The effect of mydriasis and filtration surgery on intraocular pressure in eyes with normal- tension glaucoma

Rei Sakata (reisakata-tky@umin.ac.jp)
The University of Tokyo Hospital
Koji Ueda
Miyata Eye Hospital
Asahi Fujita
The University of Tokyo Hospital
Kosuke Nakajima
Showa General Hospital
Takashi Fujishiro
The University of Tokyo Hospital
Megumi Honjo
The University of Tokyo Hospital
Shiroaki Shirato
Yotsuya Shirato Eye Clinic
Makoto Aihara
The University of Tokyo Hospital

Research Article

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Abstract

Background:

The effect of mydriasis on intraocular pressure (IOP) in normal tension glaucoma (NTG) eyes has not been investigated. In addition, although filtration surgery is a technique that can lower IOP under normal conditions and reduce IOP fluctuation, its effect on IOP after mydriasis is unknown. Against this background, we investigated the effect of mydriasis on IOP and of trabeculectomy on mydriasis-induced IOP fluctuations in the same patients with NTG.

Methods:

We identified data for NTG patients regularly monitored for more than 5 years before and after surgical periods. All patients were conservatively followed up as medical treatment and then underwent initial trabeculectomy with mitomycin C as the surgical treatment. The mean IOPs during episodes of mydriasis and non-mydriasis were calculated for each period. IOP fluctuation was defined as the IOP difference between the mydriatic and non-mydriatic states. For both periods, the mean IOP differences between the mydriatic and non-mydriatic eye were separately evaluated using the paired t-test or the Wilcoxon signed-rank test.

Results:

We included 23 eyes of 23 patients with NTG (mean age, 62.4 years). The follow-up periods were 5.7 years for medical treatment and 6.1 years after surgical treatment. The mean IOP of 14.3 mmHg decreased to 9.0 mmHg after surgery ($P < 0.01$). During medical treatment, the mean (± standard deviation) non-mydriatic and mydriatic IOPs were 14.2 ± 1.8 and 14.5 ± 1.8 mmHg, respectively. The IOP increased significantly after mydriasis (by 0.30 ± 0.11 mmHg, $P = 0.009$). After surgery, the mean non-mydriatic and mydriatic IOPs were 9.0 ± 2.5 and 9.1 ± 2.4 mmHg; the difference was 0.18 ± 0.16 mmHg ($P = 0.28$).

Conclusions:

We demonstrated for the first time that pharmacological mydriasis significantly increased IOP, but trabeculectomy could suppress not only IOP but also mydriasis-induced IOP fluctuations in patients with NTG.

Introduction

Intraocular pressure (IOP) is the only treatable factor in patients with glaucoma. However, IOP fluctuates both diurnally and seasonally and during aging (1–5), and these fluctuations are a risk factor for glaucoma progression in eyes with normal-tension glaucoma (NTG) (6). IOP is influenced principally by the balance between aqueous humor production and discharge; thus, night-time pupillary dilatation may cause IOP fluctuations attributable to decreased aqueous humor discharge. However, it is difficult to ascertain whether pupillary dilatation affects IOP fluctuations in daily life. Although physiological mydriasis may not be in play in these patients, several reports have described IOP increments in open-angle eyes (normal eyes, and those with primary open-angle glaucoma and pseudoexfoliation) after the induction of pharmacological mydriasis (7–15). However, it has not been investigated in eyes with NTG.

Mydriasis (pupil dilation) is one of the most frequently performed examinations in ophthalmic clinics and is usually achieved by applying eye drops containing a sympathomimetic agent and a parasympathetic blocker. IOP elevation can be explained by various mechanisms, including increased outflow resistance in the main pathway caused by ciliary muscle relaxation (14), increased aqueous inflow combined with decreased outflow (16), and increased outflow resistance associated with iris pigment dissemination (12). Increased secondary pathway flow may also occur, reducing IOP in certain cases (9, 17). The principal mechanism in play is thought to depend on the anatomical structure of the eye, which differs among individuals.

