Title
Impact of phacoemulsification on failure of trabeculectomy with mitomycin-C

Author(s)
Awai-Kasaoka, Nanako; Inoue, Toshihiro; Takihara, Yuji; Kawaguchi, Atsushi; Inatani, Masaru; Ogata-Iwao, Minako; Tanihara, Hidenobu

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Title: Impact of Phacoemulsification on Failure of Trabeculectomy with Mitomycin C

Authors' names: Nanako Awai-Kasaoka, Toshihiro Inoue, Yuji Takihara, Atsushi Kawaguchi, Masaru Inatani, Minako Ogata-Iwao, Hidenobu Tanihara

Authors' institutions: aDepartment of Ophthalmology and Visual Science, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; bBiostatistics Center, Kurume University School of Medicine, Kurume, Japan

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Corresponding Author: Toshihiro Inoue, Department of Ophthalmology and Visual Science, Graduate School of Medical Sciences, Kumamoto University, 1-1-1, Honjo, Kumamoto, Japan. Telephone: +81-96-373-5247; fax: +81-96-373-5249; e-mail: noel@da2.so-net.ne.jp.
Abstract

**Purpose:** To evaluate whether phacoemulsification after trabeculectomy affects postoperative intraocular pressure (IOP).

**Setting:** Kumamoto University, Kumamoto, Japan.

**Design:** Retrospective cohort study.

**Methods:** We retrospectively reviewed the medical records of 178 patients (178 eyes) with primary open-angle glaucoma or exfoliation glaucoma who underwent trabeculectomy with mitomycin C. The primary endpoints were condition A: persistent postoperative IOP of ≥21 mm Hg or additional glaucoma procedures with or without medications; condition B: postoperative IOP of ≥18 mm Hg or additional glaucoma procedures with or without medications. We performed multivariable analysis by using the Cox proportional hazards model.

**Results:** The mean follow-up period was 37.0 months. For condition A, the probabilities of treatment success at 1, 2, and 3 years were 97.9%, 95.0, and 92.7%, respectively. For Condition B, the corresponding probabilities of success were 92.3%, 84.1, and 81.8%. Thirty-seven patients (37 eyes) underwent phacoemulsification after trabeculectomy; 10 of those patients had the surgery within a year after trabeculectomy. Multivariable analysis showed that a higher pre-trabeculectomy IOP value was a significant risk factor for both conditions A and B ($P = .01$ and .0006, respectively); phacoemulsification within a year after trabeculectomy was significantly associated with trabeculectomy failure for condition B ($P = .04$).

**Conclusions:** Postoperative IOP in eyes that undergo trabeculectomy may be affected by pre-trabeculectomy IOP and phacoemulsification within a year after trabeculectomy.
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Background

When an eye with a functioning bleb after trabeculectomy requires cataract surgery, one concern is that cataract surgery may disturb bleb function and lead to increased intraocular pressure (IOP). Certain clinical studies suggested that phacoemulsification had an adverse effect on maintenance of the filtering bleb, although the effect was smaller than that of extracapsular extraction. However, some reports provided conflicting results: phacoemulsification did not have a direct impact on IOP control in eyes with filtering blebs. Thus, the true effect of phacoemulsification on IOP control after trabeculectomy remained uncertain.

The cause of an adverse effect of phacoemulsification on IOP control, if any does exist, is assumed to be surgery-induced inflammation that causes stimulation of subconjunctival scarring, which would result in the failure of bleb function. In this model, the interval between the initial trabeculectomy and subsequent phacoemulsification may be a critical factor in the failure of trabeculectomy, because the filtering bleb was suggested to need sufficient time to develop. In support of these findings, Chen et al found that a time interval of less than 6 months between trabeculectomy and cataract extraction was a risk factor for the loss of IOP control. To our best knowledge, however, no study has utilized the Cox proportional hazards model, which is a reliable method for analyzing multiple risk factors, to estimate the role of phacoemulsification as a time-dependent factor in IOP control. The purpose of this study, therefore, was to evaluate whether time-dependent phacoemulsification after trabeculectomy causes surgical failure in eyes with open-angle glaucoma (OAG).
trabeculectomy affects IOP, we performed multivariable analysis by using the Cox proportional hazards model.

METHODS

Patient Population
We retrospectively reviewed the medical records of 178 Japanese patients (178 eyes) with primary OAG or exfoliation glaucoma who underwent trabeculectomy at Kumamoto University Hospital, Kumamoto, or Nippon Telegraph and Telephone West Kyushu Hospital, Kumamoto, Japan, between January 1998 and December 2008. Patients who had an IOP value of <21 mm Hg at all three visits before trabeculectomy were excluded. When both eyes of one patient fulfilled the study inclusion criteria, we included in our analysis only the eye that was treated first. We excluded eyes with any history of ocular surgery before trabeculectomy.

