Trabeculectomy With Mitomycin for Open-Angle Glaucoma in Phakic vs Pseudophakic Eyes After Phacoemulsification

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Objective: To determine whether previous phacoemulsification adversely affects surgical prognosis of trabeculectomy with mitomycin for open-angle glaucoma.

Methods: The study is a retrospective, consecutive, comparative case series. At 2 clinical centers, we reviewed 226 medical records of eyes with open-angle glaucoma undergoing initial trabeculectomy, including 175 phakic eyes (phakic group) and 51 pseudophakic eyes that had previously undergone phacoemulsification with superior conjunctival incision (pseudophakic group). Primary outcome was the probability of success after trabeculectomy. Surgical failure was defined as an additional glaucoma surgery or 1 of the following 3 criteria: intraocular pressure (IOP) of 21 mm Hg or greater (A); IOP of 18 mm Hg or greater (B); and IOP of 15 mm Hg or greater (C). Multivariable analysis was performed using the Cox proportional hazards model.

Results: The mean follow-up period was 37.5 months. The probability of success for criteria A, B, and C at 1 and 3 years in the phakic vs the pseudophakic group was 97.8% and 92.6%, respectively, vs 78.6% and 65.1%, respectively, for criterion A (P < .001); 92.9% and 81.3%, respectively, vs 72.8% and 63.7%, respectively, for criterion B (P = .004); and 73.1% and 54.2%, respectively, vs 53.1% and 38.4%, respectively, for criterion C (P = .009). The multivariable model confirmed that pseudophakia independently contributes to surgical failure (criterion A relative risk, 4.59 [95% CI: 4.24-5.0]; criterion B, 2.88 [95% CI: 2.57-3.21]; and criterion C, 2.02 [95% CI: 1.72-2.37]). The pseudophakic group required more postoperative laser suture lysis (P = .01).

Conclusion: Previous phacoemulsification is a prognostic factor for surgical failure of trabeculectomy with mitomycin for open-angle glaucoma.

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trabeculectomy with mitomycin for OAG between phakic eyes and eyes that have undergone previous phacoemulsification. Therefore, whether previous phacoemulsification is a prognostic factor for surgical failure of trabeculectomy with mitomycin remains unknown.

The main objective of the present study was to evaluate whether previous phacoemulsification adversely affects the surgical outcomes of trabeculectomy with mitomycin for eyes with OAG. We retrospectively evaluated the surgical outcomes and prognostic factors for failure of trabeculectomy with mitomycin in phakic or phacoemulsification-treated pseudophakic eyes with OAG at 2 clinical centers.

### METHODS

#### PATIENTS

This was a retrospective cohort study of phakic eyes (phakic group) and pseudophakic eyes (pseudophakic group) with OAG (primary OAG or exfoliation glaucoma) that underwent initial trabeculectomy with mitomycin at Kumamoto University Hospital (106 eyes) or Nippon Telegraph and Telephone West Kyushu Hospital (120 eyes) from January 1, 1998, through January 31, 2009, in which medical records were reviewed. To match age between the 2 groups as closely as possible, we included only patients 60 years or older. Eyes receiving treatment with glaucoma medications that had an IOP of 22 mm Hg or greater at least once during 3 consecutive visits immediately before trabeculectomy were included in this study. The pseudophakic group included only eyes with previous phacoemulsification and posterior chamber intraocular lens implantation that involved a superior conjunctival incision. If both eyes underwent trabeculectomy with mitomycin, only the eye that was treated first was included. We excluded pseudophakic eyes that were treated with clear corneal phacoemulsification, phacoemulsification with temporal conjunctival incision, or intracapsular or extracapsular cataract extraction; aphakic eyes; eyes with previous glaucoma surgical procedures before trabeculectomy; eyes with previous vitrectomy; eyes treated with combined trabeculectomy and cataract surgery; and eyes with closed-angle glaucoma or secondary glaucoma other than exfoliation glaucoma. All study procedures adhered to the Declaration of Helsinki. According to the guideline of clinical research by the Japanese Ministry of Health, Labour, and Welfare, we opened the design of this study and provided a contact address (http://www2.kuh.kumamoto-u.ac.jp/ganka/) for patients who satisfied the selection criteria of the study. This study was approved by the institutional review board of Kumamoto University Hospital.