Among the many surgical options for glaucoma, trabeculectomy with instillation of an antimetabolite such as mitomycin C is one of the most reliable and powerful techniques for reducing IOP (18). Additional postoperative interventions (e.g., laser suture lysis) can be used, if necessary, to reduce IOP. Trabeculectomy with an antimetabolite increases aqueous flow with a relatively low risk of complications, and IOP can be safely reduced to below 10 mmHg using this technique (19, 20). This approach not only lowers the absolute value of IOP but also suppresses the long-term and/or short-term IOP fluctuations associated with many different situations (21–23). This is thought to be because the combination of peripheral iridotomy during filtration surgery and the creation of an aqueous humor flow outlet to the outside of the eye yields continuous filtration. Thus, mydriasis-induced IOP fluctuations may be eliminated in eyes that have undergone filtration surgery.

Considering this background, we examined the effect of mydriasis on IOP and of trabeculectomy on mydriasis-induced IOP fluctuations in patients with NTG in the same eye over consecutive periods of more than 10 years.

Methods

We retrospectively evaluated the medical records of Japanese NTG patients who were followed up for more than 5 years with medical treatment at the Yotsuya Shirato Eye Clinic (Tokyo, Japan) and for more than 5 years after initial trabeculectomy. All protocols and methods adhered to the tenets of the Declaration of Helsinki, and the study was approved by the Ethics Committee of the Riverside Internal Medicine Cardiology Clinic (approval ID: RSC-1811RB01). Since this was a retrospective study, the need for informed consent was waived by the committee (the Ethics Committee of the Riverside Internal Medicine Cardiology Clinic).

Inclusion criteria

1) Japanese patients with open-angle glaucoma

The diagnostic criteria for NTG were as follows: glaucomatous optic neuropathy and corresponding visual field (VF) defects as determined by Humphrey VF analysis; an IOP that was consistently normal (< 21 mmHg) in the absence of medication, as determined by Goldmann applanation tonometry; a normal open angle on gonioscopy; and the absence of any other ocular or systemic diseases that could affect the optic nerve head and/or the VF. The optic disc was examined via direct ophthalmoscopy, stereoscopic evaluation using a biomicroscope fitted with appropriate lenses, and fundus photography.

2) The surgical procedure was an initial trabeculectomy (fornix-based, with mitomycin C).

3) Patients were followed up for at least 10 years, including at least 5 years after medical management and at least 5 years after surgical management.

Exclusion criteria

1) Eyes with primary angle-closure glaucoma, pseudoexfoliation glaucoma (XFG), or secondary glaucoma.

2) The use of pilocarpine or a systemic cholinergic agonist at any time.

3) The use of oral corticosteroids.

IOP measurement

IOP was measured using Goldmann application tonometry (Haag-Streit, Köniz, Switzerland) over the entire study period. In both the medical and surgical follow-up periods, the IOP measurements were as follows: non-mydriatic (visit 1), mydriatic (visit 2), non-mydriatic (visit 3), mydriatic (visit 4), non-mydriatic (visit 5), and mydriatic (visit 6). The interval between each visit was approximately three months. One drop of 0.5% tropicamide/0.5% phenylephrine (both w/v) combination eye drops (Mydrin-P; Santen, Osaka, Japan) was instilled to induce mydriasis. After confirming adequate mydriasis (pupil diameter, 6 mm or more in a bright room), IOP measurements were performed. Thus, the IOP of each patient was measured over 10 times in mydriasis and non-mydriasis before and after trabeculectomy, respectively. The total IOP of each patient was over 40.

Surgical methods

After instillation of local anesthetic into the sub-Tenon space, a 5–6-mm fornix-based conjunctival incision was created along the limbus on the temporal side. After cauterization, a single rectangular scleral flap (3 × 3 mm) was prepared. The surgical area was soaked in 0.05% (w/v) mitomycin C for 1.5 min and then washed with 50 mL of balanced salt solution. A sclerocorneal block (vertical 0.5 mm ×

