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The Effect of Early Post-trabeculectomy Intraocular Pressure Spike in the Collaborative Initial Glaucoma Treatment Study

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Abstract

Purpose—To examine effects of early postoperative intraocular pressure (IOP) spike in patients undergoing primary trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS).

Patients and Methods—We identified patients with IOP spike ≥ 5 mmHg above the baseline IOP on postoperative day 1, as well as those without IOP increase. The Mean Deviation (MD), Pattern Standard Deviation (PSD), and Corrected PSD (CPSD) of the visual field (VF) were compared at 6 months and years 1, 2, 3, and 5 after surgery, as was the IOP.

Results—Seventeen of 300 patients (5.7%) had IOP spike. After controlling for baseline VF severity in a generalized linear regression model that addressed change in MD, PSD, and CPSD, or in a logistic regression model for ≥ 3 dB of MD change, comparison between the groups revealed no significant difference at all time points examined ($P > .05$). Patients with IOP spike had significantly higher mean IOP at years 3 and 5 of follow-up ($P \leq .04$).

Conclusions—Among CIGTS patients, early post-trabeculectomy IOP spike ≥ 5 mmHg above baseline IOP was not associated with subsequent VF loss, but was associated with significantly higher IOP during long-term follow-up.

Keywords

trabeculectomy; intraocular pressure; spike; visual field; glaucoma

INTRODUCTION

The potentially damaging effects of short-term intraocular pressure (IOP) spikes on visual function in patients with glaucoma are of concern, but are not well characterized. Some authors have reported progression of visual field (VF) loss in eyes with advanced glaucoma after IOP spikes associated with laser trabeculoplasty.^{1,2} Others have reported on VF findings after acute, transient experimental IOP elevation,³ or in those with acute angle closure glaucoma,^{4,5} but these situations may not be directly analogous to the effects of an

³A list of CIGTS investigators is found in the appendix of reference ⁶

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IOP spike lasting from hours to days in patients who have preexisting optic nerve damage from glaucoma.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) was a randomized, multicenter clinical trial of primary trabeculectomy vs. standard medical treatment in patients with newly diagnosed glaucoma. While a previous CIGTS paper reported on early postoperative complications of trabeculectomy, elevated IOP was not included among the complications considered.⁶ We examined the effect of an early post-trabeculectomy IOP spike on the VF and IOP of CIGTS subjects, compared with those who did not have an IOP spike after trabeculectomy.

METHODS

Approval was granted for this review of CIGTS subject files by the IRB of each CIGTS Study Center and the CIGTS Coordinating Center (a list is provided in Reference 6). We chose to define an IOP spike as 5 mmHg or more above the average of the 6 baseline IOP values, which represents a clinically meaningful IOP spike. We then identified CIGTS participants who had an IOP spike of 5 mmHg or greater above the baseline IOP level on postoperative day (POD) 1 in the CIGTS-designated Study Eye, as well as those who had no increase in IOP on POD 1 after trabeculectomy. Patients who had an increase in IOP that was < 5 mmHg on POD 1 were excluded, as were any fellow eyes that had trabeculectomy under the CIGTS protocol. Inclusion criteria for the CIGTS are listed elsewhere⁷ but in brief, subjects were age 25–75, had been diagnosed with primary open angle, pigmentary, or pseudoexfoliation glaucoma, had an Early Treatment Diabetic Retinopathy Study visual acuity score of 70 or better (approximate equivalent Snellen visual acuity of 20/40 or better), and had one of three combinations of qualifying IOP, VF changes, and optic disc findings, all of which required optic disc damage compatible with glaucoma. Exclusion criteria are listed elsewhere⁷ but included advanced glaucoma (CIGTS VF score > 16.0 on a 0–20 scale). Patients randomized to surgery underwent a standard trabeculectomy. Surgeons were permitted to use adjunctive 5-fluorouracil but not mitomycin C.

Baseline patient characteristics were examined for differences between the two groups (IOP spike vs. no increase in IOP), including age, gender, race, iris color, diagnosis, smoking history, presence of hypertension, diabetes mellitus, vascular or cardiac disease, or an optic disc hemorrhage at the first baseline visit. Variation in the 6 baseline IOPs was measured and compared between groups. Intra- and postoperative variables examined included type of anesthesia, location of the scleral flap, type of conjunctival incision (limbus- or fornix-based), performance of tenonectomy, use of viscoelastic substances and antifibrosis agents, and postoperative management techniques including digital ocular compression and laser suture lysis. The latter two variables were performed as considered necessary by the patient's surgeon. No data censoring was performed if patients required subsequent ocular procedures, in either group.

