Evaluation of the outcome of long-tube shunt implant surgery in uveitic glaucoma patients by analyzing the background of uveitis

Satoshi Watanabe,[1] Teruhiko Hamanaka,[2] Tetsuro Sakurai,[3] Kanae Kobayashi,[2] Nobuo Ishida,[4] Nobuyuki Ebihara[1]

[1]Department of Ophthalmology, Juntendo Urayasu Hospital, Urayasu, Japan
[2]Department of Ophthalmology, Japanese Red Cross Medical Center, Tokyo, Japan
[3]Suwa University of Science, Chino, Japan
[4]Ishida Eye Clinic, Joetsu, Japan

Correspondence to Teruhiko Hamanaka, M.D., Ph.D., Department of Ophthalmology, Japanese Red Cross Medical Center, 4-1-22 Hiroo Shibuya-ku, Tokyo, Japan; Tel.: +81-3-3400-1311, Fax: +81-3-3409-1604, E-mail: hamanaka.teruhiko@gmail.com

Short title: Long-tube shunt surgery for uveitic glaucoma

Number of Figures and Tables: Figures: 4; Tables: 5

Abstract

Purpose To evaluate the efficacy of long-tube shunt surgery (LTSS) without valve in uveitic glaucoma (UG) eyes.

Methods We retrospectively analyzed the data of 45 UG eyes that underwent only LTSS or LTSS combined with trabeculectomy (TLE) (LTSS/TLE). The UG eyes were analyzed by categorizing them into granulomatous/non-granulomatous, steroid responder/non-responder, and primary open-angle glaucoma (POAG) (POAG background)/non-POAG (non-POAG background). All granulomatous UG eyes received a continuous 3-times-daily administration of topical betamethasone post LTSS.

Results The eyes consisted of granulomatous (37 eyes, 82%)/non-granulomatous (5 eyes, 11%), steroid responder (19 eyes, 42%)/non-steroid responder (13 eyes, 29%), and 20 eyes with POAG or POAG background (p = 0.0022, 83%) among 24 cases of unilateral UG. The 5-year survival rates of only LTSS and LTSS/TLE were 66% and 100%, respectively. Kaplan-Meier survival-curve estimates in the non-granulomatous group were 100% for 6-years postoperative, while the granulomatous group showed a gradual decrease along the 6-year (81%) postoperative period. The 5-year survival rates in the steroid responder group and the non-steroid responder group eyes were 74% and 78%, respectively. No intraocular pressure (IOP) elevation was observed in the positive steroid responder eyes post LTSS.

Conclusions LTSS and LTSS/TLE were both effective in UG. Positive steroid response may be masked by LTSS in the positive responder eyes. Continuous administration of topical betamethasone post LTSS may be important for preventing an IOP spike by suppressing inflammation in the anterior chamber. LTSS combined with TLE may be recommended in the eyes with granulomatous UG, and the coexistence of a POAG/POAG background.

Keywords: long-tube shunt surgery, uveitic glaucoma (UG), granulomatous uveitis, steroid responder

Introduction

Uveitic glaucoma (UG) is known to be refractory, and multiple surgeries are often required for proper treatment. Although trabeculectomy (TLE) after the introduction of mitomycin C (MMC) or 5-fluorouracil (5-FU) has reportedly shown favorable results in cases of UG [1-6], the success rate in UG cases is inferior when compared to that in primary open-angle glaucoma (POAG) cases [7, 8], possibly due to ocular hypotension as a result of dysfunction of the ciliary body or ocular hypertension caused by scarring of the bleb as a result of chronic inflammation of the eye [9-12]. For that reason, we choose LTSS or LTSS combined with TLE as the primary surgical methods for the treatment of UG. Several previous studies have reported the outcomes of LTSS for the treatment of UG [13-21], yet to the best of our knowledge, there has been no previous study regarding LTSS in eyes with UG by analyzing the type of uveitis.

The purpose of this present retrospective study was to investigate the outcomes of LTSS without valve in UG cases and to analyze the refractory nature in the UG cases by categorizing them into granulomatous/non-granulomatous, steroid responder/non-steroid responder, and POAG background/non-POAG background.

Methods

This retrospective study involved 49 eyes of 45 consecutive Japanese UG patients (UG Group: 26 males and 19 females) who underwent LTSS or LTSS combined with TLE by a single surgeon (T.H.) from April 1993 to January 2016 at the Department of Ophthalmology, Japanese Red Cross Medical Center, Tokyo, Japan. Of the surgically treated eyes, those in which the postoperative follow-up period was less than 6 months were excluded. LTSS combined with TLE was performed in the eyes with an intraocular pressure (IOP) of greater than 35 mmHg prior to surgery and/or an end-stage visual field grading of more than Stage IV in the Aulhorn-Greve classification. The primary reason for performing combined surgery is not to escape the hypertensive period soon after the surgery, but to specifically treat the above-mentioned refractory types of glaucoma. In all eyes, except the steroid responder eyes, topical betamethasone and antiglaucoma medication was continuously administered prior to LTSS for the suppression of the anterior chamber inflammation. In all cases, no systemic steroid or antiviral treatment was administered throughout the follow-up periods. Successful outcomes post surgery were defined as a reduction of IOP of more than 20% on 2 consecutive follow-up visits, $5 < IOP \leq 21$ on 2 consecutive follow-up visits, vision of at least more than light perception, and no need for additional glaucoma surgery. Statistical analysis was made according to the following data: 1) postoperative follow-up periods, 2) patient age, 3) sex, 4) the number of glaucoma medications pre and post surgery, 5) preoperative IOP, 6) postoperative IOP, 7)

the number of glaucoma surgeries prior to LTSS, 8) the type of LTSS, 9) the outcomes of the surgeries by dividing the eyes into those that received single LTSS and those that received LTSS combined with TLE, 10) the cause of UG 11), the type of uveitis or iridocyclitis in the UG Group, and 12) steroid responders (i.e., eyes that responded to steroid application).

