学 位 論 文 の 要 旨

氏名　　原野　晃子

学 位 論 文 名　　Surgical Results of Trabeculectomy Among Groups Stratified by Prostaglandin-Associated Periorbitopathy Severity

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著　　者　　名　　Akiko Ishida (Harano), Takako Miki, Tomoko Naito, Sho Ichioka, Yuji Takayanagi, Masaki Tanito

論 文 内 容 の 要 旨
INTRODUCTION

Topical prostaglandin F2α–derived prostanoid FP receptor agonists are the most common medical treatment for glaucoma because of their excellent intraocular pressure (IOP)-lowering effect with a lower frequency of eye drop instillation and fewer systemic side effects, although the use of this medication class is associated with local side effects referred to as "prostaglandin-associated periorbitopathy syndrome" (PAP). Hypertrichosis and periocular hyperpigmentation are associated with the effects of FP agonists on hair follicles, melanogenesis, and melanocyte proliferation. FP agonists induce deepening of the upper eyelid sulcus (DUES) and enophthalmos by suppressing the differentiation of preadipocytes A mechanical insult to the eyelids in patients with DUES caused levator dehiscence leading to Müller's muscle degeneration. Thus, further remodeling of the extracellular matrix of the orbital/deeper lid tissue is associated with ptosis and hardening of lid skin. With a deep upper eyelid sulcus and no preseptal fat, lifting a tight lid without applying pressure to the globe is difficult, resulting in difficulty performing Goldmann applanation tonometry (GAT) for intraocular pressure measurement. Therefore, in the presence of ptosis and tight eyelids, PAP is not merely a cosmetic side effect, but it also affects glaucoma management.

We use our inhouse grading system, referred to as the "Shimane University PAP Grading System" (SU-PAP), to grade PAP severity based on the underlying mechanisms of PAP. The severity is divided into 4 grades, with grade 0 indicating no PAP, 1 indicating superficial cosmetic PAP, 2 indicating deep cosmetic PAP, and 3 indicating tonometric PAP. Using this system, we previously reported a difference in severity of PAP among different FP agonists and the roles of PAP in overestimation of IOP measured by GAT.

A previous study suggested that the presence of DUES was associated with a lower success rate of trabeculectomy (LEC), and presurgical use of bimatoprost was associated with a higher risk of recurrent IOP elevation than other FP agonists for up to 24 months postoperatively. In the current 2-center study, using SU-PAP, we assessed the effect of PAP severity on the surgical effectiveness of LEC in patients with primary open-angle glaucoma (POAG).

MATERIALS AND METHODS

The study protocol was approved by the Research Ethics Committee of Shimane University. The inclusion criteria required that eyes underwent LEC or LEC combined with small-incision cataract extraction (LEC-CE) between June 2018 and December 2020 at 1 of the 2 study sites; POAG; no history of previous intraocular surgery except uncomplicated small-incision cataract surgery, ab-interno minimally invasive glaucoma surgery, and any laser therapy; and completion of all postoperative visits at months 1, 3, 6, 9, and 12. The PAP severity graded by SU-PAP was recorded in the medical chart preoperatively or anterior segment photographs that allowed us to determine the SU-PAP grade were obtained preoperatively. The exclusion criteria included the presence of a conjunctival scar, phacodonesis or lensdonesis, vitreous prolapse, and total inability to perform GAT because of PAP. If both eyes were eligible, the eye with the earlier surgical day was included. In total, 139 consecutive eyes of 139 Japanese subjects (74 men, 65 women; mean age ± standard deviation, 65.7 ± 10.6 years) were included. No eye was excluded from the study because of the inability to perform GAT.