The Humphrey 24-2 full threshold VF Mean Deviation (MD), Pattern Standard Deviation (PSD), and Corrected PSD (CPSD) were compared to the baseline index at 6 months and at years 1, 2, 3, and 5 after enrollment between the two groups, as was the IOP and C/D ratio. Linear regression models were used to investigate the effect of POD 1 IOP spike on VF change (MD, PSD, and CPSD), controlling for baseline VF severity. Logistic regression analyses were performed to examine the effect of POD 1 IOP spike on MD loss of ≥ 3 dB from baseline, vs. < 3 dB loss, and linear regression analyses were used to evaluate the association of POD 1 IOP spike with mean values of the three VF parameters at each time through 5 years. Mixed linear regression was performed to investigate the effect of POD 1 IOP spike on mean follow-up IOP through 5 years. The Student's t-test was used to compare

time specific mean values of VF parameters, IOP, and C/D ratio at baseline and at 0.5, 1, 2, 3, and 5 yrs, as well as the change from baseline. Patient characteristics were analyzed with the Chi-square test, Fisher's exact test, or Student's t-test, as appropriate. The Mann Whitney U test was also used to analyze postoperative IOP data. A P-value of $< .05$ was considered significant. All analyses were performed with SAS 9.1 statistical software (SAS Institute, Cary, NC).

RESULTS

Of 300 participants randomized to initial surgery, 17 (6%) had an IOP spike of ≥ 5 mmHg on POD 1, and 261 (87%) had no increase in IOP on POD 1. The remaining 22 participants (7%) had IOP elevation < 5 mmHg on POD 1, and were excluded from analysis. The 17 patients with IOP spike had their surgical procedures performed in 9 of the 14 different CIGTS Clinical Centers, with no evidence of clustering. All patients with an IOP spike had a diagnosis of primary open angle glaucoma, and were more likely to be black ($P = .047$; Fisher's exact test) (Table 1).

Patients with an IOP spike did not have significantly different variation in IOP within the six baseline IOP measurements that were collected prior to surgery, compared to the no IOP spike group (SD 2.61 mmHg vs. 2.62 mmHg). The average range of IOP within the six baseline IOP readings was also similar between groups (IOP spike 6.85 mmHg vs. no IOP spike 6.92 mmHg), as was the proportion of patients whose IOP range at baseline was 5 mmHg or greater (12/17, 70.6%, vs. 188/261, 72.0%). The proportion of patients whose maximum IOP among the six baseline measurements was at least 5 mmHg greater than the mean baseline IOP was also similar (3/17, 17.6% vs. 52/261, 19.9%).

No other preoperative characteristics or intraoperative variables were found to be associated with an IOP spike (data not shown; all P-values $> .15$). Patients with an IOP spike were significantly more likely to be managed during follow-up with postoperative digital ocular compression on POD 1 [7/17 (41%) vs. 23/237 (10%); $P = .0008$, Fisher's exact test], and laser suture lysis at any time point [13/17 (76%) vs. 115/261 (44%); $P = .013$, Chi square test]. By POD 7, 16 patients (94%) had resolution of the IOP spike. However, at POD 30, 3 of 17 patients (18%) again had IOP ≥ 5 mmHg above baseline.

After controlling for baseline VF severity in a linear regression model for VF change measured continuously (MD, PSD, CPSD), or in a logistic regression model for VF change measured as < 3 dB vs. ≥ 3 dB (MD only), comparison between the groups revealed no significant difference at all time points examined for MD, PSD, and CPSD (all P-values > 0.05) (data not shown). Comparison of mean values of MD, PSD, and CPSD at each time point with the baseline measure using the Student's t-test revealed no significant differences, except for PSD at 5 years, which was significantly lower in the IOP-spike group (Table 2).

Subsequent ocular procedures performed in the IOP spike group during the 5-year follow-up period studied included argon laser trabeculoplasty (6 patients), cataract extraction (4 patients), and bleb revision (3 patients), and some patients had more than one subsequent procedure. Two patients had IOP spike ≥ 5 mmHg associated with these later procedures, but neither patient showed substantial change in VF indices during the time period studied. Of the 17 patients who had an IOP spike, 6 (35%) underwent further interventions for IOP above target level, which was not significantly different from the cohort without IOP spike (data not shown; $P \geq .13$, Fisher's exact test).

Under the CIGTS protocol, no patient randomized to surgery was maintained on chronic medications. The mean IOP was similar in the two groups at one year ($P = .85$), but by three

years the IOP spike group had significantly higher mean IOP ($P = .04$, t-test; Table 3) which was also observed at year 5 ($P = .004$, t-test).

