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Research Article

Current Status of Mitomycin C-Augmented Trabeculectomy in Japan Based on Collaborative Bleb-Related Infection Incidence and Treatment Study

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Abstract

Purpose: To investigate the current status and demographics of patients who underwent mitomycin C-augmented trabeculectomy (MMC-trabeculectomy) in Japan using data from the Collaborative Bleb-related Infection Incidence and Treatment Study.

Subjects and Methods: Out of 1,249 patients (1,249 eyes), we selected patients who underwent trabeculectomy alone or phacotrabeculectomy using MMC. Age at the time of surgery, type of glaucoma, pre-operative intraocular pressure (IOP) and medications, previous anti-glaucoma procedures, visual function, routine ophthalmic examination results and intra-operative complications were recorded.

Results: A total of 1,098 patients (1,098 eyes) were enrolled in this study. The mean age was 63.7±13.1 years, and there were 648 males and 450 females. The mean number of anti-glaucoma eyedrops used was 2.7 types, and 40.2% of the patients concomitantly used an oral carbonic anhydrase inhibitor. The proportion of fornix-based conjunctival incision was comparable to that of limbus-based conjunctival incision. A scleral flap was created at the superior site in 99.7% of all eyes. Primary open angle glaucoma was the most predominant glaucoma subtype, followed by secondary glaucoma and psuedoexfoliation glaucoma. Significant differences in glaucoma subtypes, age, pre-operative IOP, pre-operative medications, pre-operative visual acuity, and proportion of phacotrabeculectomy were observed. There were 31 (2.6%) intra-operative complications. The most frequent complications were failure of conjunctival closure, hyphema, and phacoemulsification-related complications. The cumulative incidence of intra-operative complications was significantly different among glaucoma subtypes.

Conclusions: Subjects in Japan who underwent MMC-trabeculectomy were predominantly advanced cases. Patient background characteristics and complications were different between glaucoma subtypes.

Keywords: *Glaucoma; Trabeculectomy; Phacotrabeculectomy; Surgical Complication*

Introduction

Reducing intraocular pressure (IOP) is the most important factor in halting glaucomatous optic neuropathy using medication, laser therapy, or a surgical procedure. In general, mitomycin C (MMC)-augmented trabeculectomy (referred to as MMC-trabeculectomy) is a common type of surgery performed on glaucoma patients. MMC-trabeculectomy should be employed when the maximal tolerable pharmacologic IOP-lowering therapy and/or laser surgery fail to deterioproportion optic nerve damage. A previous study reported no significant difference in visual field defects between the initial medical therapy and surgical therapy over five years [1], although MMC-trabeculectomy occasionally results in severe complications and deterioration of visual function [2-4]. Few reports have described the criteria for the performance of MMC-trabeculectomy on eyes with glaucoma. The Japan Glaucoma Society initiated a prospective study to investigate

the cumulative incidence and the severity of bleb-related infection (Collaborative Bleb-related Infection Incidence and Treatment Study [CBIITS] [3]. In this study, we investigated the current status and demographics of patients who underwent MMC-trabeculectomy in Japan.

Subjects and Methods

This study has been conducted according to the principles expressed in the Declaration of Helsinki. Institutional review board approval was obtained at each institution, and all of the patients gave written informed consent after a thorough explanation of the study. As described previously [5], the CBIITS was a multicenter prospective cohort study performed in Japan. The primary aim of the CBIITS was to determine the incidence of and the risk factors for bleb-related infections. A total of 34 clinical centers located in Japan participated and enrolled subjects in the CBIITS. The enrollment period was 2 years, and follow-up was performed every 6 months for up to 5 years. The enrollment criteria were as follows: any type of filtering surgery, including those performed concomitantly with cataract or other intraocular surgery; the first eye opeproportiond on after study inclusion in cases in which both eyes were treated; and an expected 1 year of follow-up at the time of surgery. The indications for surgery, the selection of the operative procedure and the operative technique, and the administration of postoperative medications or additional glaucoma treatments (either medically or surgically) were determined at the discretion of the local investigators. Consecutive eligible subjects were recruited at each clinical center. Additional visits to the clinical center or to other ophthalmology clinics occurred at the discretion of the local investigators. In this study, we focused on patients who underwent trabeculectomy alone or phacotrabeculectomy using MMC. We collected the following data concerning the study subjects: age at the time of surgery, type of glaucoma, pre-operative IOP and medications, previous anti-glaucoma procedures, visual function, routine ophthalmic examination results, and intra-operative complications. Because pseudoexfoliation glaucoma (XFG) was very common relative to the other subtypes of secondary glaucoma (SG), XFG was analyzed as an independent glaucoma subtype.