Trabeculectomy Technique
Trabeculectomy was performed as described previously. Briefly, a conjunctival flap and a half-layer scleral flap were made, and mitomycin C (MMC) was applied to the exposed tissues, as described by Kitazawa and associates. Most eyes (160 eyes) were treated with 0.4 mg/ml MMC and the other 18 eyes were treated with 0.2 mg/ml MMC at Kumamoto University Hospital (January 1998, through April 2000). Wounds were irrigated with 200 ml of balanced salt solution. A trabecular block was then excised to create a fistula in the anterior chamber, a peripheral iridectomy was performed, and the scleral flap and conjunctival incision were sutured closed.

Phacoemulsification Technique
A 2.4- to 3.0-mm grooved incision was made at the temporal cornea or sclera while the filtering bleb was avoided. After anterior capsulotomy and nuclear hydrodissection, the lens nucleus was removed by phacoemulsification. The cortical material was then aspirated by using an irrigation/aspiration handpiece. The capsular bag was filled with sodium hyaluronate, the foldable posterior chamber intraocular lens was inserted into the capsular bag, and sodium hyaluronate was aspirated from the capsular bag. There were no complications during the surgery, and antimetabolic agent injections were not given. All patients were treated with eyedrops of fluorometholone and levofloxacin hydrate for 1 month after phacoemulsification.

**Main Outcome Measures**

To assess the impact of phacoemulsification after trabeculectomy, surgical failure was defined according to the following criteria: at two consecutive follow-up visits 2 months or more after trabeculectomy, a postoperative IOP value of $\geq 21 \text{ mm Hg}$ (condition A) or $\geq 18 \text{ mm Hg}$ (condition B) with or without medication. The need for additional glaucoma procedures (filtering surgery, destruction of the ciliary body, or needling of an encapsulated bleb) was also defined as failure in both conditions described above. IOP values were determined with a Goldmann applanation tonometer. Patients who did not meet the criteria of surgical failure were considered as surgical success. We also reviewed number of antiglaucoma medications before trabeculectomy, before and after phacoemulsification if any, and the mean deviation (MD) value of the Humphrey Visual Field Analyzer before trabeculectomy.

**Statistical Analyses**

Data analysis was performed by using JMP version 8 and SAS version 9.2.
statistical package programs (SAS Institute Inc., Cary, NC). The following variables were assessed as potential prognostic factors for surgical failure by using Kaplan-Meier survival analysis: age, gender, etiology of glaucoma, concentration of MMC, number of glaucoma medications before trabeculectomy, and phacoemulsification after trabeculectomy, which was treated as a time-dependent variable. Phacoemulsification within a year of trabeculectomy and phacoemulsification more than a year after trabeculectomy were analyzed separately as time-dependent variables only for condition B, because the number of cases with failure of trabeculectomy in condition A was too small to analyze when separated by the interval between trabeculectomy and phacoemulsification. To confirm the effects of phacoemulsification on surgical failure with adjustment of its covariates, multivariable analysis was performed with the Cox proportional hazards model. We selected the covariates from variables with a probability (P) value of <.30 as determined by univariable analysis. A P value of <.05 was considered statistically significant.

RESULTS

One hundred seventy-eight patients (178 eyes) satisfied the inclusion criteria for this study. Thirty-seven eyes underwent phacoemulsification after trabeculectomy, with 10 having had the surgery within a year after trabeculectomy. There were no major complications after phacoemulsification. Table 1 gives the baseline characteristics of all patients. The mean time interval between trabeculectomy and phacoemulsification was 24.8 months (range, 0.6 to 77.6 months). The mean number of antiglaucoma medications before trabeculectomy was 2.9 ± 0.73, and all eyes had poor IOP control. The average of MD value of the Humphrey Visual Field Analyzer program 24-2,
30-2, and 10-2 were -20.67 ± 8.71 (39 eyes), -19.14 ± 8.30 (37 eyes), and -29.74 ± 4.12 (3 eyes), respectively. As Table 2 shows, the mean IOP values and number of antiglaucoma eye drops before and after phacoemulsification did not differ significantly at any time point examined.

Figure 1 presents the results of Kaplan-Meier survival curve analysis for all patients. For condition A, the probabilities of success at 1, 2, and 3 years after trabeculectomy were 97.9% (128 eyes), 95.0% (96 eyes), and 92.7% (77 eyes), respectively. The respective corresponding values for condition B were 92.3% (121 eyes), 84.1% (84 eyes), and 81.8% (66 eyes). In total, 20 and 33 of 178 patients were classified as surgical failures for condition A and condition B, respectively.