#### SURGICAL PROCEDURES

All the trabeculectomies were performed via the superior conjunctival incision. Based on conjunctival manipulation with a cotton-tipped stick during the surgery, mobile conjunctiva, which was separated from scar caused by previous phacoemulsification, was chosen in trabeculectomy for pseudophakic eyes. In all, 176 eyes received a limbus-based conjunctival flap, whereas 50 eyes at Kumamoto University Hospital after May 2005 received a fornix-based conjunctival flap. After the creation of a half-layer scleral flap, 207 eyes received 0.4-mg/mL mitomycin for 4 minutes, and the remaining 19 eyes received 0.2-mg/mL mitomycin at Kumamoto University Hospital (January 1, 1998, through April 30, 2000). For all eyes, we carefully irrigated the wound with 200 mL of balanced salt solution. A trabecular block was excised to create a fistula in the anterior chamber, after which peripheral iridectomy was performed. The scleral flap was closed with 10-0 nylon sutures. The conjunctival incision was closed with 10-0 nylon sutures for a fornix-based conjunctival flap and 10-0 nylon sutures or 7-0 silk sutures for a limbus-based conjunctival flap.

#### MAIN OUTCOME MEASURE

The main outcome measure was the probability of success in the Kaplan-Meier survival-curve analysis. Surgical failure was defined before data analysis, using the following IOP levels at 2 consecutive visits while receiving or not receiving topical glaucoma medications: 21 mm Hg or greater (criterion A); 18 mm Hg or greater (criterion B); and 15 mm Hg or greater (criterion C). Laser suture lysis (LSL) was completed within 2 months after trabeculectomy. Intraocular pressures that corresponded to criteria A, B, or C within 2 months after trabeculectomy were not considered to be surgical failures because LSL was not completed. When an additional glaucoma surgery was performed, the eye was regarded as a surgical failure for all criteria.

### Table 1. Preoperative Characteristics of the Study Eyes That Underwent Trabeculectomy With Mitomycin for Open-Angle Glaucoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phakic Eyes (n=175)</th>
<th>Pseudophakic Eyes (n=51)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye laterality, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>89 (50.9)</td>
<td>24 (47.1)</td>
<td>.63</td>
</tr>
<tr>
<td>Left</td>
<td>86 (49.1)</td>
<td>27 (52.9)</td>
<td></td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>61 (34.9)</td>
<td>17 (33.3)</td>
<td>.84</td>
</tr>
<tr>
<td>Male</td>
<td>114 (65.1)</td>
<td>34 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>72.0 (6.1)</td>
<td>78.7 (5.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Range</td>
<td>60-87</td>
<td>65-89</td>
<td></td>
</tr>
<tr>
<td>Subtype of open-angle glaucoma, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary open-angle glaucoma</td>
<td>58 (33.1)</td>
<td>13 (25.5)</td>
<td>.30</td>
</tr>
<tr>
<td>Exfoliation glaucoma</td>
<td>117 (66.9)</td>
<td>38 (74.5)</td>
<td></td>
</tr>
<tr>
<td>Preoperative intraocular pressure, mean (SD), mm Hg</td>
<td>27.1 (6.3)</td>
<td>30.9 (7.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of preoperative topical antiglaucoma medications, mean (SD)</td>
<td>2.9 (0.7)</td>
<td>3.0 (0.6)</td>
<td>.77</td>
</tr>
<tr>
<td>Preoperative visual acuity, mean (SD), logMAR</td>
<td>0.35 (0.56)</td>
<td>0.50 (0.68)</td>
<td>.09</td>
</tr>
</tbody>
</table>

*Only 1 eye per patient was included.*
DATA ANALYSES

Data were analyzed with the JMP statistical package, version 7 (SAS Institute, Inc, Cary, North Carolina). The probability of success was analyzed using a Kaplan-Meier survival curve and the log-rank test. The following variables were assessed as potential prognostic factors for surgical failure: sex, age, subtype of OAG, preoperative IOP, number of preoperative medications, previous laser trabeculoplasty, pseudophakia, mitomycin concentration, type of conjunctival flap, and postoperative LSL. To confirm the effects of the prognostic factors and identify the relative risk (RR) for surgical failure, multivariable prognostic factor analysis was performed with the Cox proportional hazards model. *P* < .05 was considered statistically significant.

RESULTS

PREOPERATIVE CHARACTERISTICS

The preoperative characteristics in the phakic and pseudophakic groups are given in Table 1. Patients in the pseudophakic group were significantly older (*P* < .01) and had a higher preoperative IOP (*P* < .001) than those in the phakic group. Other preoperative characteristics showed no significant differences between the 2 groups.

