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EFFECTS OF ARGON LASER TRABECULOPLASTY IN THE EARLY MANIFEST GLAUCOMA TRIAL

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Short title: Laser trabeculoplasty in the Early Manifest Glaucoma Trial

Abstract

Purpose: To analyze reduction of intraocular pressure (IOP) by argon laser trabeculoplasty (ALT) in the Early Manifest Glaucoma Trial, and factors influencing the effect of such treatment.

Design: Cohort study based on 127 patients from the treatment group of the Early Manifest Glaucoma Trial (EMGT), a randomized clinical trial.

Methods: Patients randomized to the treatment arm of the EMGT received a standard treatment protocol (topical betaxolol hydrochloride followed by 360°ALT) and were then followed prospectively at 3-month intervals for up to 8 years. One eye per patient was included in the analyses. We investigated the relationship between pre-ALT IOP and subsequent IOP reduction, and other factors that might have influenced the effect of ALT, including stage of the disease, trabecular pigmentation, presence of exfoliation syndrome, and treating surgeon.

Results: The mean pre-ALT IOP after betaxolol was 18.1 mmHg ± 3.9 (SD), and the mean short-term IOP reduction 3 months after ALT was 2.8 mmHg ± 3.9 (SD) (12.6% ± 20.5 SD). Pre-ALT IOP level strongly affected IOP reduction ($p < 0.001$); each 3-mmHg higher pre-ALT IOP value was associated with an additional mean IOP reduction of approximately 2 mmHg. The treating surgeons also had a significant impact on IOP reduction ($p = 0.001$), with mean values ranging from 5.8 to -1.3 mmHg.

Conclusions: In this cohort, which included many patients with low IOP levels, pre-ALT IOP markedly influenced the IOP reduction induced by ALT, seen as a much larger decrease in eyes with higher pre-ALT pressures. The treating surgeon also had a significant impact on ALT outcome.

Introduction

Argon laser trabeculoplasty (ALT) has been used to control open-angle glaucoma for more than thirty years,[1] in some cases as primary treatment, but more often as adjunctive treatment. It seems clear that the size of the pressure-lowering effect achieved with ALT depends on the level of pre-laser intraocular pressure (IOP), as indicated by several studies showing that IOP reduction (expressed in mmHg) is larger in eyes with higher untreated pressures.[2–5] Nevertheless, detailed knowledge is lacking with regard to the impact of baseline IOP on treatment effects, particularly concerning results obtained in patients with low pre-laser pressures.

We realized that it should be possible to obtain new knowledge in this area by using data collected in the Early Manifest Glaucoma Trial (EMGT). In short, this randomized clinical trial aimed to evaluate the effectiveness of IOP-reducing treatment in patients with manifest open-angle glaucoma.[6] The EMGT patients were randomized to a fixed treatment protocol (topical betaxolol plus ALT) or to no treatment. That approach differs from most other studies of ALT, which have given the laser treatment to patients with uncontrolled IOP. In EMGT pre-IOP values varied over a large range, and the study included a large proportion of patients with normal or even low IOP. This feature offered us the opportunity to study the influence of pre-laser IOP level on the pressure-lowering effect of ALT. Furthermore, treatment of the EMGT patients was not changed unless progression occurred, and thus data are available for several post-ALT years with unchanged topical therapy. Also, the use of an untreated control arm in the EMGT allowed us to evaluate any long-term non-treatment-related effects, such as whether there was a tendency for IOP to increase over time.

The purpose of the present study was to analyze the pressure-lowering effects of ALT in this group of prospectively followed patients, focusing on the role of the pre-ALT IOP level and other factors related to the IOP-reducing effects of ALT.

METHODS

The EMGT study design has been described in detail previously.[6] Briefly, this trial included patients with newly diagnosed and untreated primary open-angle glaucoma (POAG) or exfoliation glaucoma with early to moderate damage. The majority of patients were found in a large population-based screening of 44,000 elderly citizens in the cities of Malmö and Helsingborg, Sweden. Eligible eyes had glaucoma with established visual field damage, repeatedly demonstrated by the Humphrey 30-2 Full Threshold test and the Glaucoma Hemifield Test (GHT) being "outside normal limits". Patients were randomized to treatment or no treatment and prospectively followed by tonometry, perimetry, optic disc photography, and general ophthalmic examinations.

The current study included 127 of the 129 patients who were initially randomized to the EMGT treatment arm. Two patients were excluded for the following reasons: one refused ALT, and the other withdrew from the study directly after ALT. After randomization, patients received betaxolol eye drops 2 weeks before the laser procedure, which consisted of a full 360° ALT. One hour after pre-treatment of 100 msec duration were delivered to the pigmented part of the trabecular meshwork. The effect was 600–1400 mW, titrated to small bubble formation. The procedures were performed by seven surgeons who were experienced glaucoma specialists or ophthalmologists with a special interest in glaucoma.