horizontal 2.0 mm) was then prepared, followed by peripheral iridectomy, placement of three or four 10-0 nylon scleral flap sutures (MANI, Utsunomiya, Japan), adjustment of the aqueous humor flow using an additional suture, and placement of a wing conjunctival suture. In patients undergoing contemporaneous cataract surgery, a clear corneal incision was made in the superior quadrant, and the anterior chamber was filled with viscoelastic material (Viscoat 0.5 Ophthalmic Viscoelastic Substance; Alcon, Tokyo, Japan) and 1% (w/v) Healon Ophthalmic Viscoelastic Substance (AMO, Tokyo, Japan). An intraocular lens was placed in the posterior chamber. Postoperative treatment consisted of four applications of 0.1% (w/v) betamethasone and moxifloxacin ophthalmic solution after trabeculectomy alone; in patients who underwent combined surgery, diclofenac sodium ophthalmic solution was added. If postoperative bleb formation was insufficient or IOP management was necessary, laser suture lysis or bleb needling was performed at the surgeon's discretion.

Statistical methods

We evaluated the IOP during two consecutive periods in the same patients after topical medication (medical treatment) and after surgery. For both periods, the mean IOP differences (actual values) between the mydriatic and non-mydriatic eye were separately evaluated using the paired *t*-test or the Wilcoxon signed-rank test. The IOP within 6 months after surgery and the IOP immediately after laser suture lysis and needling were excluded from the IOP data after surgery. The Wilcoxon signed-rank test was used when the IOP data were not normally distributed, as revealed by the Shapiro–Wilk normality test. We also explored whether cataract surgery affected IOP. Pre- and postoperative IOP fluctuations were calculated for each group and analyzed similarly. All statistical analyses were conducted using R version 4.0.0 (Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a two-sided P-value < 0.05.

Results

Overall, 23 eyes (4 right, 19 left) of 23 NTG patients (9 men, 14 women) were followed up for more than 10 years; the mean patient age was 62.4 years. The mean follow-up period was 5.7 years (standard deviation [SD], 0.94 years) after medical treatment and 6.1 years (SD, 0.75 years) after surgical treatment. The mean IOP of 14.3 mmHg decreased to 9.0 mmHg after surgery (P < 0.01). Detailed patient demographic data are presented in Table 1.

After medical treatment, the mean IOPs in the non-mydriatic and mydriatic states were 14.2 ± 1.8 and 14.5 ± 1.8 mmHg, respectively; thus, the IOPs were significantly different (mydriatic IOP − non-mydriatic IOP = 0.30 ± 0.11 mmHg [P = 0.009]). In contrast, trabeculectomy significantly suppressed IOP fluctuations (non-mydriatic IOP, 9.0 ± 2.5 mmHg; mean mydriatic IOP, 9.1 ± 2.4 mmHg; difference, 0.18 ± 0.16 mmHg [P = 0.28]) (Figure 1). With respect to the surgical method, neither the single-surgery group (12 cases) nor the cataract combined-surgery group (11 cases) exhibited any significant IOP fluctuations after mydriasis (Figures 2 and 3).

Discussion

We examined the effect of mydriasis on IOP and of trabeculectomy on mydriasis-induced IOP fluctuations in patients with NTG who were followed up during medical treatment and after surgical treatment, yielding over 40 IOP records for more than 5 years before and after the surgery. A significant increase in IOP was observed after mydriasis; however, after filtration surgery, the IOP change was no longer significant. Although mydriasis after surgery differs from physiological mydriasis, the results suggest that filtration surgery can suppress the post-mydriatic IOP changes. Eyes with NTG have been shown to exhibit IOP fluctuations in daily life (24), perhaps because the pupil diameter affects aqueous humor dynamics. After successful filtration surgery, continuous filtration might eliminate small IOP changes.

We evaluated only long-term follow-up (≥ 10 years) data because many variables affect IOP fluctuations, which are difficult to capture using short-term data. Diurnal and seasonal IOP fluctuations are likely to be the highest in eyes with open-angle glaucoma with higher IOP (25). Therefore, we included only open-angle eyes with NTG; we thought that such effects would be minimal in such eyes.