SURGICAL CUMULATIVE PROBABILITY OF SUCCESS

The mean (SD) follow-up period in all the cases was 37.5 (31.6) months. The comparison of the Kaplan-Meier survival curve analysis between the 2 groups for criteria A, B, and C are shown in the Figure. The pseudophakic group had a significantly lower cumulative probability of success for criteria A, B, and C (*P* < .001, *P* = .004, and *P* = .009, respectively). For criterion A, the probabilities of success 1 and 3 years after trabeculectomy in the phakic group vs the pseudophakic group were 97.8% vs 78.6% and 92.6% vs 65.1%, respectively. For criterion B, the probabilities of success 1 and 3 years after trabeculectomy in the phakic group vs the pseudophakic group were 92.9% vs 72.8% and 81.3% vs 63.7%, respectively. For criterion C, the probabilities of success 1 and 3 years after trabeculectomy in the phakic group vs the pseudophakic group were 73.1% vs 53.1% and 54.2% vs 38.4%, respectively. The numbers of eyes classified as surgical failures in the phakic group vs the pseudophakic group were 21 (12.0%) vs 16 (31.4%) for criterion A, 34 (19.4%) vs 19 (37.3%) for criterion B, and 69 (39.4%) vs 30 (58.8%) for criterion C, respectively.

PROGNOSTIC FACTORS FOR FAILURE

Results of the Cox proportional hazards model are listed in Table 2. Pseudophakia and higher preoperative IOP were consistently associated with poorer surgical outcomes for criteria A, B, and C. Younger age was associated with poorer surgical outcomes for criteria B and C. Postoperative LSL was associated with poorer surgical outcome for criterion C.

NUMBER OF POSTOPERATIVE MEDICATIONS AND LSL

The pseudophakic group required a significantly greater mean (SD) number of glaucoma medications at 6 and 12 months after trabeculectomy than the phakic group (0.1 [0.5] in phakic eyes vs 0.5 [1.0] in pseudophakic eyes at 6 months [*P* < .001] and 0.2 [0.5] in phakic eyes vs 0.8 [1.1] in pseudophakic eyes at 12 months [*P* < .001]). However, the difference in the mean number of medications between the 2 groups was not significant at 24 months (*P* = .09) or later after trabeculectomy. Significantly more eyes (*P* = .01) needed postoperative LSL in the pseudophakic group (31 eyes [60.8%]) than in the phakic group (72 eyes [41.1%]).
Table 2. Cox Proportional Hazards Model Determining the Likelihood of Surgical Outcomes for All Eyes With OAG That Underwent Trabeculectomy With Mitomycin

<table>
<thead>
<tr>
<th>Variable</th>
<th>A^b</th>
<th>P Value</th>
<th>B^c</th>
<th>P Value</th>
<th>C^d</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female vs male</td>
<td>0.71 (0.32-1.47)</td>
<td>.37</td>
<td>0.94 (0.51-1.71)</td>
<td>.85</td>
<td>0.88 (0.57-1.36)</td>
<td>.58</td>
</tr>
<tr>
<td>Age per 1-year increase</td>
<td>0.96 (0.90-1.02)</td>
<td>.17</td>
<td>0.95 (0.90-1.00)</td>
<td>.048</td>
<td>0.96 (0.92-0.99)</td>
<td>.02</td>
</tr>
<tr>
<td>Subtype of OAG, EXG vs POAG</td>
<td>1.09 (0.50-2.53)</td>
<td>.84</td>
<td>1.03 (0.55-2.03)</td>
<td>.93</td>
<td>1.56 (0.97-2.58)</td>
<td>.07</td>
</tr>
<tr>
<td>Preoperative IOP per 1-mm Hg increase</td>
<td>1.08 (1.04-1.13)</td>
<td>&lt;.001</td>
<td>1.07 (1.04-1.11)</td>
<td>&lt;.001</td>
<td>1.03 (1.01-1.06)</td>
<td>.02</td>
</tr>
<tr>
<td>Preoperative medications per 1-medication increase</td>
<td>1.10 (0.84-1.86)</td>
<td>.73</td>
<td>1.06 (0.69-1.63)</td>
<td>.80</td>
<td>0.99 (0.72-1.37)</td>
<td>.95</td>
</tr>
<tr>
<td>Previous laser trabeculoplasty</td>
<td>2.09 (0.73-5.20)</td>
<td>.16</td>
<td>1.42 (0.56-3.11)</td>
<td>.43</td>
<td>1.50 (0.83-2.56)</td>
<td>.17</td>
</tr>
<tr>
<td>Pseudophakia</td>
<td>4.59 (1.94-10.98)</td>
<td>&lt;.001</td>
<td>2.88 (1.40-5.93)</td>
<td>.004</td>
<td>2.02 (1.19-3.39)</td>
<td>.009</td>
</tr>
<tr>
<td>Mitomycin dose, 0.2 vs 0.4 mg/mL</td>
<td>1.30 (0.40-3.59)</td>
<td>.64</td>
<td>1.35 (0.53-3.09)</td>
<td>.51</td>
<td>1.13 (0.53-2.20)</td>
<td>.73</td>
</tr>
<tr>
<td>Fornix vs limbus-based conjunctival flap</td>
<td>1.97 (0.71-5.01)</td>
<td>.18</td>
<td>1.52 (0.68-3.21)</td>
<td>.30</td>
<td>1.28 (0.72-2.17)</td>
<td>.39</td>
</tr>
<tr>
<td>Postoperative LSL</td>
<td>0.83 (0.40-1.70)</td>
<td>.61</td>
<td>1.11 (0.61-2.01)</td>
<td>.73</td>
<td>1.62 (1.07-2.49)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EXG, exfoliation glaucoma; IOP, intracocular pressure; LSL, laser suture lysis; OAG, open-angle glaucoma; POAG, primary OAG; RR, relative risk.