Treatment was unchanged as long as progression did not occur. Progression was defined as worsening of visual fields according to pre-defined criteria[6] based on computerized analyses using glaucoma change probability maps,[7] which have been shown to offer high sensitivity and specificity.[8,9] Glaucoma progression could also be identified as worsening of the disc, which was assessed by masked readings at a disc photography reading center.[6,10] The protocol included a "safety hatch" that entailed an exception to the principle of unchanged therapy; in short, if the IOP in treated eyes exceeded 25 mmHg at two consecutive follow-up visits, additional pressure-lowering eye drops were prescribed. The extra drug was dorzolamide during the earlier phase of the trial but was later changed to latanoprost. This exception resulted in only a few changes in therapy (see the results section).

Patients were followed at 3-month intervals. At each visit, tonometry was performed by certified technicians using calibrated Goldmann applanation tonometers. Technicians were masked to the patient's study group (treated or untreated) and to earlier IOP values, and follow-up measurements were performed at approximately the same time of day whenever possible.

Pressure-reducing effect

Analyses of the IOP-reducing effect of ALT included one eye of each patient; if both eyes were eligible, one was randomly selected. We used follow-up IOP measurements obtained every 3 months during the first year after ALT (n = 4) and every 6 months during the second year (n = 2), and all available 12-month measurements from the third year onwards. Only IOP values recorded up to the time of progression were included, since treatment could have been changed after that point, and could thus affect IOP.

Pre-ALT IOP was defined as the last IOP measurement before ALT, i.e. the eyes were then treated with betaxolol. The reduction in IOP achieved by ALT was defined as the difference between the pre-ALT IOP value and the IOP value at the 3-month follow-up visit.

The mean and median IOP measurements for all patients remaining in the study at each time point are not reported here, because such values would be misleading. Inasmuch as higher IOP was associated with faster progression,[11,12] patients with lower initial IOP levels would have gradually become more over-represented among the non-progressing group. Therefore, we instead calculated IOP slopes over time for each patient, which was done to assess changes that only included IOP values recorded while the patient was still in the study and had not reached progression or received treatment according to the safety hatch exception (see above). The patients were subsequently divided into those with at least five IOP measurements during follow-up and those with fewer than five such values, because errors in measurement changes over time can be particularly large when only a few observations are available. One patient with a single IOP measurement after ALT was excluded from these analyses.

Statistical significance of the difference between pre-ALT IOP and IOP 3 months after ALT was evaluated by two-tailed t-tests. Similarly, the t-test was applied to compare the exfoliation and POAG patients with regard to the mean IOP reduction 3 months after ALT.

Factors influencing pressure reduction

We also evaluated factors that might have influenced short-term (3-month) IOP reduction by ALT. The primary aim was to study the influence of pre-ALT IOP, but we also considered possible effects of the following: the treating surgeon, stage of the disease defined by the perimetric mean deviation (MD, average of 2 baseline fields), trabecular pigmentation (grades 0–3), and presence of exfoliations (dilated examination).

A stepwise multiple linear regression analysis of IOP reduction was performed using pre-ALT IOP, baseline MD, diagnosis (exfoliation glaucoma or POAG), and trabecular pigmentation grade as independent variables.

We used two-way ANOVA to analyze the influence of the treating surgeon on total IOP reduction and on percentage pressure reduction. Pre-ALT IOP values were included in the analysis to discern any interaction between surgeon and pre-ALT IOP. Eyes were divided into three different pressure groups with equal IOP intervals (based on pre-ALT measurements): ≤16, 17–23, and ≥24 mmHg. Two-way ANOVA using Type III sums of squares was employed to handle unbalanced data resulting from differences in the numbers of treated patients per surgeon and pre-ALT group.

All statistical calculations were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Follow-up time ranged from at least 3 months to a maximum of 8 years (mean 57 months, median 60 months). Among the 127 patients, 3 were lost to follow-up during the study period. Sixty-four patients progressed, and 14 died. For 9 patients who either discontinued betaxolol or had a change of therapy, we included IOP values only as long as treatment remained unchanged.

Baseline characteristics

Baseline characteristics of the 127 patients are shown in Table 1. Sixty-four percent were female; 119 (94%) had primary open-angle glaucoma, and 8 (6%) had exfoliation glaucoma. Mean baseline IOP was 20.7 mmHg. Almost all patients had slight to moderate trabecular pigmentation, and 92 (72.5%) had early field loss with a perimetric MD better than –6 dB.