The relationship between physiological mydriasis (a change in pupil diameter) and IOP changes is difficult to study; thus, we explored how pharmacological mydriasis affected IOP changes. The IOP increase after pharmacological mydriasis has been attributed to ciliary muscle paralysis caused by parasympathetic blockers (7). The ciliary muscles control the tension of the trabecular meshwork; when these muscles relax, traction is reduced and aqueous humor outflow decreases, increasing IOP. Harris et al. (7) reported an increase in IOP after the application of 1% (w/v) cyclopentolate to 2% of normal eyes and 23% of eyes with open-angle glaucoma. Sympathomimetics also appear to affect the IOP. Phenylephrine hydrochloride (an α1-adrenergic agonist) differs from epinephrine in that it lacks a hydroxyl group at the 4-position of the benzene ring. This agent induces mydriasis, which is maximal within 60 min. Tropicamide/phenylephrine combination treatment has been also reported to result in elevated IOP. Kim et al. (14) reported significant IOP elevation in normal participants with open-angle glaucoma after the application of 2.5% (w/v) phenylephrine and 1% (w/v) tropicamide. Shaw et al. (9) found significant IOP elevations in 32% of patients with open-angle glaucoma after the application of 2.5% (w/v) phenylephrine and 1% (w/v) tropicamide. In a study enrolling normal eyes and eyes with primary open-angle glaucoma (POAG) and PE glaucoma, elevated IOP was observed after mydriasis in all except the normal eyes; however, these changes were not significant (15). The relationship between pharmacological mydriatics and IOP change is listed in Table 2. The drug concentration of 0.5% phenylephrine/0.5% tropicamide (both w/v) combination (a sympathomimetic agent/parasympathetic blocker) we used in this study was much lower than that reported in other studies.

Table 2

Relationship between pharmacological mydriatics and intraocular pressure

Author(s)	Year	Subjects	Main results
Harris LS	1968	POAG, normal	IOP elevation was seen in 23% of open-angle glaucoma
Valle O	1976	POAG	as for provocative test
Shaw BR	1986	POAG	significant pressure elevation occurred in 37 eyes (32%)
Hancox	2002	OAG, cataract, medical retina	change in IOP following dilatation was seen in all three groups (mean 0.4 mmHg)
Pukrushpan P	2006	Non-glaucoma patients	post-dilatation IOP was equivalent to pre-dilatation IOP
Shihadeh WA	2011	PE	PE were at risk of developing delayed post-dilation IOP rises
Qian CX	2012	normal	35% of patients had IOP elevation of > 2 mm Hg
Kim JM	2012	normal	a significant increase in IOP after dilation
Atalay E	2015	POAG, PE glaucoma, normal	glaucoma patients experienced a higher rate of IOP elevation
Our study	2021	NTG	IOP increased significantly in the medically treated period

POAG (OAG); primary open-angle glaucoma, PE; psudoexfoliation, NTG; normal tension glaucoma, IOP; intraocular pressure

Even if IOP is well-managed in the outpatient clinic, glaucoma may progress, as reflected by large IOP fluctuations (6, 26, 27). Trabeculectomy is the most common surgical treatment for glaucoma, reducing not only IOP per se but also suppressing IOP fluctuations (21–23, 28). In one report on diurnal IOP variation after trabeculectomy/mitomycin C, such surgery significantly reduced not only the mean IOP but also IOP fluctuations during both day and night (23). Even earlier, filtration surgery was reported to reduce the mean diurnal IOP, range of diurnal variation, and day-to-day IOP variability (28).

IOP fluctuations caused by postural changes are thought to be short-term (minutes) in nature (29), as are fluctuations induced by mydriasis. Hirooka et al. (21) reported that the mean IOP difference between the sitting and supine positions was 4.1 ± 1.6 mmHg during the medication period; this difference reduced to 2.2 ± 1.5 mmHg after trabeculectomy. Both studies cited above found that IOP fluctuations were well-controlled after successful trabeculectomy. Sawada et al. (22) investigated the IOP fluctuations caused by postural changes in Japanese patients with glaucoma. The IOP difference between the sitting and lateral decubitus positions was 3.3 mmHg in the eye drop group, but only 1.0 mmHg in the trabeculectomy group; thus, surgery significantly suppressed the IOP fluctuations caused by postural changes.