The type of uveitis was diagnosed as granulomatous and non-granulomatous via observation of the clinical course, angle appearances, the changes in the choroid/retina using fundus fluorescein angiography (FFA), aqueous humor tap in unilateral UG, and histopathology of the obtained TLE specimens. Steroid responders were determined by the clinical observation of more than 6 mmHg decrease of IOP within 1 month after ceasing betamethasone or more than 6 mmHg increase of IOP within 1 month after the initiation of betamethasone before LTSS. In the patients with unilateral UG, steroid response was examined in the fellow eye according to the Armaly technique [22]. As procedures of LTSS or LTSS combined with TLE were performed as described elsewhere [23], and all tubes were inserted into the anterior chamber and mitomycin-C (MMC) was used in all TLE operations. The timing of the surgery was adjusted to suppress the inflammation of the eyes by prescribing topical steroid. In cases of the combined LTSS/TLE, the tube tip was ligated with a 7-0 nylon suture via 3-1-1 insertion without venting slits. If the IOP exceeded 21 mmHg at more than 4 weeks after the surgery, the ligation suture was released by use of an argon laser. R version 3.4.0 software (The R Project For Statistical Computing, www.r-project.org) was used for the statistical analyses, and Kaplan-Meier survival-curve analysis and the log-rank test were used to summarize the cumulative probability of success. A P-value of < 0.05 was considered statistically significant. This study was approved by the Institutional Review Board (IRB) of the Japanese Red Cross Medical Center, Tokyo, Japan.

Results

In this retrospective study, the data of 45 UG eyes of 41 patients were analyzed. Four eyes were excluded from the study due to no release of the tube ligature because TLE was effective during the observation periods (Table 1). The mean follow-up period was 1527.18 ± 1010.66 days, the mean patient age was 55.00 ± 14.35 years, and the percentage ratio of female subjects was 42.2% (n = 17). The mean number of glaucoma medications used before LTSS was 3.42 ± 1.01, and were significantly reduced after LTSS (1.28 ± 1.50, $p = 3.47\times10^{-10}$) (Table 1). The rate of glaucoma medication reduction from pre and post LTSS was 37.4% (Table 1). The mean number of times that glaucoma surgery was performed before LTSS was 0.88 ± 0.9 times (Table 2). Twenty-four eyes (53.3%) underwent combined LTSS with TLE (Table 2). The types of LTSS performed were Baerveldt 250 (16 eyes), Baerveldt 350 (UG Group: 18 eyes), and Double Plate Molteno® Glaucoma Drainage Device (Molteno® Ophthalmic Ltd., Dunedin, New Zealand) implantation (11 eyes) (Table 2). The reason for LTSS combined with TLE was due to an

Aulhorn-Greve visual field classification of greater than Stage IV in 9 eyes, an elevated IOP of more than 35 mmHg in 16 eyes, or both in 2 eyes.

The mean pre- and postoperative IOPs at the final follow up of all treated eyes, the eyes that received only LTSS, and the eyes that received LTSS combined with TLE, were 33.76 ± 10.74 mmHg and 14.31 ± 5.68 mmHg, 29.94 ± 10.60 mmHg and 15.14 ± 6.57 mmHg, and 37.50 ± 10.03 mmHg and 13.58 ± 4.79 mmHg, respectively. Significant decreases of IOP were found ($p < 0.0001$) in all treated eyes, regardless of the type of surgery performed.

Kaplan-Meier survival-curve estimates of all eyes were 98% for 1 year, 92% for 3 years, and 84% for 5 years (Fig. 1). Kaplan-Meier survival-curve estimates of the eyes that received only LTSS were 95% for 1 year, 84% for 3 years, and 66% for 5 years. Kaplan-Meier survival-curve estimates of the eyes that received LTSS combined with TLE were 100% for 1 year, 100% for 3 years, and 100% for 5 years. Significant difference was observed between the two groups ($p = 0.0115$) (Fig. 2).

FFA examination was performed in all cases of sarcoidosis (8 eyes) and in the cases of uveitis of an unknown cause (9 eyes). In 8 cases of unilateral uveitis, an aqueous humor sample was obtained. As is shown in Table 3, infection due to cytomegalovirus (CMV, $n = 6$ eyes, one of which was diagnosed at the clinic previously visited) and varicella-zoster virus (VZV, $n = 3$ eyes, one of which was diagnosed from clinical manifestations of skin) was detected in the obtained samples among 8 eyes with Posner-Schlossman syndrome (PSS). The cases with negative results or no examination of the aqueous humor tap were diagnosed as PSS. Other types of uveitis were diabetic iritis ($n = 2$ eyes), congenital syphilis ($n = 2$ eyes), iritis due to psoriasis ($n = 1$ eye), Behçet's disease ($n = 1$ eye), and unknown ($n = 9$ eyes). Granulomas in obtained TLE specimens were observed in the eyes with sarcoidosis ($n = 2$ eyes), CMV infection ($n = 1$ eye), congenital syphilis ($n = 1$ eye), and VZV infection ($n = 1$ eye). The type of uveitis was divided into three categories; 1) granulomatous ($n = 37$ eyes), 2) non-granulomatous ($n = 5$ eyes), and 3) unknown ($n = 3$ eyes). All eyes diagnosed as PSS were categorized as granulomatous UG due to large mutton-fat-like keratic precipitates being seen during observation. The mean pre- and postoperative IOPs in the eyes with granulomatous and non-granulomatous UG were 34.21 ± 11.61 mmHg and 14.82 ± 5.53 mmHg and 28.60 ± 1.34 mmHg and 13.40 ± 3.78 mmHg, respectively. Significant decrease of IOP was found in both granulomatous ($p = 2.00 \times 10^{-12}$) and non-granulomatous ($p = 3.80 \times 10^{-3}$) UG. Preoperative IOPs in the granulomatous UG cases were significantly higher than those in the non-granulomatous UG cases ($p = 0.008$). No significant difference was found between the granulomatous UG and non-granulomatous UG groups in postoperative IOPs ($p = 0.488$) and IOP decreases between the pre- and postoperative IOP ($p = 0.101$). Kaplan-Meier survival-curve estimates revealed no significant difference among the different types of LTSS ($p = 0.698$). Although the Kaplan-Meier survival-curve estimate findings showed no significant difference in the probability of success between the granulomatous group and the non-granulomatous group ($p = 0.4360$), the probability of success in the non-granulomatous UG group was found to be 100% for 6 years, while that in the granulomatous UG

group was found to gradually decrease along the 6-year period post surgery (Fig. 3).