Statistical Analysis

JMP version 11 (SPSS Japan Inc., Tokyo, Japan) was used for statistical analysis. The log minimum angle of resolution (MAR) visual acuity values were used for the analysis of visual function. The visual perception of finger counting and hand motion was replaced by a value of 2 or 3, respectively. Age, pre- and post-operative IOP, Humphrey visual field mean deviation (MD), and refractive error were considered as continuous variables, which were expressed as the means ± standard deviation. Sex, systemic diseases, history of intraocular surgery, lens status, glaucoma subtype, type of surgery, type of conjunctival incision, site of scleral flap, intra- and post- operative complications, and post-operative procedures and surgeries were considered as categorical variables. Repeated-measures ANOVA was used to compare the IOP values. the Pearson correlation coefficient test for P-values less than 0.05 were considered statistically significant.

Results

Patient demographics

As previously reported [5], the CBIITS enrolled 1,249 eyes of 1,249 cases. Of these, 151 eyes were excluded from the present study for the following reasons: 38 eyes had been treated with surgical techniques other than trabeculectomy alone or trabeculectomy combined with phacoemulsification and intraocular lens implantation; 65 eyes had undergone surgery without adjunctive MMC treatment; and 48 eyes lacked follow-up data because the cases were lost to follow-up before the 1 - year follow-up examination. A total of 1,098 eyes of 1,098 cases satisfied the enrollment criteria in this study. Table 1 summarizes the demographics of the enrolled subjects. The mean age was 63.7 ± 13.1 years, and there were 648 males and 450 females. The mean equivalent refractive error among phakic eyes at the time of surgery was -2.5 ± 4.1 D. Mean number of anti-glaucoma eyedrops was 2.7 types, and 40.2% of the subjects concomitantly used an oral carbonic anhydrase inhibitor. A majority of the patients (83.4%) underwent MMC-trabeculectomy alone. In 2.7% of the cases, the eyes were concomitantly treated with 5-fluorouracil at the time of surgery. The proportion of fornix-based conjunctival incision (FBCI) was comparable to that of limbus-based conjunctival incision (LBCI). Only 0.3% surgeries were approached at the inferior site.

Parameter	
Age (range) (years)	63.7 ± 13.1 (13 - 92)
Male: female (%)	59.0: 41.0
Pre-IOP (range) (mmHg)	25.4 ± 9.6 (70 – 12)
Pre-operative visual acuity logMAR	0.423 ± 0.60
Pre-refractive error* (range) (D)	-2.5 ± 4.1 (-12.2 – 13.3)
Pre-eyedrops (range)**	2.7 ± 1.1 (0 - 6)
Oral CAI	40.2%
Pre-MD §(range)(dB)	-18.5 ± 8.0 (0.8 - -33.34)
Previous glaucoma surgery (range)(times)	1.3 ± 0.70(0 – 6)
Trabeculectomy: phaco-trabeculectomy (%)	83.4: 16.6
MMC only: MMC+5FU (%)	97.3: 2.7
Conjunctival incision (Fornix-base: limbal base) (%)	56.9: 43.1
Bleb location (%) (superior: superior temporal: superior nasal: inferior)	68.0: 18.4: 13.3: 0.3