^a Only 1 eye per patient (n=226) was included.

^b Eyes had an IOP of 21 mm Hg or greater or had undergone an additional glaucoma surgical procedure.

^c Eyes had an IOP of 18 mm Hg or greater or had undergone an additional glaucoma surgical procedure.

^d Eyes had an IOP of 15 mm Hg or greater or had undergone an additional glaucoma surgical procedure.

SURGICAL COMPLICATIONS

There were no significant differences in the surgical complications between the 2 groups (Table 3). In addition, 34 eyes in the phakic group (19.4%) underwent cataract surgery after trabeculectomy. There was a significant difference (P=.047) in the incidence of cataract surgery between the eyes with primary OAG and eyes with exfoliation glaucoma when we defined failure as cataract surgery for Kaplan-Meier survival curve analysis and used the log-rank test. The probability of success at 1 and 3 years in eyes with primary OAG eyes vs eyes with exfoliation glaucoma was 95.3% and 89.6%, respectively, vs 94.0% and 75.2%, respectively. Adjustment for age (RR, 0.96 [95% CI, 0.90-1.02]) and hypotony (2.42 [95% CI, 0.50-2.53]) by the Cox proportional hazards model revealed that exfoliation glaucoma independently contributed to the incidence of cataract surgery (2.33 [P=.04]).

The aim of this study was to determine whether previous phacoemulsification is associated with poorer surgical outcomes of trabeculectomy with mitomycin for OAG. The pseudophakic group in our study had a significantly lower cumulative probability of success for criteria A, B, and C. The adjustment for the other potential prognostic factors by the Cox proportional hazards model revealed that previous phacoemulsification independently contributes to the prediction of surgical failure as follows: for criterion A, RR of 4.59 (P<.001); for criterion B, 2.88 (P=.004); and for criterion C, 2.02 (P=.009) (Table 2). Consistent with this result, pseudophakic eyes required significantly more medications at 6 and 12 months after trabeculectomy and postoperative LSL than did the phakic group. These results indicate that previous phacoemulsification is a significant prognostic factor for surgical failure of trabeculectomy with mitomycin for OAG.

There have been several studies on surgical outcomes of trabeculectomy for phakic or pseudophakic eyes.6-20 For phakic eyes, Scott et al7 showed that the probability of success 1 year after trabeculectomy with mitomycin was 92.7%, with success defined as an IOP of 21 mm Hg or less and no reoperation. For pseudophakic eyes, Prata Júnior and colleagues17 showed that 70% of eyes treated with trabeculectomy with mitomycin were deemed successes (IOP, ≤21 mm Hg with or without glaucoma medications) with a mean follow-up of 11.5 months. Fontana et al21 reported that the probability of success 2 years after trabeculectomy with mitomycin in pseudophakic eyes was 67%, with success defined as an IOP of 18 mm Hg or less and an IOP reduction of at least 20%. However, these studies do not differentiate eyes treated with phacoemulsification from those treated with conventional cata-
tract operations and do not include comparative data with the surgical outcomes of phakic eyes. Furthermore, the Fluorouracil Filtering Surgery Study Group\(^1\) has shown that trabeculectomy with fluorouracil has a poor prognosis in eyes with previous cataract surgery. Heuer et al\(^9\) have reported that aphakic eyes have poorer surgical outcomes of trabeculectomy with fluorouracil compared with phakic eyes with previous unsuccessful filtering surgery. These studies also seem to include eyes that have been treated with cataract operations other than phacoemulsification. Our study is unique in its direct comparison of surgical outcomes of trabeculectomy with mitomycin between phakic and pseudophakic eyes, including only eyes treated with phacoemulsification.