The eyes in the UG Group were also divided into steroid responder (n = 19 eyes) and non-steroid responder (n = 13 eyes). Thirteen eyes could not be determined due to no available data. Pre- and postoperative IOPs in the eyes with steroid and non-responder were 31.84 ± 7.52 mmHg and 15.84 ± 6.22 mmHg and 35.62 ± 14.08 mmHg and 14.23 ± 4.44 mmHg, respectively. A significant decrease of IOP was found in both the steroid responder ($p = 2.58\times10^{-8}$) and non-steroid responder ($p = 1.19\times10^{-4}$) groups. There was no significant difference between the steroid responder and non-steroid responder groups in preoperative IOPs (p = 0.3893), postoperative IOPs (p = 0.3993), and IOP decreases between pre- and postoperative IOP (p = 0.2527). Kaplan-Meier survival-curve estimates showed that the 5-year survival rates in the eyes in the steroid and non-steroid responder groups were 74% and 78%, respectively (Fig. 4); no significant difference was observed between the non-steroid and steroid responder groups (p = 0.9230). Except in 2 eyes, all eyes showed no or slight anterior chamber inflammation at the time of LTSS. In those 2 eyes of the 2 patients in which failure occurred due to an inadequate control of IOP post LTSS, moderate inflammation was observed in the anterior chamber at the time of LTSS, despite the administration of topical betamethasone and antiglaucoma medication prior to LTSS. A 3-times-daily treatment of topical betamethasone was administered in all patients with granulomatous UG after LTSS, except in 2 eyes of 2 patients with congenital syphilis, in order to avoid irreversible changes in the outflow routes. No systemic steroid or antiviral treatment was administered throughout the follow-up periods. Retrobulbar injections of triamcinolone were administered in 6 eyes of 4 patients with sarcoidosis (Patients 1, 3, 8, and 19) due to decreased vision caused by posterior uveitis. Despite the continuous 3-times-daily administration of topical betamethasone, recurrence of iritis was observed in 2 eyes with sarcoidosis (22%), 1 eye with CMV-associated iridocyclitis (20%), 3 eyes with PSS (60%), and 1 eye with VZV (33%). However, no IOP spike of more than 20 mmHg was observed in all patients with granulomatous UG after LTSS. The number of recurrences, the IOP at each recurrence, and the follow-up periods in the eyes with granulomatous UG are listed in Table 4.

There were 24 patients with unilateral UG (CMV: n = 6 eyes; PSS: n = 13 eyes; VZV: n = 3 eyes; unknown: n = 2 eyes). Of those 26 eyes, there were 20 eyes composed of POAG (n = 7 eyes) and with an IOP of more than 18 mmHg (n = 13 eyes) in the fellow eye (p = 0.0022, 83%). All eyes with POAG and 11 eyes with IOP of more than 18 mmHg in the fellow eyes were prescribed topical glaucoma medication. In 2 fellow eyes with IOP of more than 18 mmHg, glaucoma medication was not administered.

The reasons of the surgical treatment failure were an IOP of more than 22 mmHg (n = 5 eyes), an insufficient IOP decrease of less than 20% (n = 1 eye), and plate exposure (n = 1 eye) (Table 5). Corneal edema occurred in 4 eyes (Patient 3: sarcoidosis with narrow angle; Patient 4: congenital syphilis; Patient 36: PSS; Patient 40: CMV-associated iritis). Corneal transplantation was later performed in 2 of those 4 eyes (Patient 4 and Patient 40).

Discussion

The specific type of glaucoma surgery that should be applied in patients with UG has been of great concern to glaucoma specialists. Three studies of tube versus TLE for the treatment of UG are currently in the published literature. Iverson et al. reported that the 5-year success rate of Baerveldt and TLE were 75% and 38%, respectively [8]. Bettis et al. reported that the average periods post surgery of Ahmed valve and TLE failure were 21.8 months and 8.36 months, respectively [24]. On the other hand, Kwon et al. reported that in cases that underwent LTSS without valve and TLE, no significant difference in IOP was observed beyond 3-months postoperative [25]. It should be noted that one possible reason for the refractive nature of UG may be the recurrence of uveitis even after the glaucoma surgery [12, 25].

In our study, the 5-year survival rates using both single LTSS and LTSS combined TLE were 66% and 100%, respectively (Fig. 2). In all eyes with both single LTSS and LTSS combined TLE, the 5-year survival rate was 84% (Fig. 1). Molteno et al. reported that 5-year survival rate in UG cases when using the Molteno implant was 87% [18]. Recently, there have been two reports of UG patients treated with the Baerveldt implant, and in both of those studies, the survival rate achieved at 5-years postoperative was approximately 75% [13, 19]. However, the 5-year survival rate of our single LTSS in UG cases was 66% (Fig. 2). There may be two reasons for the lower 5-year survival rate in our study. Racial difference may possibly be the biggest reason for this, thus suggesting that compared with other races [26], LTSS in Japanese patients with POAG may have intense fibrosis around the plate. The other reason may be that the ratio of UG due to granulomatous disease (n = 37 eyes, 82%) was very high in our study. In addition, 9 eyes (25%) with sarcoidosis were included in our study, which is a much higher number of eyes than in the other report [19]. Iwao et al. reported that granulomatous uveitis was more susceptible to surgical failure with MMC-augmented TLE [7]. In UG due to granulomatous inflammation including sarcoidosis [27] and congenital syphilis [28], granuloma in the Schlemm's canal reportedly caused occlusion of the canal, which may result in refractory glaucoma. Therefore, yet except in the congenital syphilis cases, a continuous 3-times-daily administration of topical betamethasone was prescribed in the patients with granulomatous UG even after LTSS. Kaplan-Meier survival-curve estimate findings showed no significant difference in the probability of success between the non-granulomatous group and the granulomatous group (p = 0.4360). However, in the non-granulomatous group, the probability of success was found to be 100% for 6 years, while that in the granulomatous group was found to gradually decrease over the 6-year period post surgery (Fig. 3). In addition, among the 7 failed eyes, 6 eyes were granulomatous UG (Table 5). Although no significant difference was found between the non-granulomatous group and the granulomatous group in regard to the survival curves due to the small sample size in the non-glaucomatous group, these findings do suggest that granulomatous UG has a refractory nature.