Table 1: *Demographics.*

*MAR: logarithmic minimum angle of resolution; D: diopter; CAI: carbonic anhydrase inhibitor; MD: mean deviation; MMC: mitomycin C; 5FU: 5-fluorouracil; *phakic eyes only; **fixed combination calculated as 2; §HFA30-2 only*

Comparison of parameters among glaucoma subtypes

As shown in Figure 1, primary open angle glaucoma (POAG) was the most predominant glaucoma subtype (43.3%), followed by SG (21.9%), and XFG (8.1%). Normal tension glaucoma (NTG) was observed in 6.0% of the cases. We investigated the differences in demographic characteristics between glaucoma subtypes after elimination of unclassified eyes (Table 2). Significant differences in age (Figure 2), pre-operative IOP (Figure 3), pre-operative medication score (Figure 4), pre-operative logMAR (Figure 5), the proportion of phacotrabeculectomy (Figure 6), and sex (Table 2) between glaucoma subtypes were detected.

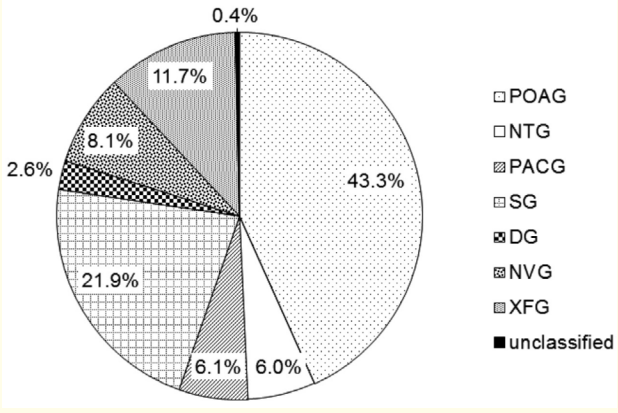

Figure 1: *Distribution of glaucoma subtypes.*

POAG: primary open angle glaucoma; NTG: normal tension glaucoma; PACG: primary angle-closure glaucoma; SG: secondary glaucoma; DG: developmental glaucoma; NVG: neovascular glaucoma; XFG: psuedoexfoliation glaucoma

	Age (Years)		Pre-Operative Logmar		Pre-Operative Iop(Mmhg)		Pre-Operative Medication Score		Sex (%)	Simple Vs. Combined (%)
	Mean ± SD	95%CI	Mean ± SD	95%CI	Mean ± SD	95%CI	Mean ± SD	95%CI	Male	Combined
POAG	64.0 ± 0.6	62.9 - 65.1	0.31 ± 0.51	0.26 - 0.35	22.4 ± 7.4	21.7 - 23.1	3.2 ± 1.5	3.1 - 3.4	59.0	19.0
NTG	63.2 ± 1.5	60.3 - 66.1	0.13 ± 0.37	0.04 - 0.23	15.2 ± 4.6	14.1 - 16.4	2.2 ± 1.1	2.0 - 2.5	43.9	13.6
PACG	69.6 ± 1.5	66.7 - 72.4	0.40 ± 0.56	0.27 - 0.54	24.7 ± 9.1	22.5 - 27.0	3.4 ± 1.5	3.1 - 3.8	37.3	31.3
SG	59.9 ± 0.8	58.4 - 61.5	0.51 ± 0.63	0.43 - 0.59	31.1 ± 10.2	29.7 - 32.4	3.8 ± 1.5	3.6 - 4.0	57.3	12.0
DG	41.2 ± 2.3	36.8 - 45.7	0.74 ± 0.74	0.46 - 1.03	27.2 ± 10.3	23.2 - 31.2	3.9 ± 1.3	3.4 - 4.4	64.3	10.7
NVG	62.6 ± 1.3	60.1 - 65.0	1.17 ± 0.67	1.03 - 1.31	34.0 ± 9.8	31.9 - 36.1	3.7 ± 1.4	3.4 - 4.0	75.3	4.5
XFG	72.6 ± 1.1	70.5 - 74.7	0.27 ± 0.42	0.19 - 0.34	25.0 ± 7.5	23.7 - 26.4	3. 5 ± 1.4	3.2 - 3.7	70.3	19.5