We found a significant IOP increase after mydriasis during the drug-treatment period in eyes NTG for the first time, but this was suppressed after filtration surgery. Although this was not a cross-sectional study (unlike previous reports), rather a long-term preoperative/postoperative work, we consider that the reliability of our study might be relatively high. However, given the small number of patients, further study is needed to determine whether filtration surgery indeed better suppresses IOP fluctuations compared to medical treatment.

Our study had several limitations. First, the number of cases studied was relatively small. A short data collection period would be acceptable if only IOP fluctuations were evaluated. Nevertheless, at least 12 IOP measurements were performed over the 3-year follow-up period (six each in the presence and absence of mydriasis; 4 visits/year). If the follow-up period was extended to 5 years, at least 20 measurements were taken (10 each in the presence and absence of mydriasis). In addition, the IOP measurement time points were “scattered” between the morning and afternoon. Since this was a retrospective study, IOP measurement times could not be unified. In addition to diurnal variations, IOP measurements are susceptible to errors and seasonal variations; more measurements increase reliability. This is the main reason why we chose a follow-up period of ≥ 10 years; the number of available subjects was small, and a very long follow-up was essential. In addition, automatic static VF testing was performed routinely. In open-angle glaucoma patients, the IOP increases after such testing (30); thus, any IOP fluctuation may not have been clearly separated from other effects. The aqueous humor outflow resistance increases when the angle narrows on the induction of a continuous mydriatic state in the dark (31). The stress caused by VF testing affects ciliary aqueous humor production via the sympathetic nervous system (32). Ni et al. (30) reported that 109 open-angle glaucoma patients (109 eyes) exhibited a significant increase (1.2 mmHg) in the mean IOP after automatic, static VF examination. However, we believe that any effect of VF testing on IOP was minimized because we allowed all participants to rest between the VF examination and IOP measurement. Regarding the surgical method, a single procedure markedly reduced IOP (33); there was no significant difference in this context between a single procedure and combined procedures (34, 35). There is no indication that combined surgery lowers IOP better. Thus, we considered it safe to include the combined cataract surgery group in our overall population. Finally, since we included only NTG patients, who were believed to show small IOP fluctuations, data for high IOP or XFG eyes, in which IOP fluctuations would be expected to be greater (25), are required in the future.

In conclusion, we investigated the effects of mydriasis on IOP and of filtration surgery on mydriasis-induced IOP fluctuations in NTG eyes by using long-term preoperative/postoperative data including the total IOP of each patient was over 40 times. During the preoperative drug-treatment period, a significant increase in IOP was observed after mydriasis, but no significant IOP change was observed after filtration surgery. Filtration surgery has been reported to reduce IOP and limit IOP fluctuations, we suggest that this surgery can also suppress mydriasis-induced IOP fluctuations.

Declarations

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Authors' contributions

Study conception and design: Makoto Aihara, Shiroaki Shirato, Acquisition of data: Koji Ueda, Rei Sakata, Asahi Fujita, Kosuke Nakajima, Takashi Fujishiro, Megumi Honjo, Shiroaki Shirato, Makoto Aihara Analysis of interpretation of data: Koji Ueda, Rei Sakata, Makoto Aihara, Drafting of manuscript: Koji Ueda, Rei Sakata, Makoto Aihara, Critical revision: Shiroaki Shirato, Makoto Aihara

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are not publicly available due to [them containing information that could compromise research participant privacy/consent] but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All protocols and methods adhered to the tenets of the Declaration of Helsinki, and the study was approved by the Ethics Committee of the Riverside Internal Medicine Cardiology Clinic (approval ID: RSC-1811RB01). Since this was a retrospective study, the need for informed consent was waived by the committee (the Ethics Committee of the Riverside Internal Medicine Cardiology Clinic).