Although the variances were not significantly different in the two groups at any time point, indicating that the t-test is appropriate and valid, we noted the median IOP at years 3 and 5 in the IOP spike group (16.8 and 17.5 mmHg, respectively) was slightly lower than the mean IOP (17.8 and 18.8 mmHg, respectively), indicating a possible effect of outliers on the mean IOP. To address this possible effect, the Mann-Whitney U test was used to compare the two groups, which revealed P values of .053 and .017 at years 3 and 5, respectively. In a mixed regression model which included baseline IOP and race, the effect of an IOP spike on follow-up IOP remained significant ($P = .028$), whereas race (Black vs. White plus Other) did not have a significant effect ($P = .19$). Baseline IOP was the strongest independent predictor of follow-up IOP ($P = .002$). In a separate analysis, time was not a predictor of MD in a mixed model of longitudinal MD, adjusting for baseline MD, in patients with IOP spikes ($P = .900$).

If a postoperative IOP spike is defined as a rise in IOP of 10 mmHg from the baseline IOP, then 6 patients fulfilled the entry criteria. In a separate analysis, no significant differences were found between those 6 patients and the group of patients without IOP spike ($N = 261$) at any time point for any of the variables studied (data not shown; $P \geq .158$), though few firm conclusions can be drawn from a study population of that size.

DISCUSSION

The 17 patients in the CIGTS who had an IOP spike of ≥ 5 mmHg on POD 1 after primary trabeculectomy were not more likely to have progression of VF loss than those without any IOP increase, despite a significantly higher mean IOP over long-term follow-up. Notably, this spike above baseline untreated IOP represents a higher IOP value than might be typical for a patient who undergoes trabeculectomy after initial medical treatment.

We found no other studies that examined the long-term effects of an IOP spike after glaucoma procedures. Some authors have anecdotally reported rapid progression of VF loss after an IOP spike following laser trabeculoplasty^{1,2} or laser capsulotomy⁸ in eyes with advanced glaucoma. Other authors have reported on loss of visual acuity at 3 months after trabeculectomy in eyes with endstage glaucoma, and early elevations in IOP were considered to be possibly contributory in some cases.^{9,10} However, patients with endstage glaucoma were excluded from recruitment into the CIGTS, and therefore comparison between our results and those from prior studies is difficult. The patients in our study who experienced an IOP spike generally had early glaucoma, though three (18%) had moderately advanced glaucoma, with baseline MD < -10.00 dB (82 subjects [14%] had MD < -10.00 dB in the CIGTS study population as a whole). Our study results therefore do not preclude a detrimental long-term effect of an IOP spike on patients with advanced or endstage glaucoma. In addition, the small number of those with an IOP spike in our study warrants emphasis, and a real difference in VF prognosis might have been found with a larger group with IOP spike, although we discern no evidence to support this in our data.

The only risk factor identified for development of an IOP spike was Black race. The small number of IOP spike patients precludes an extensive discussion of possible causes, although it is possible that some Black populations are predisposed to higher levels of inflammation.^{11,12} Other authors have noted an association between use of ophthalmic viscoelastic surgical devices such as sodium hyaluronate intraoperatively and IOP spike at 4–6 hours after trabeculectomy and at POD 1,¹³ but our findings do not support this association,

possibly due to differences in surgical technique. In addition, IOP spike patients did not show greater variation in baseline IOP than those without a spike.

Although follow-up after IOP spike was not uniform in our study, it did not differ significantly from the rest of the CIGTS participants. In addition, all 17 patients had at least 10 months of follow up, and 16 of 17 had two years of follow up. This should represent an adequate time period to observe the effects of an acute event on the VF, based on the literature regarding VF progression following optic disc hemorrhage,^{14,15} and acute angle closure glaucoma.^{4,5}

Our data show a POD 1 IOP spike ≥ 5 mmHg is predictive of significantly higher untreated IOP at years 3 and 5 after trabeculectomy. Other authors have reported on the predictive value of POD 1 IOP after trabeculectomy, and some have found no association with IOP outcomes at one year,¹⁶ while others have found higher IOP on POD 1 predicted a poor prognosis at 1.5 – 2 years.^{17,18} The CIGTS represents a unique population for study of the natural history of trabeculectomy function because of the length of prospective data collection and because the protocol prohibited chronic use of ocular hypotensive medications in the surgical group. Despite the higher mean IOP over follow-up in the IOP spike group, the IOP spike group's VF outcomes did not differ from those who had no IOP spike, possibly because the mean IOP over follow-up was still considerably lower than the baseline mean IOP (-8.7 mmHg at 5 years, a decrease of 32%).

Although to our knowledge this study population represents the largest such study on this topic, a notable limitation of this study is the small number of patients with IOP spike, which limits our ability to assess risk factors for IOP spike. The population studied had mild to moderate glaucoma, and this limits the generalizability of the study. Other limitations include the variable follow-up of patients in both groups, and the bias inherent in a self-selected population that agreed to enter a 5-year, prospective glaucoma study. The CIGTS was not designed to answer the question studied; this investigation represents an analysis of a hypothesis that was posed after the study was conducted. Further, larger studies with a broader range of baseline VF loss are needed to confirm the applicability of our results to all subjects who experience an IOP spike after trabeculectomy.