Table 2: *Comparison among glaucoma subtypes.*

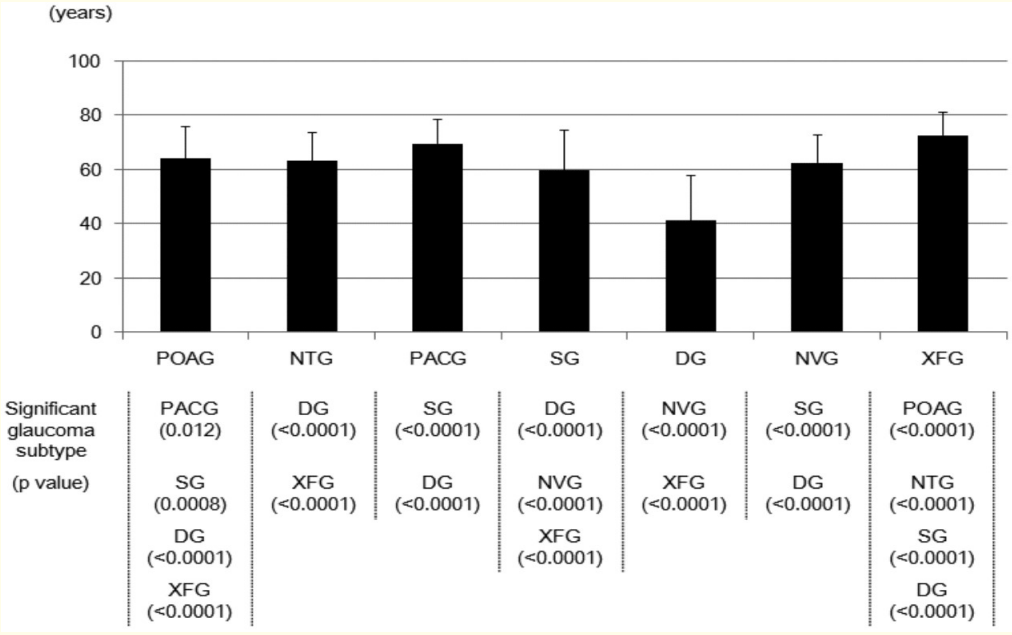

Figure 2: *Comparison of age between glaucoma subtypes.*

POAG: primary open angle glaucoma; NTG: normal tension glaucoma; PACG: primary angle-closure glaucoma; SG: secondary glaucoma; DG: developmental glaucoma; NVG: neovascular glaucoma; XFG: psuedoexfoliation glaucoma

