SM. The uniocular therapeutic trial in the management of elevated intraocular pressure. *Surv Ophthalmol.* 1980; 25:203–205. [PubMed: 7466599]
6. Dunham CN, Spaide RF, Dunham G. The contralateral reduction of intraocular pressure by timolol. *Br J Ophthalmol.* 1994; 78:38–40. [PubMed: 8110696]
7. al-Sereiti MR, Coakes RL, O'Sullivan DP, Turner P. A comparison of the ocular hypotensive effect of 0.025% bromocriptine and 0.25% timolol eye drops in normal human volunteers. *Br J Clin Pharmacol.* 1989; 28:443–447. [PubMed: 2590602]
8. Wilson RP, Kanal N, Spaeth GL. Timolol: its effectiveness in different types of glaucoma. *Ophthalmology.* 1979; 86:43–50. [PubMed: 530564]
9. Zimmerman TJ, Kass MA, Yablonski ME, Becker B. Timolol maleate: efficacy and safety. *Arch Ophthalmol.* 1979; 97:656–658. [PubMed: 371597]
10. Perkins ES. Influence of the fifth cranial nerve on the intra-ocular pressure of the rabbit eye. *Br J Ophthalmol.* 1957 May; 41:257–300. [PubMed: 13426465]
11. Weekers L. Modification experimentales de l'ophtalmotonous. Reaction ophtalmotonique consensuelle. *Arch Ophthalmol (Paris).* 1924; 41:641–658.
12. Latina MA, Sibayan SA, Shin DH, et al. Q-switched 532-nm Nd:YAG laser trabeculoplasty (selective laser trabeculoplasty): a multicenter, pilot, clinical study. *Ophthalmology.* 1998; 105:2082–2088. [PubMed: 9818610]
13. McIlraith I, Strasfeld M, Colev G, Hutnik CM. Selective laser trabeculoplasty as initial and adjunctive treatment for open-angle glaucoma. *J Glaucoma.* 2006; 15:124–130. [PubMed: 16633226]
14. Rhodes KM, Weinstein R, Saltzman RM, et al. Intraocular pressure reduction in the untreated fellow eye after selective laser trabeculoplasty. *Curr Med Res Opin.* In press.
15. Diestelhorst M, Kriegelstein G. The effect of trabeculectomy on the aqueous humor flow of the unoperated fellow eye. *Graefes Arch Clin Exp Ophthalmol.* 1991; 229:274–276. [PubMed: 1869066]
16. Yarangumeli A, Koz OG, Kural G. The effect of trabeculectomy on the intraocular pressure of the unoperated fellow eye. *J Glaucoma.* 2003; 12:108–113. [PubMed: 12671464]
17. Vysniauskiene I, Shaarawy T, Flammer J, Haefliger IO. Intraocular pressure changes in the contralateral eye after trabeculectomy with mitomycin C. *Br J Ophthalmol.* 2005; 89:809–811. [PubMed: 15965155]
18. Leung DY, Kwong YY, Yuen HK. Intraocular pressure changes in the contralateral eye after trabeculectomy with mitomycin C [letter]. *Br J Ophthalmol.* 2006; 90:250. [PubMed: 16424552]
19. Musch DC, Lichter PR, Guire KE, Standardi CL. CIGTS Study Group. The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. *Ophthalmology.* 1999; 106:653–662. [PubMed: 10201583]
20. Kass MA. Standardizing the measurement of intraocular pressure for clinical research: guidelines from the Eye Care Technology Forum. *Ophthalmology.* 1996; 103:183–185. [PubMed: 8628552]
21. Musch DC, Gillespie BW, Niziol LM, et al. Collaborative Initial Glaucoma Treatment Study Group. Factors associated with intraocular pressure before and during 9 years of treatment in the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology.* 2008; 115:927–933. [PubMed: 17964655]
22. Jampel HD, Musch DC, Gillespie BW, et al. Collaborative Initial Glaucoma Treatment Study Group. Perioperative complications of trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS). *Am J Ophthalmol.* 2005; 140:16–22. [PubMed: 15939389]