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Table 1

Selected baseline and intraoperative characteristics of the CIGTS population studied. IOP = intraocular pressure; MD = mean deviation; PSD = pattern standard deviation; CPSD = corrected pattern standard deviation

	IOP spike (N = 17)*	No IOP increase (N = 261)*	P-value
Age (yrs)	57.6 ± 10.9	58.4 ± 10.7	0.77 [†]
Baseline IOP (mmHg)	27.5 ± 5.1	27.5 ± 5.8	0.98 [†]
Vertical Cup/Disc ratio	0.64 ± 0.19	0.70 ± 0.16	0.15 [†]
MD (dB)	-4.85 ± 3.58	-5.80 ± 4.31	0.37 [†]
PSD (dB)	5.35 ± 2.90	6.03 ± 3.63	0.45 [†]
CPSD (dB)	4.64 ± 3.24	5.37 ± 3.78	0.44 [†]
Black race	10 (59%)	91 (35%)	0.047 [∂]
Diabetes mellitus	4 (23.5%)	37 (14%)	0.18 [∂]
Intraoperative viscoelastic	4 (23.5%)	71 (27%)	0.92 [∂]

* mean ± standard deviation;

[†] Student two-sample t-test, 2-tail;

[∂] Fisher's exact test, 2-tail

Table 2

Comparison of MD, PSD, and CPSD measures between those with a POD 1 IOP spike and those with no IOP increase. MD = mean deviation; PSD = pattern standard deviation; CPSD = corrected pattern standard deviation. All measures in dB.

Variable	IOP spike (N = 17)*	No IOP increase (N = 261)*	P-value [†]
MD month 6	-5.36 ± 3.89 (N = 17)	-5.82 ± 4.59 (N = 253)	0.70
MD year 1	-4.40 ± 3.81 (N = 16)	-5.75 ± 4.73 (N = 249)	0.27
MD year 2	-4.17 ± 3.98 (N = 16)	-5.75 ± 4.94 (N = 235)	0.21
MD year 3	-4.31 ± 4.38 (N = 14)	-5.48 ± 4.73 (N = 218)	0.37
MD year 5	-3.57 ± 4.63 (N = 13)	-5.39 ± 4.77 (N = 201)	0.18
PSD month 6	4.83 ± 3.10 (N = 17)	5.56 ± 3.63 (N = 253)	0.42
PSD year 1	4.90 ± 2.84 (N = 16)	5.48 ± 3.51 (N = 249)	0.52
PSD year 2	4.89 ± 3.17 (N = 16)	5.64 ± 3.69 (N = 235)	0.43
PSD year 3	4.66 ± 2.52 (N = 14)	5.66 ± 3.85 (N = 218)	0.34
PSD year 5	4.30 ± 2.21 (N = 13)	5.85 ± 3.76 (N = 201)	0.033
CPSD month 6	4.16 ± 3.30 (N = 17)	4.88 ± 3.89 (N = 253)	0.46
CPSD year 1	4.33 ± 2.78 (N = 16)	4.80 ± 3.68 (N = 249)	0.61
CPSD year 2	4.33 ± 3.34 (N = 16)	4.93 ± 3.92 (N = 235)	0.55
CPSD year 3	3.83 ± 2.42 (N = 14)	4.95 ± 4.10 (N = 218)	0.13
CPSD year 5	3.31 ± 2.47 (N = 13)	5.15 ± 3.92 (N = 200)	0.10

* Mean ± standard deviation

[†] Student two-sample t-test, 2-tail

Table 3

Comparison of postoperative intraocular pressure (IOP) between participants with IOP spike vs. with no IOP increase on postoperative day (POD) 1.

	IOP spike (N = 17)[*]	No IOP increase (N = 261)[*]	P-value[†]
POD 1 IOP	37.2 ± 5.2 (N = 17)	11.5 ± 7.9 (N = 261)	< 0.001
Month 6 IOP	14.7 ± 6.2 (N = 17)	13.5 ± 4.8 (N = 253)	0.35
Year 1 IOP	14.5 ± 4.6 (N = 16)	14.2 ± 5.2 (N = 249)	0.85
Year 2 IOP	16.9 ± 6.6 (N = 16)	14.8 ± 5.2 (N = 235)	0.13
Year 3 IOP	17.8 ± 5.8 (N = 14)	14.8 ± 5.1 (N = 223)	0.040
Year 5 IOP	18.8 ± 6.3 (N = 13)	14.7 ± 4.8 (N = 203)	0.004

^{*} Mean ± standard deviation;

[†] Student two-sample t-test, 2-tail