Steroid responder cases are a major problem in the treatment of UG. The diagnosis of corticosteroid-induced glaucoma was determined via the Armaly technique in the fellow eyes of the unilateral UG cases. In the eyes of the bilateral UG cases, steroid response is best confirmed when the steroid is discontinued [22]. The reason for our strong attention to the steroid responders is that we have tried to continue to apply topical betamethasone at least 3-times daily post surgery in the eyes with granulomatous UG in order to prevent the collapse of the Schlemm's canal, as discussed above. It is interesting to note that in all eyes with unilateral uveitis or iridocyclitis that were found to have strong steroid positive responder in the fellow eye, continuous administration of topical betamethasone after LTSS did not result in IOP elevation. Despite of continuous topical betamethasone in the eyes with granulomatous UG, we experienced 7 eyes with recurrence of iritis or uveitis (Table 4). Although topical ganciclovir treatment for CMV is reportedly effective for preventing corneal endothelial cell loss, 32% of the patients in that study with longer disease duration required filtering surgeries [29]. In the cases in this present study, there were two major reasons for not administering antiviral medication. The first reason was that in most of the herpetic iridocyclitis eyes, LTSS or LTSS combined TLE was administered prior to the introduction of treatment with antiviral medication. The second reason was that the administration of topical antiviral medication is not covered by official Japanese health insurance treatment policy. However, those eyes with herpetic iridocyclitis did not show an IOP spike after ligation release of the tube without using antiviral treatment, but with continuous administration of topical betamethasone, which may greatly help further the optic nerve damage.

Coexistence of a POAG background with UG may be another obstacle against the achievement of good IOP control after LTSS. In the cases with unilateral uveitis, it may be possible to evaluate the coexistence of a POAG background by examining the fellow eye. Considering the rather low IOP and higher prevalence of normal-tension glaucoma in Japanese subjects [30], the eyes with an IOP of 18 mmHg, or more than 18 mmHg, are regarded as having POAG or a POAG background. Thus, a POAG background is defined as a high risk of developing POAG with an IOP of more than 18 mmHg. The significantly high ratio of the eyes with POAG or a POAG background in our patients was observed in unilateral UG ($p = 0.0022$, 83%). Among 7 failed eyes in this present study (Table 5), 4 eyes (58%) with POAG/POAG background in the fellow eye of UG, 6 eyes with granulomatous UG (86%), and 3 eyes (43%) with positive steroid responder were found. Even though the number of failed eyes was small, granulomatous UG or a POAG/POAG background suggested that those eyes may have a refractory nature and be risk factors for surgical failure post LTSS. Considering the 100% survival rate of LTSS combined with TLE at 5-years postoperative in this study, LTSS combined with TLE should be selected in the eyes with a high risk of failure.

Corneal edema due to corneal endothelial cell loss after LTSS was the primary complication that threatened visual function in our study, and we experienced 4 eyes that later required corneal transplantation. All eyes with corneal edema received either no, or one, glaucoma surgery prior to

undergoing LTSS. Among the 4 eyes that underwent corneal transplantation, 2 eyes were herpetic iridocyclitis and PSS. Antiviral medication may have prevented endothelial damage. However, among 7 eyes with recurrent iritis despite continuous administration of topical betamethasone (Table 4), 5 eyes were herpetic iridocyclitis, and no corneal edema was experienced in those eyes during the observation periods. Ocular hypotension also was not observed in those eyes after LTSS, possibly because of the good timing of the tube ligature release at approximately 7-weeks post single LTSS [31] or the intentional suture release in the cases that underwent LTSS combined with TLE [32].

In conclusion, continuous administration of topical betamethasone post LTSS may be important for preventing an IOP spike by suppressing inflammation in the anterior chamber. In addition, positive steroid response may be masked by LTSS, as no IOP elevation was observed in the positive steroid responder eyes. LTSS combined with TLE may be recommended in the eyes with granulomatous UG, and the coexistence of a POAG/POAG background.

Acknowledgements The authors wish to thank John Bush for editing the manuscript.

Contributors TH: study concept and design, data acquisition, management, and interpretation, drafting of the manuscript, and review of the published literature. SW: data acquisition and interpretation, drafting of the manuscript, and review of the published literature. KK: data acquisition. NI: data acquisition and management, and manuscript final version approval. TS: data analysis. NE: manuscript final version approval.

Funding None declared.

Competing interests / Financial disclosure None declared.

Ethics approval This study was approved by the Institutional Review Board (IRB) of the Japanese Red Cross Medical Center, Tokyo, Japan.

References

1. Jampel HD, Jabs DA, Quigley HA (1990) Trabeculectomy with 5-fluorouracil for adult inflammatory glaucoma. Am J Ophthalmol 109:168-173.
2. Towler HM, McCluskey P, Shaer B, Lightman S (2000) Long-term follow up of trabeculectomy with intraoperative 5-fluorouracil for uveitis-related glaucoma. Ophthalmology 107:1822-1828.