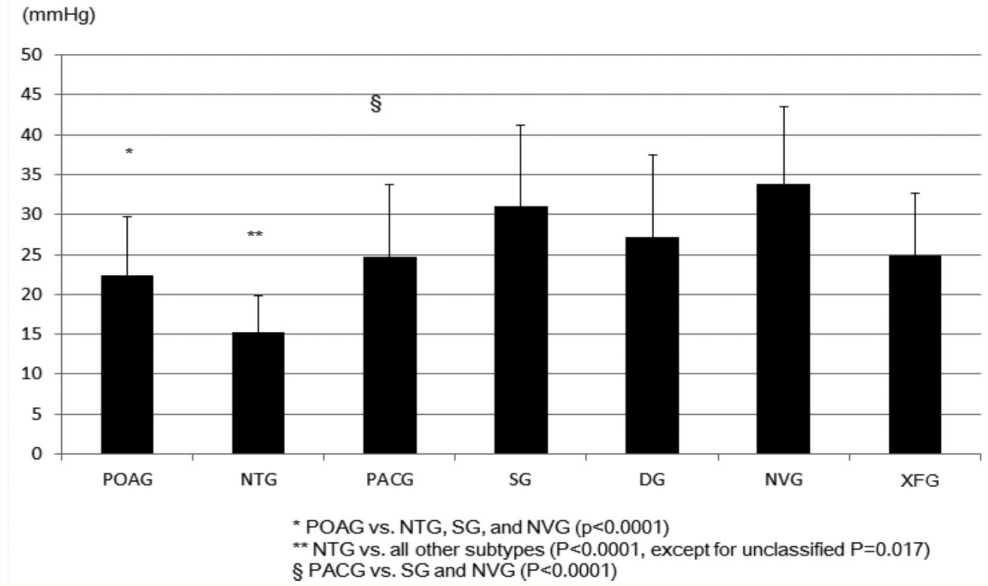

Figure 3: *Comparison of pre-operative intraocular pressure between glaucoma subtypes.*
POAG: primary open angle glaucoma; NTG: normal tension glaucoma; PACG: primary angle-closure glaucoma; SG: secondary glaucoma; DG: developmental glaucoma; NVG: neovascular glaucoma; XFG: psuedoexfoliation glaucoma

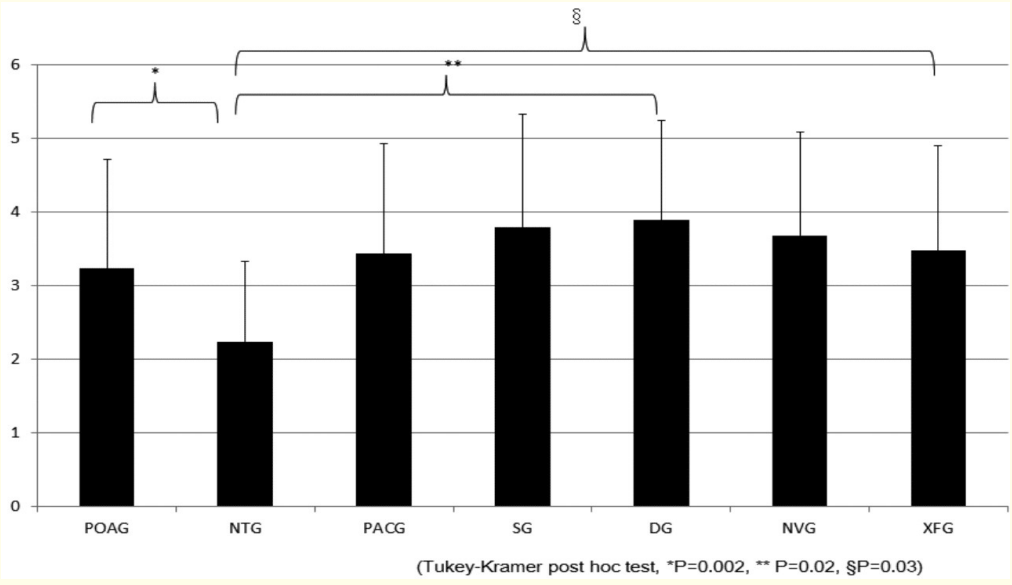

Figure 4: *Comparison of pre-operative medications between glaucoma subtypes.*
POAG: primary open angle glaucoma; NTG: normal tension glaucoma; PACG: primary angle-closure glaucoma; SG: secondary glaucoma; DG: developmental glaucoma; NVG: neovascular glaucoma; XFG: psuedoexfoliation glaucoma