Short- and long-term pressure reduction

The mean pre-ALT IOP after betaxolol treatment was low, 18.1 mmHg. Mean short-term IOP reduction (3 months after ALT) was 2.8 mmHg ($p < 0.001$) or 12.6%. The pressure-lowering effect was larger in patients with exfoliation glaucoma than in those with POAG: 6.6 vs. 2.5 mmHg ($p = 0.003$). However, this difference was not significant in the multivariate analysis (cf. below and Table 2). The mean of all IOP slopes over time was slightly positive (0.19 mmHg/year ± 0.75) for the 113 patients with five or more post-ALT IOP measurements (Figure 1). Compared to those subjects, the 13 patients with fewer than five such measurements had greater mean IOP slopes, although those results may have been sensitive to measurement errors and were likely influenced by the selected characteristics and short follow-up of these 13 cases (Figure 1).

Factors influencing intraocular pressure reduction

Pre-ALT IOP was a significant factor influencing the magnitude of IOP reduction (Table 2 and Figures 2 and 3). Every 3 mmHg of higher pre-ALT IOP was associated with an additional IOP reduction of approximately 2 mmHg ($p < 0.001$; $r^2 = 0.47$). Patients with a pre-ALT IOP below 15 mmHg had no mean pressure lowering (Figures 2 and 3).

The surgeon performing ALT was another factor with a significant impact on IOP reduction (Table 2) ($p = 0.001$). The mean IOP reduction among the seven surgeons ranged from 5.8 to -1.3 mmHg. No interaction was found between surgeon and pre-ALT pressure in the three different IOP groups (i.e., ≤ 16, 17–23, and ≥ 24 mmHg), and this applied when presenting the IOP reduction in mmHg (p = 0.458) (Figure 4), and as percentages (p = 0.591). IOP reduction was not significantly affected by baseline perimetric MD or the presence of exfoliations or trabecular pigmentation (Table 2).

DISCUSSION

The present results regarding EMGT patients show a mean IOP reduction of 2.8 mmHg 3 months after ALT, and the IOP slopes suggest that the mean pressure-lowering effect decreased slightly over time. Higher pre-ALT IOP was associated with a considerably and significantly better pressure-reducing influence of ALT. Moreover, the treating surgeon (p = 0.001) was another important factor related to the effectiveness of ALT.

The current study had strengths and weaknesses. Among the former were the prospective nature of the EMGT, the broad recruitment through a large population study, the long-term follow-up, and the fact that all patients randomized to the treatment arm were treated according to the standard protocol, regardless of their pre-ALT IOP. The last-mentioned feature enabled us to analyze the importance of pre-ALT levels even at low IOP levels. Another advantage of our investigation was that EMGT included an untreated control arm, and the results from this group were useful when evaluating measured IOP changes over time. A weakness of our study was that it did not include many eyes with very high pre-ALT IOP values, since untreated mean IOP levels over 30 mmHg were an exclusion criterion, and all patients received topical betaxolol before the laser procedure. The small number of patients with pseudoexfoliation decreased the power to detect differences between exfoliation glaucoma and POAG. Also, two other factors to some extent limited the generalizability of the results: all patients had early to moderate damage, and almost all patients were Caucasian.

Compared to the current observations, most previous studies have reported larger pressure reductions when using ALT. The Glaucoma Laser Trial (GLT)[13] reported a mean IOP reduction of 9 mmHg after primary ALT, the Advanced

Glaucoma Intervention Study (AGIS)[14] showed just under 7 mmHg, Agarwal et al.[15] found 6.8 mmHg. In Moorefields Primary Treatment Trial, IOP reduction was 14 mmHg after 6 monhts, but from a high average pre-treatment level of 35 mmHg.[16] Other investigators[17–25] have published values ranging from 5.9 to 12.1 mmHg. There are three possible explanations for these differences:

1. First, and most important, the mean baseline IOP was higher in all of the mentioned studies compared to our investigation. Therefore, it is interesting to note that the mean pressure reductions in the GLT and AGIS were close to those predicted from the regression line in Figure 2. Both those trials studied the effects of 360° ALT, as was also done in the EMGT.
2. Second, patients in the EMGT received primary betaxolol, which further reduced the mean pre-ALT pressure.
3. Third, regression to the mean occurs in almost all studies that require a minimum IOP level for eligibility,[14,21,22,25–28] and this phenomenon results in an apparent increase in treatment effects. However, as expected, this was not observed in the untreated control group in the EMGT,[29] because no minimum IOP was required for eligibility.