3. Ceballos EM, Beck AD, Lynn MJ (2002) Trabeculectomy with antiproliferative agents in uveitic glaucoma. J Glaucoma 11(3):189-196.
4. Noble J, Derzko-Dzulynsky L, Rabinovitch T, Birt C (2007) Outcome of trabeculectomy with intraoperative mitomycin C for uveitic glaucoma. Can J Ophthalmol 42:89-94.
5. Kaburaki T, Koshino T, Kawashima H, Numaga J, Tomidokoro A, Shirato S, Araei M (2009) Initial trabeculectomy with mitomycin C in eyes with uveitic glaucoma with inactive uveitis. Eye (Lond) 23:1509-1517.
6. Chawla A, Mercieca K, Fenerty C, Jones NP (2013) Outcomes and complications of trabeculectomy enhanced with 5-fluorouracil in adults with glaucoma secondary to uveitis. J Glaucoma 22:663-666.
7. Iwao k, Inatani M, Seto T, Takihara Y, Ogata-Iwao M, Okinami S, Tanihara H (2014) Long-term outcomes and prognostic factors for trabeculectomy with mitomycin C in eyes with uveitic glaucoma: a retrospective cohort study. J Glaucoma 23:88-94.
8. Iverson SM, Bhardwaj N, Shi W, Sehi M, Greenfield DS, Budenz DL, Kishor K (2015) Surgical outcomes of inflammatory glaucoma: a comparison of trabeculectomy and glaucoma-drainage-device implantation. Jpn J Ophthalmol 59:179-186.
9. Baudouin C, Pisella PJ, Fillacier K, Goldschild M, Becquet F, De Saint Jean M, Béchetoille A (1999) Ocular surface inflammatory changes induced by topical antiglaucoma drugs: human and animal studies. Ophthalmology 106:556-563.
10. Ophir A, Ticho U (1992) Delayed filtering bleb encapsulation. Ophthalmic Surg 23:38-39.
11. Skuta GL, Parrish RK 2nd (1987) Wound healing in glaucoma filtering surgery. Surv Ophthalmol 32:149-170.
12. Shimizu A, Maruyama K, Yokoyama Y, Tsuda S, Ryu M, Nakazawa T (2014) Characteristics of uveitic glaucoma and evaluation of its surgical treatment. Clin Ophthalmol 26:2383-2389.
13. Ceballos EM, Parrish RK 2nd, Schiffman JC (2002) Outcome of Baerveldt glaucoma drainage implants for treatment of uveitic glaucoma. Ophthalmology 109:2256-2260.
14. Tan AN, Cornelissen MF, Webers CAB, Erckens RJ, Berendschot TTJM, Beckers HJM (2018) Outcomes of severe uveitic glaucoma treated with Baerveldt implant: can blindness be prevented? Acta Ophthalmol 96:24-30.
15. Da Mata A, Burk SE, Netland PA, Baltatzis, Christen W, Foster CS (1999) Management of uveitic glaucoma with Ahmed glaucoma valve implantation. Ophthalmology 106:2168-2172.
16. Ozdal PC, Vianna RN, Deschenes J (2006) Ahmed valve implantation in glaucoma secondary to chronic uveitis. Eye (Lond) 20:178-183.
17. Gil-Carrasco F, Salinas-VanOrman E, Recillas-Gispert C, Paczka JA, Gilbert ME, Arellanes-Garcia L (1998) Ahmed valve implant for uncontrolled uveitic glaucoma. Ocul Immunol Inflamm 6:27-37.
18. Molteno AC, Sayawat N, Herbison P (2001) Otago glaucoma surgery outcome study : long-term

results of uveitis with secondary glaucoma drained by Molteno implants. Ophthalmology 108:605-613.
19. Chhabra R, Tan SZT, Au L, Spencer AF, Fenerty CH, Jones NP (2018) Long-term outcomes and complications of Baerveldt glaucoma drainage implants in adults with glaucoma secondary to uveitis. Ocul Immunol Inflamm 13:1-8.
20. Rachmiel R, Trope GE, Buys YM, Flanagan JG, Chipman ML (2008) Ahmed glaucoma valve implantation in uveitic glaucoma versus open-angle glaucoma patients. Can J Ophthalmol 43:462-467.
21. Krishna R, Godfrey DG, Budenz DL, Escalona-Camaano E, Gedde SJ, Greenfield DS, Feuer W, Scott IU (2001) Intermediate-term outcomes of 350-mm(2) Baerveldt glaucoma implants. Ophthalmology 108:621-626.
22. Ritch R (1996) Chapter 55. In: Ritch R, Shields MB, Krupin T (eds) The Glaucomas, 2nd edn. Mosby, St Louis, pp 1178
23. Gedde SJ, Feuer WJ, Shi W, Lim KS, Barton K, Goyal S, Ahmed IIK, Brandt J; Primary Tube Versus Trabeculectomy Study Group (2018) Treatment Outcomes in the Primary Tube Versus Trabeculectomy Study after 1 Year of Follow-up. Ophthalmology 125:650-663.
24. Bettis DI, Morshedi RG, Chaya C, Goldsmith J, Crandall A, Zabriskie N (2015) Trabeculectomy With Mitomycin C or Ahmed Valve Implantation in Eyes With Uveitic Glaucoma. J Glaucoma 24:591-599.
25. Kwon HJ, Kong YXG, Tao LW, Lim LL, Martin KR, Green C, Ruddle J, Crowston JG (2017) Surgical outcomes of trabeculectomy and glaucoma drainage implant for uveitic glaucoma and relationship with uveitis activity. Clin Exp Ophthalmol 45:472-480.
26. Broadway DC, Chang LP (2001) Trabeculectomy, risk factors for failure and the preoperative state of the conjunctiva. J Glaucoma 10:237-249.
27. Hamanaka T, Takei A, Takemura T, Oritsu M (2002) Pathological study of cases with secondary open-angle glaucoma due to sarcoidosis. Am J Ophthalmol
134:17-26.
28. Hayashi S, Hamanaka T, Takemura T (2012) Pathological Study of Secondary Glaucoma due to Congenital Syphilis - A New Theory of Vasculitis in the Schlemm's Canal. J Clin Exp Ophthalmol 3:249.
29. Su CC, Hu FR, Wang TH, Huang JY, Yeh PT, Lin CP, Wang IJ (2014) Clinical outcomes in cytomegalovirus-positive Posner-Schlossman syndrome patients treated with topical ganciclovir therapy. Am J Ophthalmol 158:1024-1031.
30. Iwase A, Suzuki Y, Araie M, Yamamoto T, Abe H, Shirato S, Kuwayama Y, Mishima HK, Shimizu H, Tomita G, Inoue Y, Kitazawa Y; Tajimi Study Group, Japan Glaucoma Society (2004) The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. Ophthalmology 111:1641-1648.
31. Kawamorita S, Hamanaka T, Sakurai T (2014) The early postoperative complications in two different tube ligation methods in Baerveldt implant surgery. J Curr Glaucoma Pract 8:96-100.
32. Hamanaka T, Otora K, Ono K, Ishida N (2014) Long-term results of non-valved Glaucoma drainage implant surgery and glaucoma drainage implant combined with trabeculectomy. Indian J Ophthalmol

62:911-916.