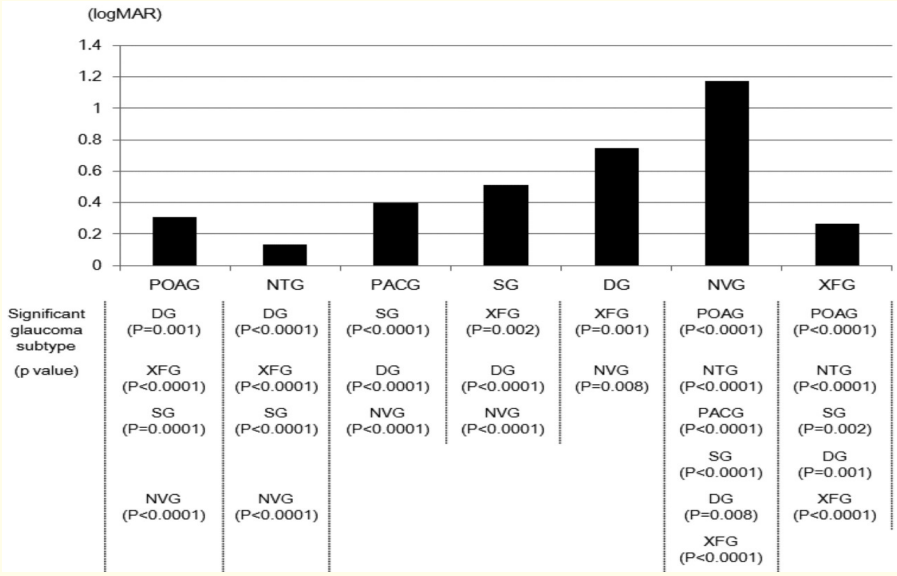

Figure 5: *Comparison of pre-operative logMAR between glaucoma subtypes.*
POAG: primary open angle glaucoma; NTG: normal tension glaucoma; PACG: primary angle-closure glaucoma; SG: secondary glaucoma; DG: developmental glaucoma; NVG: neovascular glaucoma; XFG: psuedoexfoliation glaucoma; MAR: minimum angle of resolution

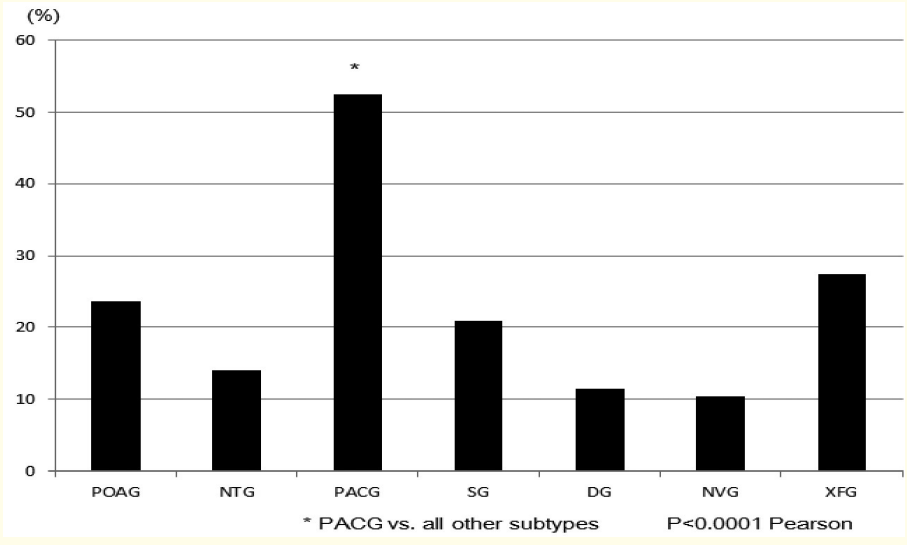

Figure 6: *Comparison of proportion of phacotrabeculectomy between glaucoma subtypes.*
POAG: primary open angle glaucoma; NTG: normal tension glaucoma; PACG: primary angle-closure glaucoma; SG: secondary glaucoma; DG: developmental glaucoma; NVG: neovascular glaucoma; XFG: psuedoexfoliation glaucoma

Intra-operative complications

There were 61 (5.6 %) intra-operative complications (Table 3). The frequent complications were hyphema (3.5 %) and failure of conjunctival closure (0.7 %). Ten eyes (0.9 %) exhibited phacoemulsification-related complications, predominantly rupture of the posterior lens capsule (5 eyes). There was a significant difference in the cumulative incidence of intra-operative complications between glaucoma subtypes. NVG showed highest cumulative incidences of intra-operative complications than other glaucoma subtypes (Figure 7). Intra-operative complications were different among glaucoma subtypes. Hyphema was a major complications in NVG eyes, while, phacoemulsification-related complications were popular in PACG eyes.