Our observation that IOP reduction diminished over time agrees with the results of many published studies.[20,22,24,26,30–32] Nevertheless, few of the cited investigations specified the magnitude of the decreasing effect, although Shingleton et al.[33] did report a 2.4 mmHg increase in IOP over a 10-year follow-up. There are several possible explanations for the observed IOP elevations. For instance, it is often assumed that IOP will increase over time in glaucoma, but it seems unlikely that this occurred in the EMGT patients, because IOP remained stable in the untreated control group, except in eyes with exfoliation glaucoma.[29] Subsensitivity to betaxolol is another factor that might have contributed to an upward IOP drift. Several studies have reported subsensitivity to timolol, whereas the results of other well-designed investigations, including one double-masked long-term study using placebo-treated controls,[34] have indicated that timolol treatment is not associated with a reduced effect over time.[35,36]

Thus, our findings demonstrate that IOP before the laser procedure was the most important factor influencing the effect of the treatment. The magnitude of this impact was impressive: every mmHg higher pre-ALT IOP was associated with 2/3-mmHg greater pressure reduction. However, even if this magnitude is noteworthy, the larger treatment effects with higher pre-laser IOP levels is not surprising, but has been shown in several earlier studies.[2–5,16] The size of the pressure reduction in our study is similar to that reported by Grinich and co-workers[4] but is substantially larger than that noted by Traverso et al.[5] No previous investigations have revealed a relationship between pre-ALT IOP level and IOP reduction in a large number of eyes with normal-tension glaucoma.

We have not found any data to corroborate our observation of an apparent lack of treatment effects in eyes with IOP levels around 15 mmHg or lower. Grinich et al.[4] detected no influence of ALT on eyes with IOP below approximately 20 mmHg, but the great majority of their patients had considerably higher pre-ALT IOP values compared to our subjects. In light of the lack of positive results in eyes with such low pre-laser IOP, and the fact that in some eyes the pressure was actually higher after ALT, it might be best to observe caution when considering ALT treatment for patients with IOP levels in the mid teens. This is speculative but it would clearly be of interest to find out whether or not our observation is supported by data from other prospective studies.

In our investigation, the treating surgeon had a large and significant influence on the effectiveness of ALT. It seems that this issue has not been specifically examined in earlier studies, although Rosenthal et al.[17] and Elsås and Johnsen[26] have described increasing success as surgeons gradually gained experience in ALT, and Tuulonen et al.[37] found evidence that ALT results were better when the procedure was performed by ophthalmology specialists than when it was conducted by residents. All surgeons performing ALT in the EMGT had considerable experience and were certified, and hence we were somewhat surprised to find such obvious differences between them. Clearly, this is an aspect that should be investigated further in existing databases from other studies. If our observation can be confirmed, it would be desirable to ascertain what factors determine surgical success in order to improve laser protocols and ultimately also future results of ALT.

We found larger IOP reductions in eyes with exfoliation glaucoma, but pre-laser IOP levels were higher in those eyes compared to non-exfoliation eyes, and exfoliation status was not a significant factor in the multivariate analysis. Considering the small number of eyes with exfoliation glaucoma in our material, it is obvious that non-significant findings might be explained by insufficient statistical power regarding exfoliation status. Many studies have shown that IOP reduction is larger in exfoliation glaucoma than in POAG,[2,5,19,22,32,38] even after performing multivariate analyses to correct for differences in pre-ALT IOP between these two types of the disease.[3]

There is no agreement as to whether the pressure-lowering effect of ALT is influenced by trabecular pigmentation or pigmentation grade,[3–5,22,24,37,38] and we found no significant impact of either of those aspects in our investigation. However, it should be reiterated that the power of our study was low in this context, because only 7 patients had a non-pigmented trabecular meshwork.

In conclusion, our results show that the mean IOP level of 18.1 mmHg in the EMGT patients before 360° ALT was decreased 2.8 mmHg by the laser treatment, and this effect diminished somewhat over an 8-year period. The success of ALT in lowering pressure was most markedly affected by the pre-ALT IOP level, and the treating surgeon also had a significant impact.

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C. Contribution of Authors

Design of the study (AH, BB); conduct of the study (AH, BB, MCL, DP); collection of data (AH, DP); data analyses (AH, BB, DP); interpretation of the data (AH, BB, DP, MCL); preparation of the data (BB, DP); review and approval of the manuscript (AH, DP, BB, MCL).

D. Statement about Conformity with Author Information

The study was approved both by the Ethics Committee of Lund University, Sweden, and the Committee in Research Involving Human Subjects at the State University of New York, and all patients provided written informed consent.

The Early Manifest Glaucoma Trial is registered as: NIH Clinical Trials.gov identifier NCT00000132. Date of registration: September 23, 1999.