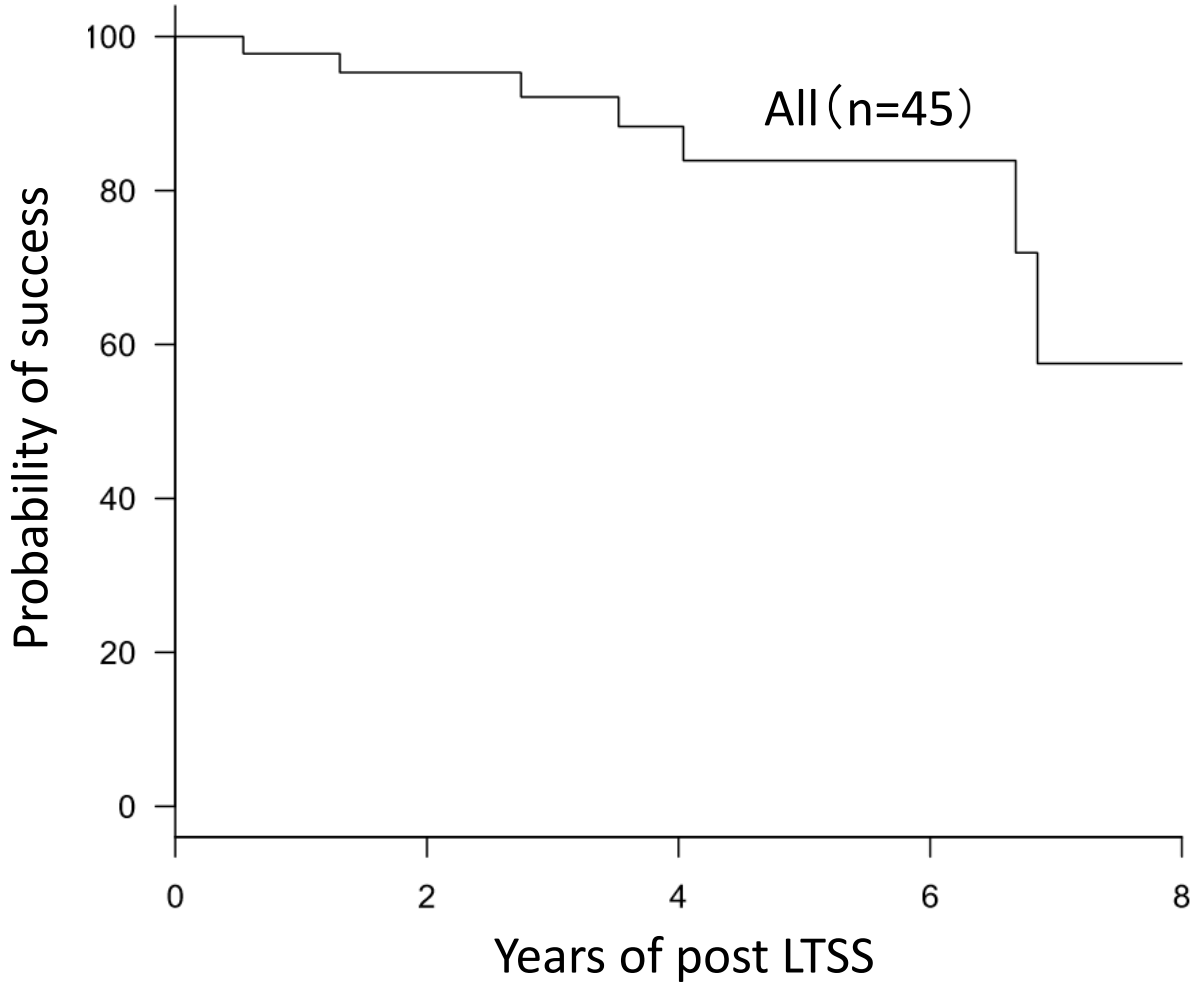
Figure Captions

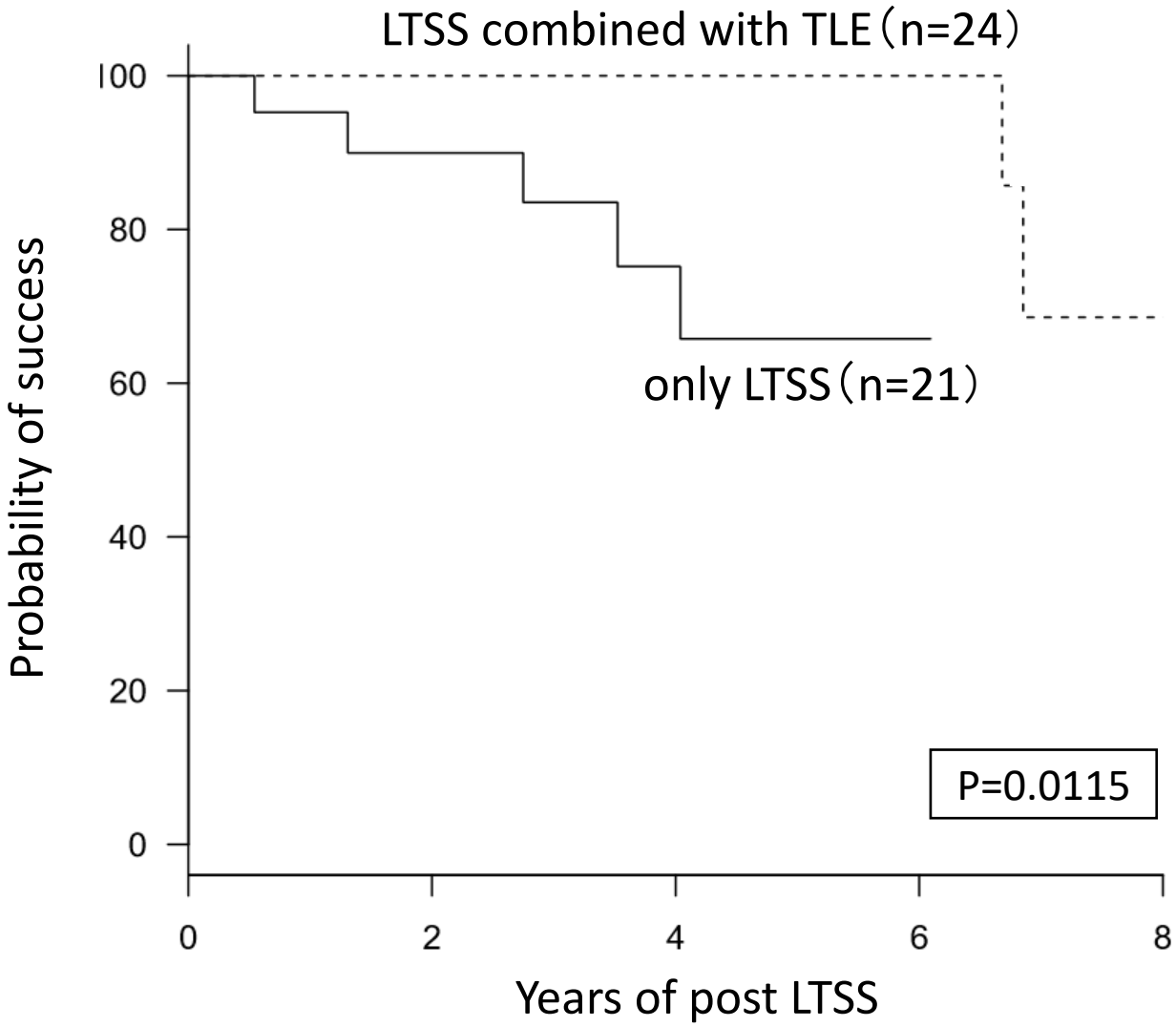
Fig. 1 Graph showing the Kaplan-Meier survival-curve estimates of all eyes that received only LTSS and LTSS combined with TLE ($n = 45$)