23. Lichter PR, Musch DC, Gillespie BW, et al. CIGTS Study Group. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology*. 2001; 108:1943–1953. [PubMed: 11713061]
24. Yip JL, Aung T, Wong TY, et al. Socioeconomic status, systolic blood pressure and intraocular pressure: the Tanjong Pagar Study. *Br J Ophthalmol*. 2007; 91:56–61. [PubMed: 16928704]
25. Bhorade AM, Gordon MO, Wilson B, et al. Ocular Hypertension Treatment Study Group. Variability of intraocular pressure measurements in observation participants in the Ocular Hypertension Treatment Study. *Ophthalmology*. 2009; 116:717–724. [PubMed: 19243824]
26. Simmons, RJ. Filtering operations. In: Chandler, PA.; Grant, WM.; Epstein, DL., editors. *Chandler and Grant's Glaucoma*. 3rd ed. Philadelphia, PA: Lea & Febiger; 1986. p. 428–429.
27. Schwartz AL, Whitten ME, Bleiman B, Martin D. Argon laser trabecular surgery in uncontrolled phakic open angle glaucoma. *Ophthalmology*. 1981; 88:203–212. [PubMed: 7231908]
28. Priot EL, Stone HH. On the ophthalmotonic consensual reaction and its relationship to aqueous humor dynamics. *Am J Ophthalmol*. 1956; 42:50–58. [PubMed: 13339903]
29. Gibbens MV. The consensual ophthalmotonic reaction. *Br J Ophthalmol*. 1988; 72:746–749. [PubMed: 3191075]
30. Drance SM. The uniocular therapeutic trial in the management of elevated intraocular pressure. *Surv Ophthalmol*. 1980; 25:203–205. [PubMed: 7466599]
31. Kaufman, PL. Pressure dependent outflow. In: Ritch, R.; Shields, MB.; Krupin, T., editors. *The Glaucomas*. 2nd ed. Vol. vol 1. St. Louis, MO: Mosby; 1996. p. 307–335.
32. Dunham CN, Spaide RF, Dunham G. The contralateral reduction of intraocular pressure by timolol. *Br J Ophthalmol*. 1994; 78:38–40. [PubMed: 8110696]
33. Cox CE, Fitzgerald CR, King RL. A preliminary report on the supraoptic nucleus and control of intraocular pressure. *Invest Ophthalmol*. 1975; 14:26–28. [PubMed: 1110132]
34. Tamm ER, Flugel C, Stefani FH, Lütjen-Drecoll E. Nerve endings with structural characteristics of mechanoreceptors in the human scleral spur. *Invest Ophthalmol Vis Sci*. 1994; 35:1157–1166. [PubMed: 8125727]

Figure 1.
Intraocular Pressure (IOP) over Time in Fellow (Dashed; Censored for IOP Lowering Events) and Study Eyes (Solid)

Table 1

Descriptive Statistics for the Fellow Eye Intraocular Pressure (mmHg) over Time (censored for Intraocular Pressure Lowering Events)

Time Point	N	Mean	Standard Deviation	Minimum	Maximum
Baseline	299	23.9	4.9	13	42
3 Months	255	23.1	5.5	11	44
6 Months	165	21.9	4.9	8	39
12 Month	133	21.0	4.2	12	33.5
18 Months	119	21.4	4.7	13.5	43
24 Months	115	21.1	4.3	12	42
36 Month	107	21.2	4.8	12	46
48 Months	99	20.9	4.2	13.5	38.5
60 Months	89	20.7	4.2	11.5	40

Table 2
Occurrence of Censoring Events Argon Laser Trabeculoplasty, Trabeculectomy and Cataract Extraction up to Month 60

Time	ALT (n=50*)		Trabeculectomy (n=175)		Cataract Extraction (n=32)	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
0-3 months	1	2	30	17.14	0	0
3-6 months	1	2	90	51.43	0	0
6-12 months	10	20	25	14.29	1	3.13
12-18 months	8	16	5	2.86	1	3.13
18-24 months	8	16	2	1.14	4	12.5
24-30 months	3	6	5	2.86	5	15.63
30-36 months	2	4	0	0	3	9.38
36-42 months	3	6	2	1.14	4	12.5
42-48 months	1	2	3	1.71	1	3.13
48-54 months	2	4	4	2.29	2	6.25
54-60 months	0	0	1	0.57	1	3.13

ALT= Argon Laser Trabeculoplasty.