Despite the reduction of conjunctival disruption in phacoemulsification compared with other conventional cataract operations and the use of clinically unscarred conjunctiva for trabeculectomy, pseudophakic eyes had a poorer prognosis than did phakic eyes in the present study. This indicates that pathomechanisms, other than conjunctival scarring directly induced by surgical incision during cataract surgery, could cause the poorer surgical prognosis of trabeculectomy in pseudophakic eyes. Several mechanisms could explain the poorer surgical outcomes in the pseudophakic group.\(^2,10\) The first explanation is the increased number of conjunctival fibroblasts and inflammatory cells in the pseudophakic eyes after phacoemulsification. Broadway and colleagues\(^7\) reported that a conjunctiva area that was distant from the clinically scarred regions by a previous conjunctival incision contained more fibroblasts and inflammatory cells compared with eyes without a previous conjunctival incision. If increased fibroblasts and inflammatory cells in the conjunctiva contributed to poorer prognosis in pseudophakic eyes, then clear corneal phacoemulsification would improve the surgical outcomes. In contrast with this hypothesis, Shingleton and colleagues\(^2\) reported no statistically significant difference in final IOPs between 12 pseudophakic eyes with previous temporal clear corneal phacoemulsification and 35 pseudophakic eyes with conjunctival incision, although the probability of success with a Kaplan-Meier survival curve or multivariable analysis were not evaluated. The second explanation is alterations in the nature of the aqueous humor by breakdown of the blood-aqueous barrier after previous intraocular surgery.\(^2,22\) The fibroblast chemoattractant activity might be increased in aqueous humor after phacoemulsification, promoting subconjunctival fibrosis after trabeculectomy. Eyes that underwent trabeculectomy at Kumamoto University Hospital or Nippon Telegraph and Telephone West Kyushu Hospital after clear corneal phacoemulsification and fulfilled selection criteria in this study seem to have the lower probability of success than that of the phakic group for all the criteria, although we do not show the result because of the small sample size. This might suggest that the poorer surgical outcomes in the pseudophakic group result from not only the first pathomechanism, the widespread increased number of conjunctival fibroblasts and inflammatory cells in the pseudophakic group after phacoemulsification, but also the second pathomecha-

According to the results of the Cox proportional hazards model, higher preoperative IOP was found to be a prognostic factor for failure of trabeculectomy in criteria A, B, and C. This result agrees with those of previous studies.\(^4,18,23,24\) Higher preoperative IOP might reflect the severity of glaucoma, resulting in poorer response for treatment to reduce IOP. In addition, our present study shows that younger age is a significant prognostic factor for surgical failure for criteria B and C. Our result is compatible with previous findings.\(^3,10\) More vigorous wound-healing response in younger patients might be associated with subconjunctival fibrosis after trabeculectomy. Moreover, our data indicate that postoperative LSL is a prognostic factor for surgical failure for criteria C, which is in agreement with previous studies.\(^3,10\) The need for postoperative LSL might reflect lower filtration through the scleral flap even immediately after trabeculectomy.

This study had some limitations due to its retrospective nature. First, studies with medical record review are subject to selection bias. We minimized this bias by the use of a consecutive case series. Second, we could not determine bleb morphologic features after trabeculectomy. Moreover, the difference in inflammation levels between phakic and pseudophakic eyes may have been observed because of disrupted blood-aqueous barrier after phacoemulsification. Third, we evaluated postoperative IOP during treatment with topical glaucoma medications, although previous phacoemulsification is a significant prognostic factor for surgical failure after adjustment for other potential prognostic factors by the Cox proportional hazards model.

In conclusion, pseudophakic eyes with OAG have a higher risk for surgical failure of trabeculectomy with mitomycin than do phakic eyes with OAG, even after phacoemulsification with a smaller conjunctival incision than that used in conventional cataract operations has been performed. It is hoped that further studies will reveal which mechanism causes surgical failure of trabeculectomy in pseudophakic eyes.

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Author Contributions: Dr Inatani had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Additional Contributions: Mao Miyagawa, BHS, assisted in this study.
REFERENCES


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