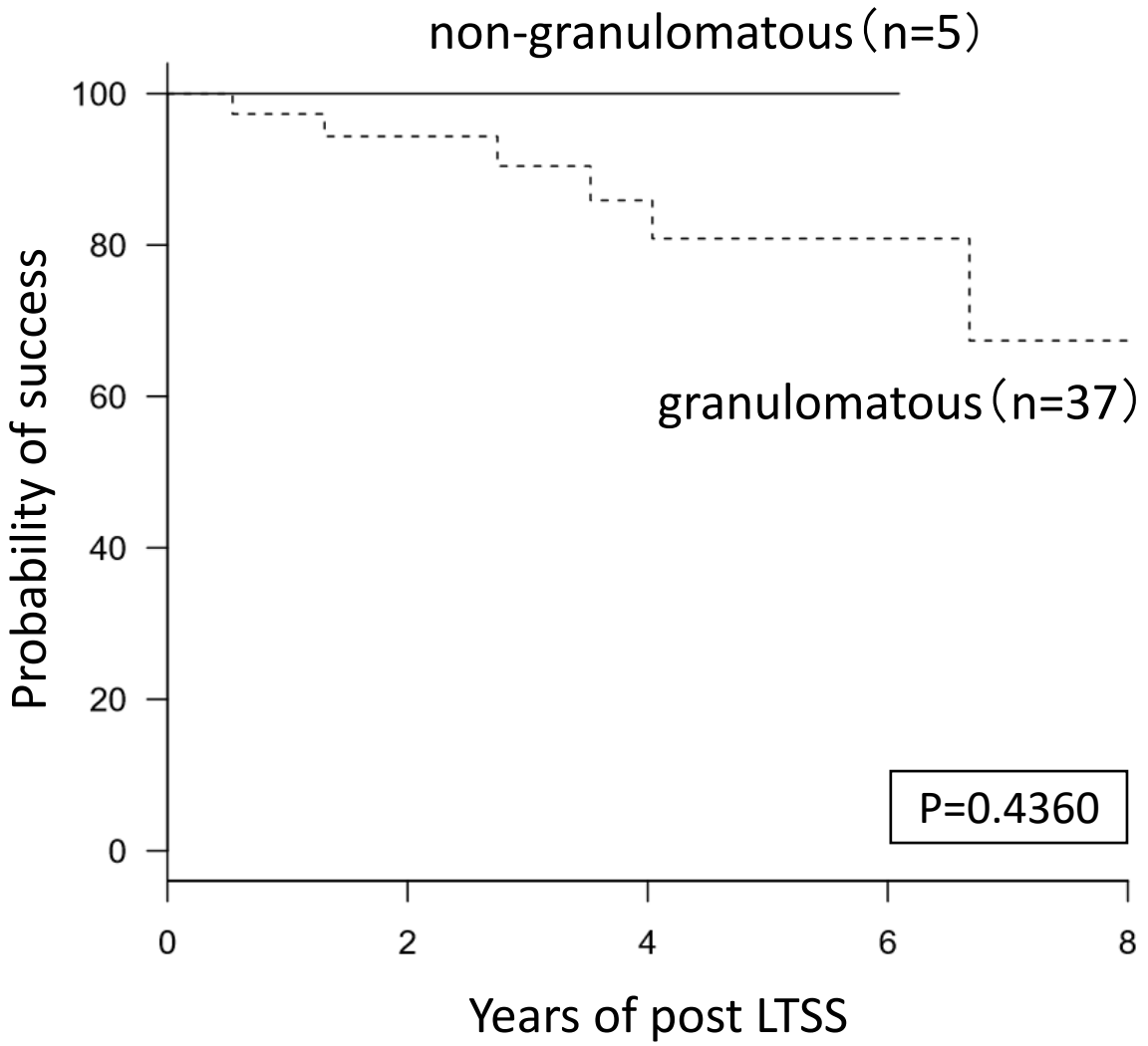
Fig. 2 Graph showing the Kaplan-Meier survival-curve estimates of all eyes that received only LTSS in the UG Group ($n = 21$) and all eyes that received LTSS combined with TLE ($n = 24$). Significant difference was observed between the two groups ($p = 0.0115$)

Fig. 3 Graph showing the Kaplan-Meier survival-curve estimates in the non-granulomatous group ($n = 5$ eyes) and the granulomatous group ($n = 37$ eyes). The survival rate in the non-granulomatous UG group was found to be 100 for 6 years, while that in the granulomatous UG group was found to gradually decrease along 6-years post surgery ($p = 0.4360$)

Fig. 4 Graph showing the Kaplan-Meier survival-curve estimates in the non-steroid responder group ($n = 13$ eyes) and the steroid responder group ($n = 19$ eyes). The 5-year survival rates in the eyes in the steroid and non-steroid responder groups were 74% and 78%, respectively. No significant difference was observed between the non-steroid and steroid responder groups ($p = 0.9230$)


All（n=45）
Probability of success
100
80
60
40
20
0
0
2
4
6
8
Years of post LTSS


LTSS combined with TLE（n=24）
only LTSS（n=21）
P=0.0115
Probability of success
100
80
60
40
20
0
0
2
4
6
8
Years of post LTSS


non-granulomatous（n=5）
granulomatous（n=37）
Probability of success
100
80
60
40
20
0
0
2
4
6
8
Years of post LTSS
P=0.4360