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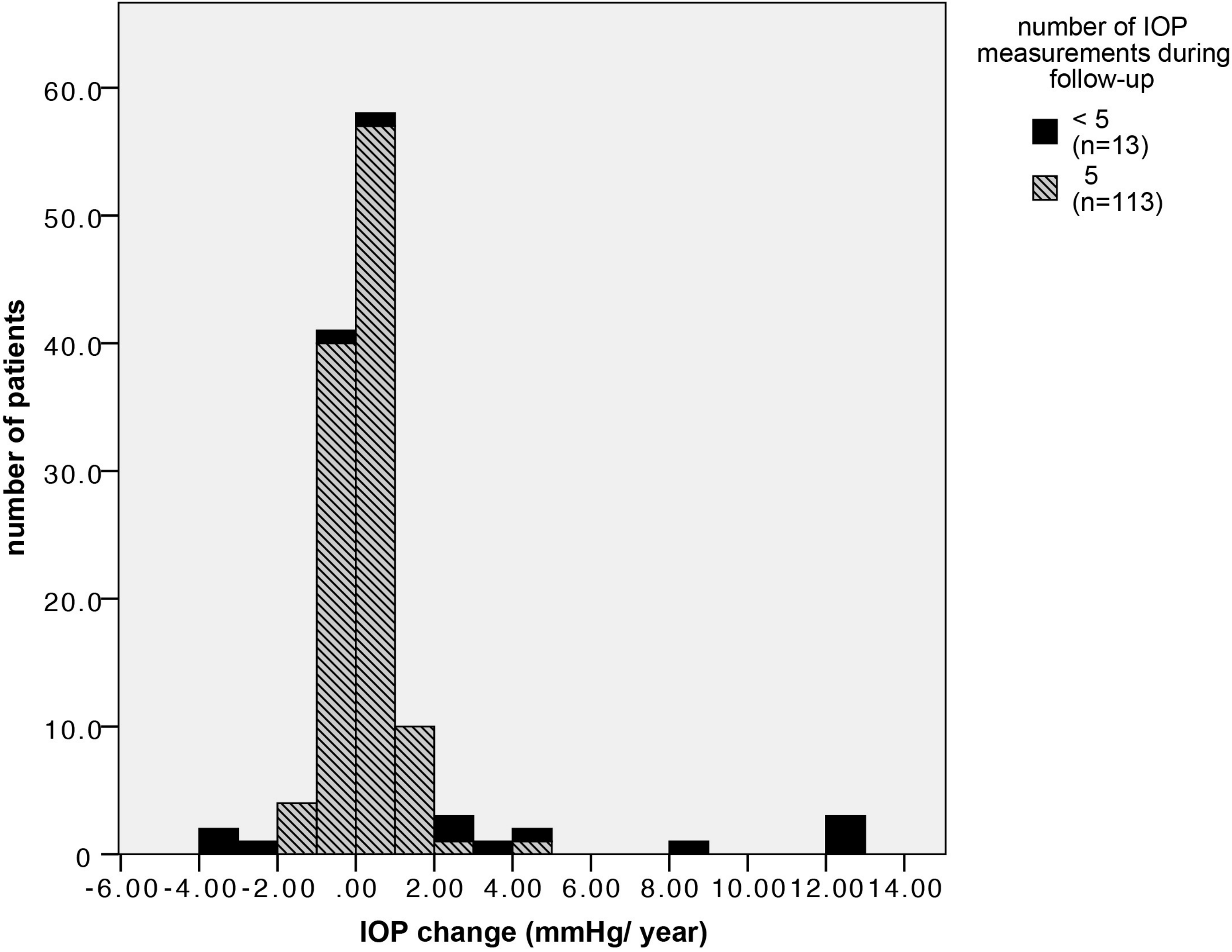
Figure captions

FIGURE 1. Change in intraocular pressure (IOP) over time after treatment with argon laser trabeculoplasty in the Early Manifest Glaucoma Trial. Change in IOP over time was calculated by linear regression analysis. The regression line for the 113 patients with five or more IOP measurements during follow-up has a slightly positive slope (0.19 mmHg/year), much smaller than the slope seen for the 13 patients with fewer than five IOP measurements (3.58 mmHg/year).