Consent for publication

Not applicable

Competing interests

All authors have nothing to disclose

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Tables

Table 1

Clinical Characteristics of the Patients

	Total	Single trabeculectomy	Cataract surgery combined
Eyes (number)	23	11	12
Age (years)	62.4 ± 12.5	57.3±13.4	67.9 ± 7.5
Gender	Males, 4; Females,19	Male 1; Females,10	Males, 3; Females, 9
Lateral	Right, 9; Left, 14	Right, 8; Left, 3	Right, 1; Left, 11
Best-corrected visual acuity	−0.020 ± 0.18	−0.057 ± 0.22	0.019 ± 0.088
Refraction (diopters)	−5.6 ± 4.2	−6.3 ± 2.8	−4.7 ± 5.0
Central corneal thickness (μm)	489 ± 33	497 ± 40	483 ± 23
Mean deviation (dB)	−11.3 ± 7.0	−8.7 ± 5.7	−14.2 ± 6.9
Pattern Standard Deviation (dB)	10.2 ± 4.6	9.2 ± 3.9	11.3 ± 4.8
Follow-up period (years)	Preoperative 5.7 ± 0.9 Postoperative 6.1 ± 0.7	Preoperative 5.5 ± 0.8 Postoperative 6.0 ± 0.7	Preoperative 6.0 ± 0.9 Postoperative 6.1 ± 0.8
Mean intraocular pressure (mmHg)	Preoperative 14.3 ± 1.8 Postoperative 9.0 ± 2.4	Preoperative 15.1 ± 1.3 Postoperative 9.4 ± 2.3	Preoperative 13.4 ± 1.7 Postoperative 8.5 ± 2.5

Table 2

Relationship between pharmacological mydriatics and intraocular pressure

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Qian CX	2012	normal	35% of patients had IOP elevation of >2 mm Hg
Kim JM	2012	normal	a significant increase in IOP after dilation
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Our study	2021	NTG	IOP increased significantly in the medically treated period

POAG (OAG); primary open-angle glaucoma, PE; psudoexfoliation, NTG; normal tension glaucoma, IOP; intraocular pressure

Figures

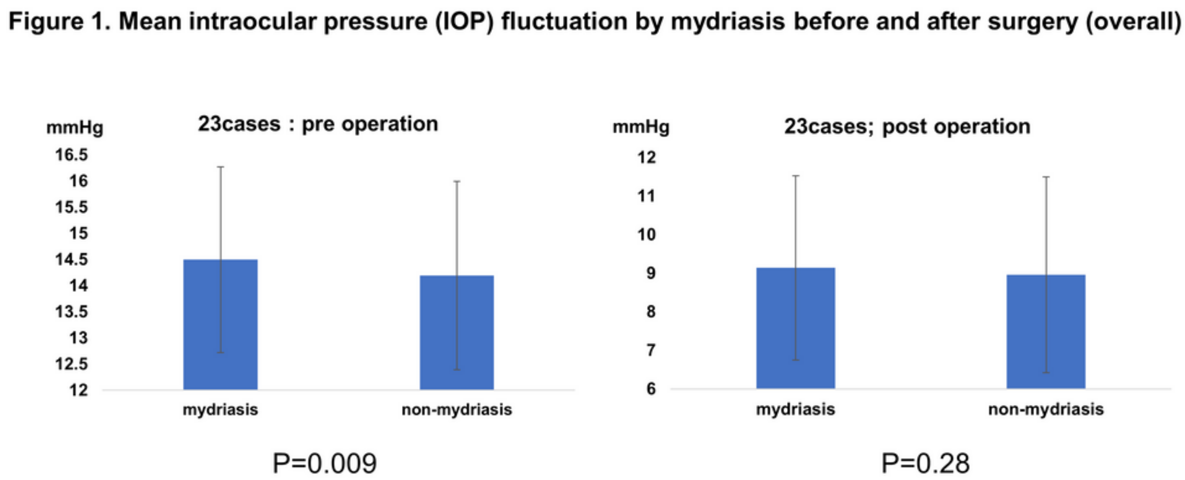

Figure 1

Mean intraocular pressure fluctuation by mydriasis before and after surgery (overall)

Among the 23 NTG patients, the mean IOP (non-mydriasis) was 14.2 ± 1.8 mmHg, and the IOP (mydriasis) was 14.5 ± 1.8 mmHg during the medical treatment period. The mean IOP (non-mydriasis) was 9.0 ± 2.5 mmHg and IOP (mydriasis) was 9.1 ± 2.4 mmHg during the surgical treatment period.