As Tables 3 and 4 demonstrate, according to univariable analysis, a higher pre-trabeculectomy IOP value was a prognostic factor for surgical failure for both conditions A and B (P = .0092 and .0003, respectively). A noteworthy finding was that phacoemulsification within a year after trabeculectomy was also identified as a prognostic factor for surgical failure for condition B (P = .04). The probabilities of treatment success at 1, 3, and 5 years after trabeculectomy for eyes with only trabeculectomy plus MMC were 93.5%, 80.1%, and 73.4%, respectively (Figure 2). Corresponding values for phacoemulsification more than a year after trabeculectomy were 92.6%, 92.6%, and 92.6%, respectively, but similar values for phacoemulsification within a year after trabeculectomy were 80.0%, 64.0%, and 48.0% (Figure 2).

The Cox proportional hazards model was used to evaluate the relative risks associated with three variables for condition A (Table 5) and four variables for condition B (Table 6). For condition A, a higher pre-trabeculectomy IOP was a significant risk factor for surgical failure (P = .01), but phacoemulsification was not. For condition B, significant risk
factors for surgical failure included a higher pre-trabeculectomy IOP ($P = .0006$) and phacoemulsification within a year after trabeculectomy ($P = .04$).

**DISCUSSION**

Phacoemulsification after trabeculectomy has been widely accepted as having a potential adverse effect on bleb survival by inducing ocular inflammation. In the present study, we used the Cox proportional hazards model to analyze postoperative phacoemulsification as a time-dependent variable with other potential factors and found that phacoemulsification within a year after trabeculectomy was a significant independent risk factor for failure to keep the IOP value below 18 mm Hg after trabeculectomy with MMC (relative risk = 2.87, $P = .0396$; Table 6).

Phacoemulsification more than a year after trabeculectomy with MMC was not a significant risk factor, however (Table 6). The model provided by Shields, in which a filtering bleb needs sufficient time to develop,$^{12}$ may explain this result. In other words, once the filtering bleb develops successfully, phacoemulsification after trabeculectomy may not affect its function. In agreement with this model, Chen et al reported that an interval of 6 months or less between trabeculectomy and cataract extraction was significantly associated with reoperation for glaucoma.$^{7}$ Moreover, Manoj et al analyzed the effect of phacoemulsification more than 2 years after trabeculectomy (21 eyes) and found that the IOP value after phacoemulsification was not significantly higher compared with that before phacoemulsification at any time point examined.$^{11}$ These findings together may indicate that a filtering bleb may require 1 to 2 years to be stabilized against phacoemulsification.

We previously reported that pseudophakic eyes with OAG that underwent
initial trabeculectomy had a significantly lower cumulative probability of success of trabeculectomy than did phakic eyes with OAG that underwent the same treatment.\textsuperscript{15} This result suggests that the adverse effect of phacoemulsification on the success of subsequent trabeculectomy may last for years. Thus, it would seem desirable for OAG patients to undergo phacoemulsification after trabeculectomy rather than before trabeculectomy.

According to the Cox proportional hazards analysis in the present study, a higher pre-trabeculectomy IOP value was a prognostic factor for surgical failure for both conditions A and B (Tables 5 and 6, respectively). Previous studies including ours reported the same risk factor for trabeculectomy failure.\textsuperscript{15-17} A higher pre-trabeculectomy IOP value reflects greater deterioration of the aqueous outflow pathway, which suggests a lower standby capacity, in which case a collapse of 50\% of bleb function may be critical.

This study had some limitations as follows. Because of the retrospective manner, the selection bias may exist in this study, leading conclusions based on some glaucoma populations which were different from those in prospective studies. Other limitation was the small number of the eyes (10 eyes) which underwent phacoemulsification within a year after trabeculectomy.

In conclusion, the postoperative IOP in eyes that undergo trabeculectomy may be significantly affected by the pre-trabeculectomy IOP value and phacoemulsification within a year after trabeculectomy.
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Legends

FIGURE 1: Kaplan-Meier survival curves for the probability of surgical success over time for all 178 patients (178 eyes) who underwent trabeculectomy with mitomycin C (MMC) for condition A (persistent postoperative IOP value of $\geq 21$ mm Hg or additional glaucoma procedures, solid line) and condition B (postoperative IOP value of $\geq 18$ mm Hg or additional glaucoma procedures, dotted line).

FIGURE 2: Kaplan-Meier survival curves for the probability of surgical success over time in 141 patients who were treated with trabeculectomy with mitomycin C (MMC) only (solid line); phacoemulsification within a year after trabeculectomy with MMC (dotted line); or phacoemulsification more than a year after trabeculectomy with MMC (dashed line) for condition B (postoperative IOP value of $\geq 18$ mm Hg or additional glaucoma surgery).