Table 3

Fellow Eye Censored Intraocular Pressure (mmHg) Compared to Baseline during Follow Up.

Time	N	Baseline	Follow Up	Change	P-value*
Mean (Standard Deviation)					
3 Months	254	23.51 (4.61)	23.11 (5.51)	0.40 (4.18)	0.1256
6 Months	164	22.20 (3.84)	21.93 (4.94)	0.27 (3.55)	0.3385
12 Month	132	21.76 (3.87)	21.02 (4.15)	0.73 (3.37)	0.0134
18 Months	118	21.55 (3.77)	21.47 (4.72)	0.08 (3.68)	0.8028
24 Months	114	21.41 (3.72)	21.08 (4.32)	0.33 (3.49)	0.3099
36 Month	106	21.39 (3.56)	21.28 (4.83)	0.11 (3.90)	0.7750
48 Months	98	21.22 (3.63)	20.91 (4.18)	0.31 (3.37)	0.3635
60 Months	88	21.40 (3.52)	20.77 (4.18)	0.63 (3.14)	0.0654

* Paired t-test

Table 4

Correlations Between the Fellow Eye Change from Baseline (Censored for Intraocular Pressure Lowering Events) and the Study Eye Change from Baseline Throughout the Follow Up Period

<u>Change From Baseline</u>	<u>Correlation</u>	<u>P-value</u>
3 Month Change	0.27	<0.0001
6 Month Change	−0.01	0.8716
12 Month Change	0.12	0.1593
18 Month Change	0.14	0.1393
24 Month Change	−0.04	0.6807
36 Month Change	0.06	0.5345
48 Month Change	0.15	0.1397
60 Month Change	0.15	0.1575

Table 5

Mixed Model of Factors Associated with Fellow Eye Intraocular Pressure from 3 Months through 5 Years of Follow Up.

Variable	Estimate	Standard Error	P-value
Time (Years)	0.26	0.07	0.0005
Fellow Eye Baseline Intraocular Pressure	0.62	0.04	<0.0001
Education	−0.34	0.14	0.0129
Other Vascular Disease	1.36	0.50	0.0069
Censor Trabeculectomy	−10.67	0.25	<0.0001
Censor Argon Laser Trabeculoplasty	−3.59	0.45	<0.0001
Censor Cataract Extraction	0.45	0.61	0.4597

Table 6

Descriptive Statistics for the Fellow Eye Intraocular Pressure (mmHg) over Time Using the Last Observation Carry-Forward Analysis

Time	N	Mean	Standard Deviation	Min	Max
Baseline	299	23.9	4.9	13	42
3 Months	255	23.1	5.5	11	44
6 Months	261	23.3	5.7	8	44
12 Month	262	23.0	5.6	8	44
18 Months	263	23.3	5.7	8	44
24 Months	263	23.4	5.6	12	44
36 Month	263	23.5	5.8	12	46
48 Months	263	23.6	5.7	12	46
60 Months	263	23.6	5.8	11.5	46

Last Observation Carry-Forward Analysis Showing Fellow Eye Intraocular Pressure (mmHg) Compared to Baseline during Follow Up

Table 7

Time	N	Baseline	Follow Up	Change	P-value [*]
Mean (Standard Deviation)					
3 Months	254	23.5 (4.6)	23.1 (5.5)	0.4 (4.2)	0.1256
6 Months	260	23.5 (4.6)	23.3 (5.7)	0.2 (4.2)	0.3777
12 Month	261	23.5 (4.6)	23.0 (5.6)	0.5 (4.2)	0.0756
18 Months	262	23.5 (4.6)	23.4 (5.7)	0.1 (4.4)	0.6104
24 Months	262	23.5 (4.6)	23.4 (5.6)	0.1 (4.3)	0.6491
36 Month	262	23.5 (4.6)	23.5 (5.8)	-0.0 (4.5)	0.9461
48 Months	262	23.5 (4.6)	23.6 (5.7)	-0.1 (4.5)	0.7374
60 Months	262	23.5 (4.6)	23.6 (5.8)	-0.1 (4.5)	0.6405

^{*} Paired t-test