Figure 2. Mean IOP fluctuation by mydriasis before and after surgery in cases of a single procedure

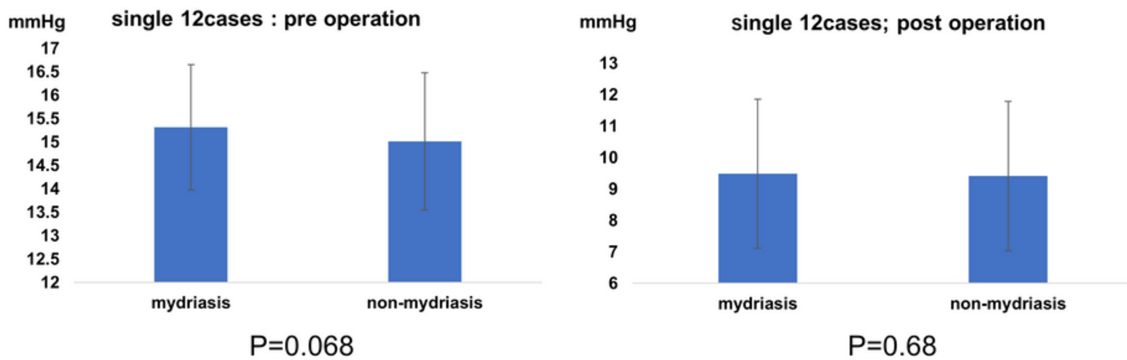

Figure 2

Mean intraocular pressure fluctuation by mydriasis before and after surgery in cases of a single procedure

In a single surgery (12 cases), the mean IOP (non-mydriasis) was 15.0 ± 1.5 mmHg, and the IOP (mydriasis) was 15.3 ± 1.3 mmHg during the medical treatment period. The mean IOP (non-mydriasis) was 9.4 ± 2.4 mmHg and IOP (mydriasis) was 9.5 ± 2.4 mmHg during the surgical treatment period.

Figure 3. Mean IOP fluctuation by mydriasis before and after surgery in cases of the triple procedure

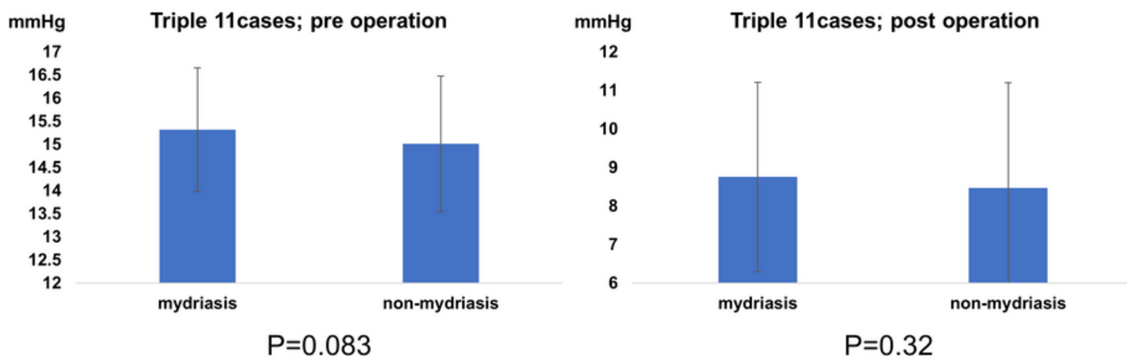

Figure 3

Mean intraocular pressure fluctuation by mydriasis before and after surgery in cases of the triple procedure

In cataract combined surgery (11 cases), the mean IOP (non-mydriasis) was 13.3 ± 1.8 mmHg, and the IOP (mydriasis) was 13.6 ± 1.8 mmHg during the medical treatment period. The mean IOP (non-mydriasis) was 8.5 ± 2.7 mmHg and IOP (mydriasis) was 8.8 ± 2.5 mmHg during the surgical treatment period.