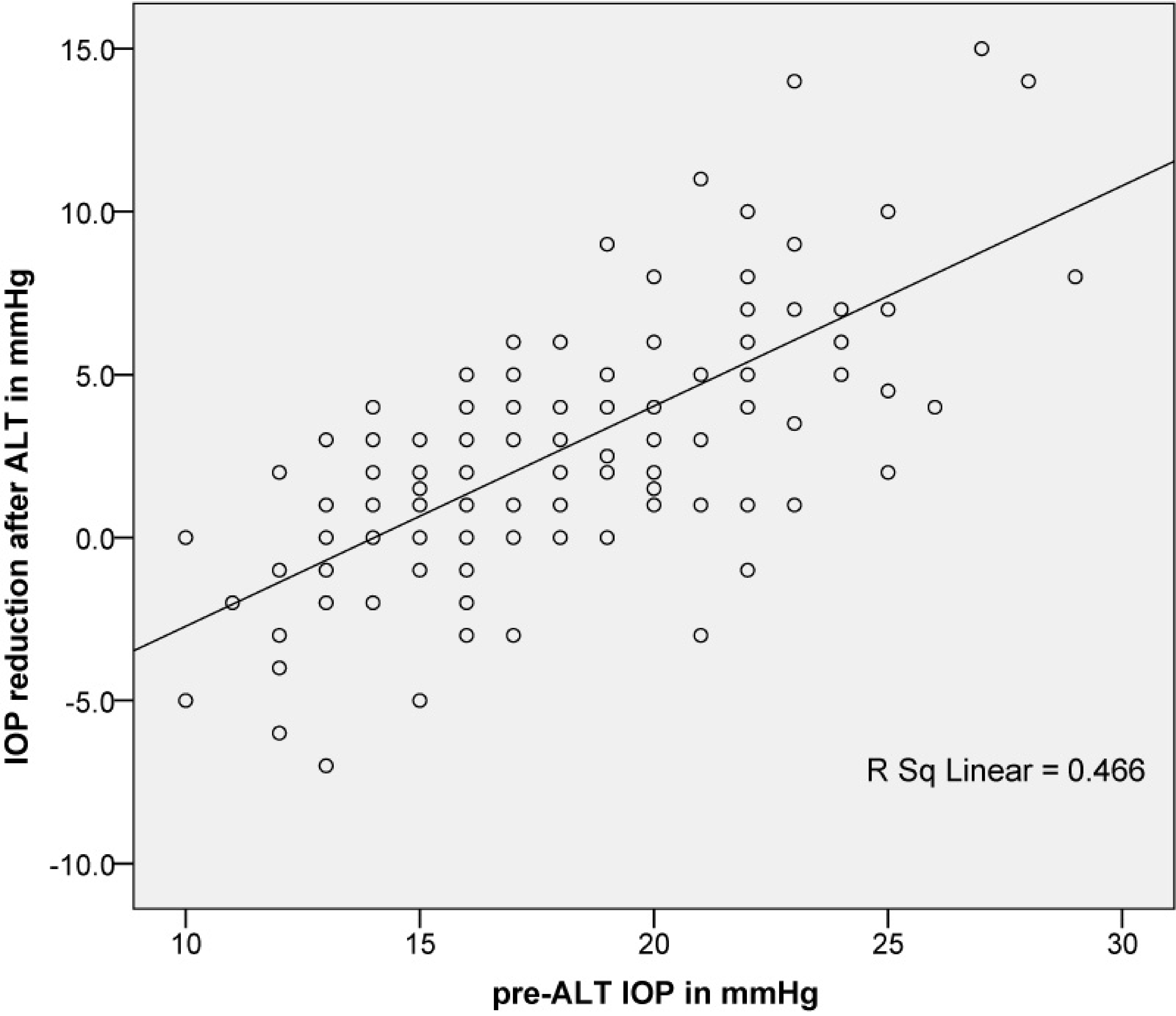
FIGURE 2. Pre-argon laser trabeculoplasty (pre-ALT) intraocular pressure (IOP) and total ALT-induced IOP reduction in mmHg in patients from the Early Manifest Glaucoma Trial. Pre-ALT IOP was an important factor determining total IOP reduction by ALT. Each 3-mmHg higher pre-ALT IOP was related to an additional IOP reduction of approximately 2 mmHg.