Intra-operative complications		Cases (%)	
Phaco-related # of cases (%)	Post capsule rupture	5	10(0.9%)
	Damage of Tinn's zonule	2	
	Vitreous herniation in anterior chamber	2	
	IOL capture	1	
Failure of conjunctival closing # of cases (%)			8(0.7%)
Hyphema # of cases (%)			38(3.5%)
Others # of cases (%)			5(0.5%)
Total # of cases (%)			61(5.6%))

Table 3: *Intra-operative complications.*

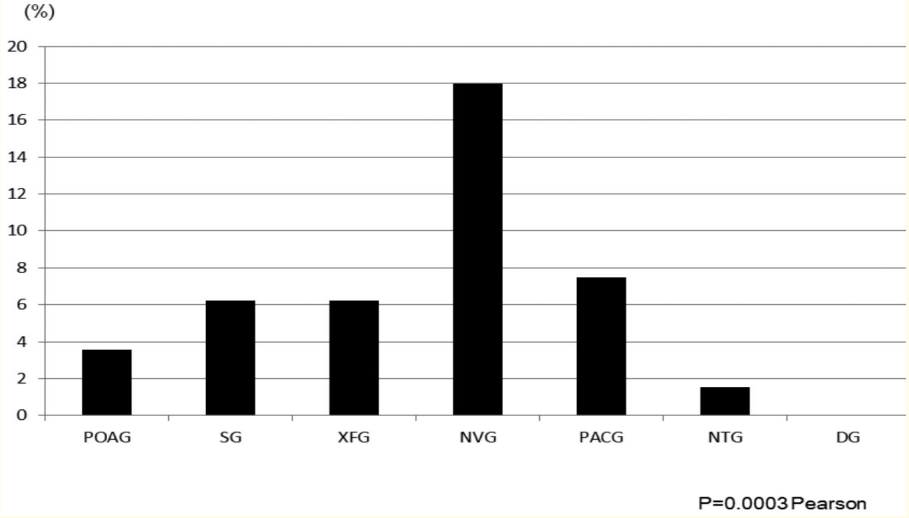

Figure 7: *Comparison of intra-operative complications between glaucoma subtypes.*
POAG: primary open angle glaucoma; NTG: normal tension glaucoma; PACG: primary angle-closure glaucoma; SG: secondary glaucoma; DG: developmental glaucoma; NVG: neovascular glaucoma; XFG: psuedoexfoliation glaucoma

Discussion

The current large-scale study revealed which patients received MMC-trabeculectomy in Japan. The institutes that participated in this study were limited to those employing a councilor of the Japan Glaucoma Society; therefore, the results of the current study may represent the current status of MMC-trabeculectomy in Japan. These results clearly revealed that patients receiving MMC-trabeculectomy had severely damaged glaucomatous neuropathy based on their MD of -18.5 dB on the HFA and their use of 2.7 types of anti-glaucoma eyedrops.

According to the Tajimi study [6], 72% of the total glaucoma population 40 years of age or older exhibited NTG, followed by 6% for POAG. In contrast, the proportions of patients with NTG and POAG were 8.1% and 43.3%, respectively, in our study. Based on the results of this study, the need for MMC-trabeculectomy was significantly different between glaucoma subtypes. It is well known that NVG is the most refractive glaucoma. Indeed, eyes with NVG showed a significantly higher pre-operative IOP and received more types of anti-glaucoma eyedrops. Among all glaucoma subtypes, NVG is the most likely to require MMC-trabeculectomy.

It is controversial whether trabeculectomy alone is associated with a better prognosis than phacotrabeculectomy among eyes with open angle glaucoma. Some previous articles reported a negative effect of lens extraction concomitant with trabeculectomy [7, 8]. Among eyes that were phakic at the time of surgery, 76.5% underwent trabeculectomy alone. However, 47.5% of eyes with PACG underwent trabeculectomy alone ($P < 0.0001$, Pearson Chi-square test). It may be widely accepted that lens extraction is a useful procedure when performed concomitantly with trabeculectomy, possibly by resolving a narrow angle. Moreover, the present study indicates that PACG may more frequently result in phacoemulsification-related complications than other glaucoma subtypes. It is necessary to pay attention to eyes with PACG when performing phacotrabeculectomy.