All surgeries were performed under standard sub-Tenon anesthesia using 2% lidocaine. LEC was performed in the superior hemisphere. After creation of a limbal-based conjunctival peritomy of less than 1 quadrant, a half-thickness 3–4 × 3–4-mm scleral flap was created. After the first flap was dissected, 0.04% mitomycin C was applied for 3 minutes followed by rinsing with balanced salt solution. Under the first scleral flap, a four-fifths–thickness second flap was created inside the scleral bed of the first flap, and then the trabecular tissue was excised en bloc in the second scleral flap. After a peripheral iridectomy was performed, the first scleral flap was closed with 5-8 interrupted 10-0 nylon sutures. The conjunctiva was readapted with 10-0 nylon or 10-0 absorbable suture. At the end of surgery, 2 mg of betamethasone sodium phosphate was injected subconjunctivally. For LEC alone, surgeries were performed under miosis induced by topical 1% pilocarpine. When the combined procedure was performed, the cataract surgery was performed through a clear corneal incision. Postoperatively, topical antibiotics was applied 4 times daily for 1 to 2 months, and 0.1% betamethasone was applied 4 times daily for 2 to 3 months in all cases. After combined surgery, topical nepafenac was also applied 3 times daily for 2 to 3 months.

The SU-PAP grading system classifies the severities of PAP into 4 grades based on the appearance and difficulty performing GAT. The grades were constructed on the basis of the underlying mechanisms of each PAP factor as described previously. Grade 0 (no PAP) was defined as no prostaglandin-associated cosmetic changes; grade 1 (superficial cosmetic PAP) was defined as the presence of eyelid hyperpigmentation or eyelash growth; grade 2 (deep cosmetic PAP) was defined as the presence of at least 1 of DUES, blepharochalasis involution, periorbital fat loss, and enophthalmos; and grade 3 (tonometric PAP) was defined as difficulty performing GAT or reduced reliability of GAT due to the presence of PAP-related DUES, hardening of eyelids, ptosis, or enophthalmos.

Successful IOP control was assessed by survival curve analysis in which the uncensored date was defined as the postoperative period of longer than 90 days and the day of surgical intervention other than LSL, IOP reduction of less than 20%, postoperative IOP exceeding 15 mmHg (definition A) or 12 mmHg (definition B), and a postoperative IOP below 6 mmHg.

RESULTS AND DISCUSSION

Survival curve analyses revealed that the success rates for IOP control were significantly worse in eyes with higher SU-PAP grades compared to eyes with lower grades for both definitions A ($P < 0.0001$) and B ($P < 0.0001$). At 12 months postoperatively, the success rates for grades 0, 1, 2, and 3 were 86%, 68%, 40%, and 0%, respectively, for definition A, and 86%, 61%, 36%, and 0%, respectively, for definition B. The reasons for surgical failure in survival curve analyses included interventions other than LSL ($P < 0.0001$) and IOP reduction less than 20% ($P = 0.010$), IOP exceeding 15 mmHg ($P = 0.016$) or 12 mmHg ($P < 0.0001$) were all associated with surgical failure, whereas IOP under 6 mmHg was not ($P = 0.31$). Factors associated with surgical failure were assessed using a proportional hazard model for definitions A and B. For definition A, compared with SU-PAP grade 0, grade 2 (risk ratio [RR], 5.82, $P = 0.0043$) and grade 3 (RR, 12.2, $P = 0.0003$) were associated with surgical failure. For definition B, grade 1 (RR, 3.53, $P = 0.040$), grade 2 (RR, 6.65, $P = 0.0021$), and grade 3 (RR, 12.0, $P = 0.0003$) were associated with surgical failure. Differences in age, gender, preoperative IOP and medications, SERE, and simultaneous cataract surgery were not associated with surgical failure in either model.

Survival curve analyses and proportional hazard models clearly showed that the surgical success of LEC was affected by the PAP severity.

CONCLUSION

The preoperative presence of severe PAP worsened the 1-year success rate of LEC in patients with POAG. To retain the surgical effectiveness, we recommend that treating physicians pay attention to patients with severe PAP, because PAP is an avoidable side effect, by switching or stopping the causative medications.