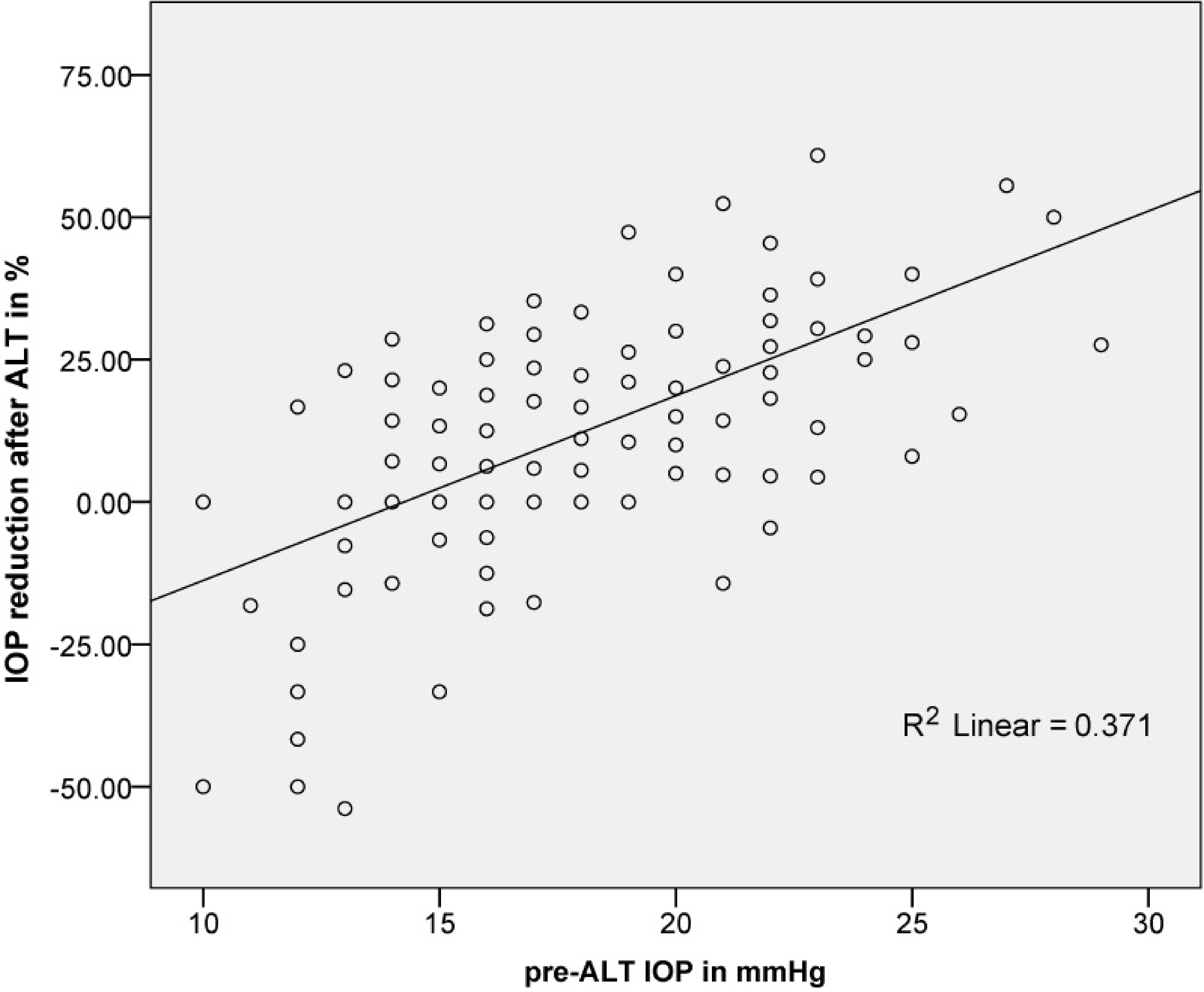
FIGURE 3. Pre-argon laser trabeculoplasty intraocular pressure (IOP) and percentage ALT-induced IOP reduction in patients from the Early Manifest Glaucoma Trial. Pre-ALT IOP was an important factor determining percentage IOP reduction by ALT.

FIGURE 4. Pre-argon laser trabeculoplasty and ALT-induced intraocular pressure (IOP) reduction for each surgeon in the Early Manifest Glaucoma Trial. Eyes were divided into three groups according to pre-ALT IOP levels. Pressure reduction depended significantly on treating surgeon and different levels of pre-ALT IOP.