In this study, the frequency of intra-operative complications was 5.6%. The most frequent complication was hyphema, and 16.4% of these complications were associated with cataract surgery. Although MMC-trabeculectomy is associated with a relatively low frequency of intra-operative complications, our previous study revealed that MMC-trabeculectomy resulted in bleb-related infection in 2.5% of cases after five years of follow-up [3]. Further, DeBry., *et al*. reported that the risks of endophthalmitis and blebitis over the 5 years following MMC-trabeculectomy were 7.5% and 6.3%, respectively [2]. Other post-operative complications include hypotony leading to the development of hypotonic maculopathy, shallow anterior chamber, and corneal-lenticular touch resulting in bullous keratopathy and cataract development. The post-operative complications observed in this study will be reported elsewhere. In short, a total proportion of post-operative complications was 14.3%, which is higher than that of intraoperative complication. The management of trabeculectomy may be important during both the intra- and post-operative periods.

In the current study, the proportion of FBCI was slightly higher than that of LBCI. FBCF is considered to be an easier technique to perform and to be associated with a lower incidence of buttonholing than LBCI [9,10]. In contrast, the primary disadvantage of FBCI is the difficulty in achieving water-tight would closure at the limbus. Previous articles reported no statistically significant difference success proportion or complications between LBCI and FBCI [11,12]. In the current study, a site of conjunctival incision among eyes showing a failure of conjunctival closure was LBCI.

A scleral flap was created at the superior site in 99% of all eyes. The surgeons probably recognized that a filtering bleb located in the inferior site is associated with an increased risk of bleb-related infections, as reported previously [13-15].

Our study has several limitations. First, all surgeries were performed in Japan across 34 centers, and this geographical and ethnic homogeneity could limit the applicability of the findings to clinical settings outside Japan. Second, the surgical technique was not identical among centers or surgeons because the indication for surgery and the selection of the operative procedure were determined at the discretion of each investigator. Therefore, inter-observer differences might have affected the results. We reported the current status of MMC-trabeculectomy, including indications and perioperative complications, in Japan based on a large-scale prospective study. Other reports from this study will be published elsewhere.

In general, medical treatment and laser treatment are considered to have higher priority than surgical treatment, including filtering surgery, because MMC-trabeculectomy is associated with a high risk for operation-related complications. Primary surgery reduces IOP further than primary medication but is associated with greater eye discomfort. One trial suggested that loss of visual field at five years is not significantly different between medication and trabeculectomy as the initial treatment [16]. However, the indications for filtering surgery vary depending on the treatment center and/or the physician. In this study, the mean pre-operative MD on the HFA was -18.5 dB, and this result indicates very advanced glaucomatous optic neuropathy among the enrolled patients. Many of the ophthalmologists who participated in this study may be concerned with operation-related complications. Thus, they might apply as many non-surgical approaches as possible before performing surgery.

Recently, other surgical procedures, referred to minimally invasive glaucoma surgeries (MIGS), have been proposed as alternatives to MMC-trabeculectomy [17-19]. MIGS appear to be safer than MMC-trabeculectomy, although the evidence that IOP reduction is similar between MIGS and MMC-trabeculectomy is insufficient [20,21]. Most studies regarding effectiveness of MIGS have shown an IOP in the mid- to low-teens at best, which is insufficient to halt glaucomatous optic neuropathy, especially among eyes with NTG or advanced glaucomatous optic neuropathy. Moreover, we must consider cost effectiveness. Trabeculectomy and tube shunt are cost-effective compared with medical treatment alone, and trabeculectomy is the most cost-effective treatment of all [22]. From the perspectives of quality of life and cost effectiveness, surgical approaches that are less invasive and more effective than MMC-trabeculectomy may be necessary.

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