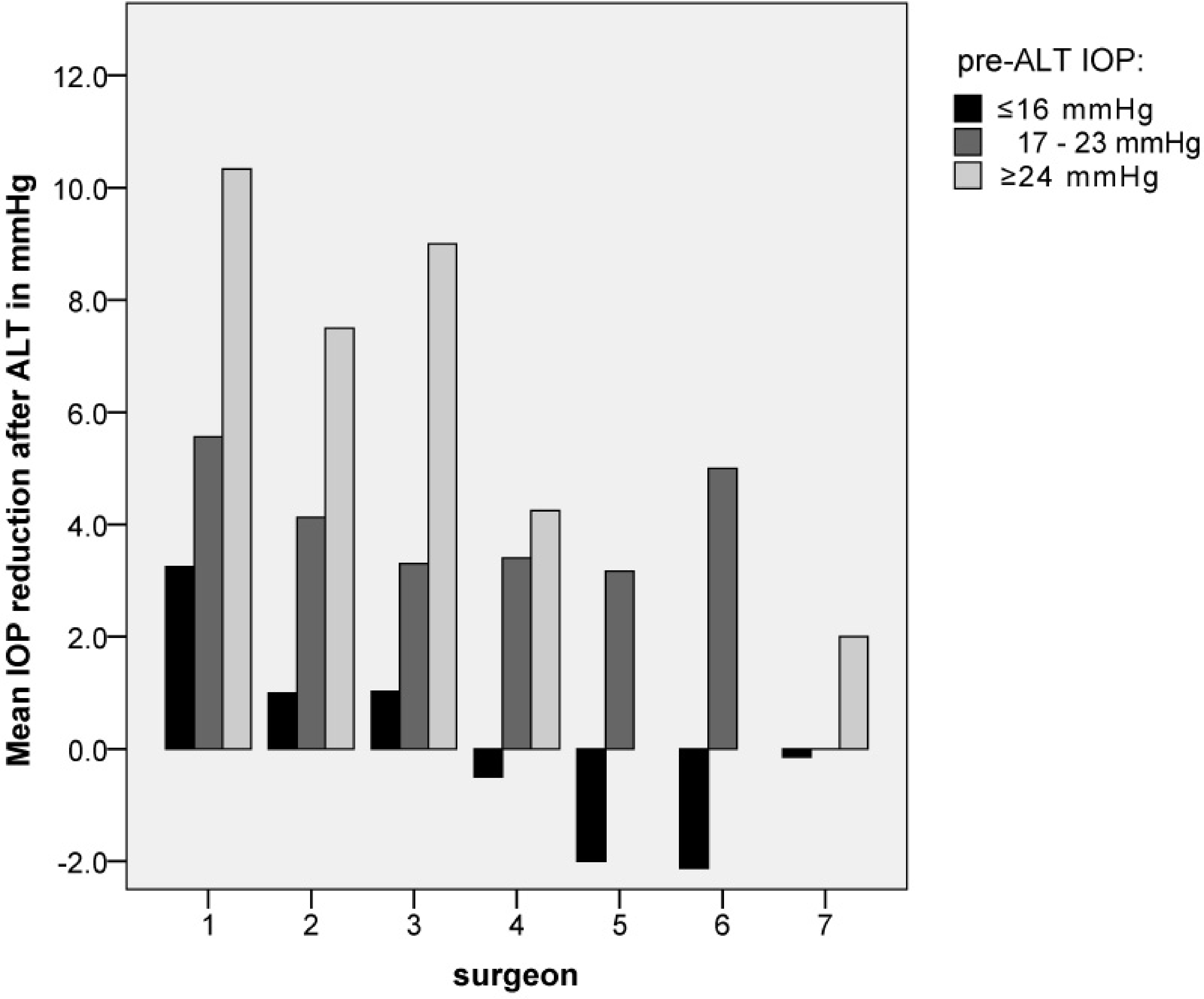


number of IOP measurements during follow-up
< 5 (n=13)
5 (n=113)
number of patients
60.0
50.0
40.0
30.0
20.0
10.0
0
-6.00
-4.00
-2.00
.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
IOP change (mmHg/ year)


15.0
10.0
5.0
0.0
-5.0
-10.0
IOP reduction after ALT in mmHg
R Sq Linear = 0.466
10
15
20
25
30
pre-ALT IOP in mmHg



75.00
50.00
25.00
0.00
-25.00
-50.00
IOP reduction after ALT in %
10
15
20
25
30
pre-ALT IOP in mmHg
R2 Linear = 0.371



pre-ALT IOP:
≤16 mmHg
17 - 23 mmHg
≥24 mmHg
Mean IOP reduction after ALT in mmHg
12.0
10.0
8.0
6.0
4.0
2.0
0.0
-2.0
1
2
3
4
5
6
7
surgeon

Table 1. Baseline Characteristics before Argon Laser Trabeculoplasty in the Early Manifest Glaucoma Trial

Characteristic		n (%)	Mean ± SD (median [range])
Age in years		127 (100)	68.6 ± 4.8 (68.2 [58.2 to 78.9])
Sex	Female	81 (63.8)	---
	Male	46 (36.2)	
Diagnosis	Primary open-angle glaucoma	119 (93.7)	---
	Exfoliation glaucoma	8 (6.3)	
Trabecular pigmentation	Grade 0	7 (5.5)	---
	Grade 1	50 (39.4)	
	Grade 2	62 (48.8)	
	Grade 3	8 (6.3)	
Intraocular pressure before any treatment		127 (100)	20.7 ± 4.0 (20 [13 to 30])
Intraocular pressure immediately before argon laser trabeculoplasty in mmHg	All groups	127 (100)	18.1 ± 3.9 (18 [10 to 29]]
	Group 1: 10 to 16 mmHg	48 (37.8)	---
	Group 2: 17 to 23 mmHg	67 (52.8)	
	Group 3: 24 to 29 mmHg	12 (9.4)	

Baseline mean deviation in dB	127 (100)	–4.8 ± 3.7 (–4.2 [–14.7 to –1.3])

Table 2. Factors Potentially Affecting Intraocular Pressure Reduction Achieved by Argon Laser Trabeculoplasty in the Early Manifest Glaucoma Trial

Variables		n	Stepwise multiple linear regression Beta (p-value)	Univariate two-way ANOVA p-value[a] (p-value)[b]
Intraocular pressure immediately before argon laser trabeculoplasty (ALT)		127	0.683 (< 0.001)	< 0.001 (< 0.001)
Baseline perimetric deviation		127	–0.092 (0.182)	---
Trabecular pigmentation grade	0 1 2 3	7 50 62 8	0.002 (0.981)	---
Exfoliations	Yes No	8 118	0.072 (0.297)	---
Surgeon	No. 1 No. 2 No. 3 No. 4 No. 5 No. 6 No. 7	23 8 54 11 9 9 13	---	0.001 (0.01)

[a]Total intraocular pressure reduction achieved by ALT as dependent variable.
[b]Percentage intraocular pressure reduction achieved by ALT as dependent variable.