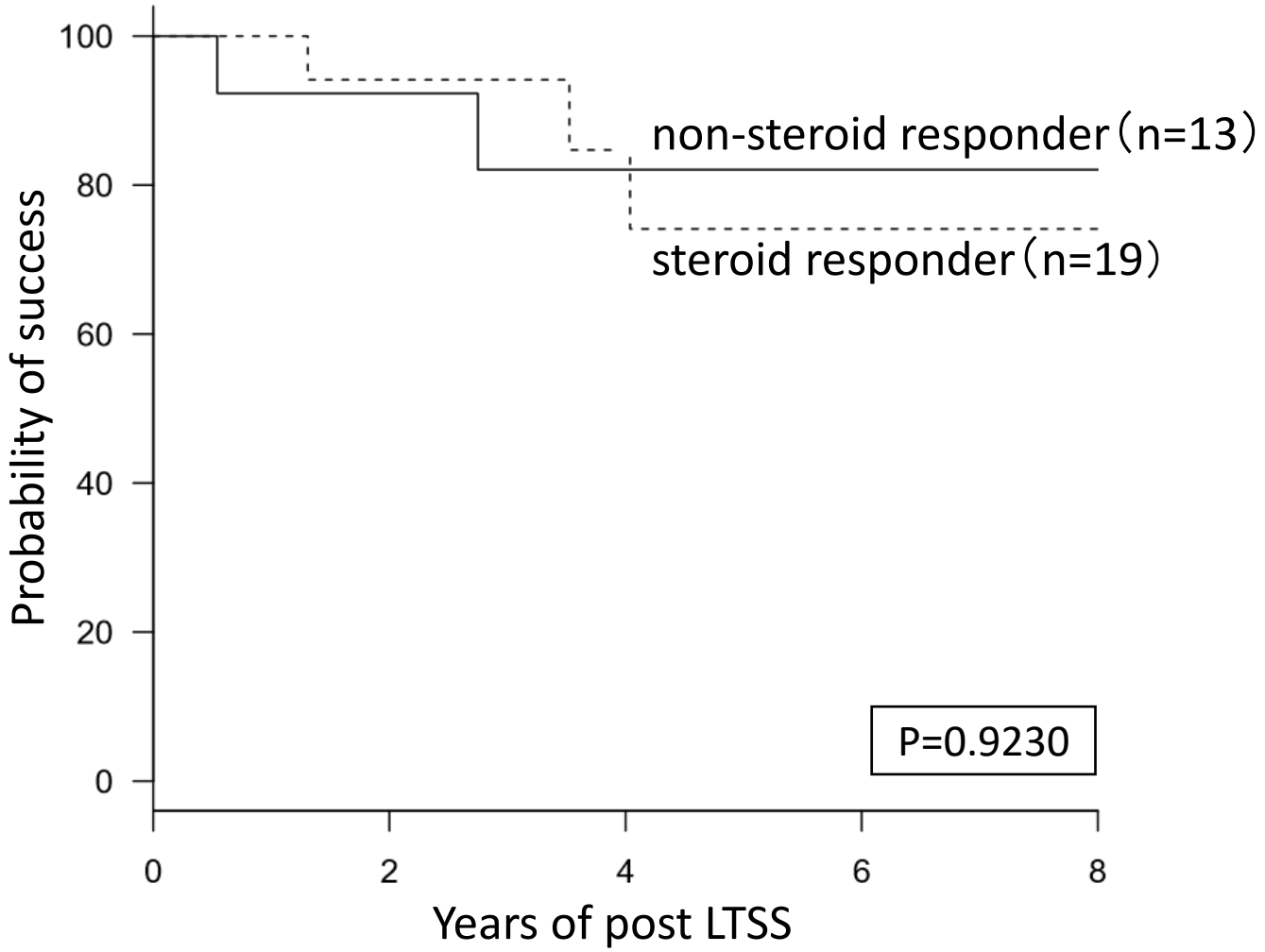

100
80
60
40
20
0
Probability of success
non-steroid responder（n=13）
steroid responder（n=19）
P=0.9230
0
2
4
6
8
Years of post LTSS

Table 1 Mean pre- and postoperative IOP and number of glaucoma medications used

	UG Group *n* = 45
Preoperative IOP (mmHg)	33.76 ± 10.74
Postoperative IOP (mmHg)	14.31 ± 5.68
Glaucoma medications (Preoperative)	3.42 ± 1.01
Glaucoma medications (Postoperative)	1.28 ± 1.50

IOP, intraocular pressure; UG, uveitic glaucoma.

Table 2 The number of previous glaucoma surgeries and the glaucoma surgery data in this study

	UG Group *n* = 45
Prior incisional glaucoma surgery	0.88 ± 0.9 (0-4 times)
The number of the eyes with combined LTSS with TLE (%)	24 (53.3%)
Types of LTSS	
Baerveldt 250	16
Baerveldt 350	18
Double-plate Molteno	11

LTSS = long tube shunt surgery; TLE: trabeculectomy

Table 3 Causes of UG

Etiology	Number (eyes)
Sarcoidosis	8
Posner-Schlossman syndrome	13
Cytomegalovirus	6
Varicella-zoster virus	3
Diabetic iritis	2
Congenital syphilis	2
Iritis due to psoriasis	1
Behçet's disease	1
Unknown	9

UG = uveitic glaucoma

Table 4 Recurrence of iritis in granulomatous UG despite 3-times-daily administration of topical betamethasone

Patient number	Diagnosis	Number of recurrences	Observation period (days)	IOP at recurrence
8	Sarcoidosis	1	2127	18
13	PSS	1	2014	15
19	Sarcoidosis	3	1108	20
21	PSS	3	867	20
23	CMV	1	749	12
30	VZV	1	4480	18
42	PSS	2	3193	26※

UG = uveitic glaucoma; PSS = Posner-Schlossman syndrome; CMV = cytomegalovirus; VZV = varicella-zoster virus

※ The eyes of Patient 42 underwent Baerveldt combined with TLE. Ligation of the tube was released after the recurrence of iridocyclitis, which caused elevation of IOP to 26 mmHg, and no IOP spike has been observed since then.

Table 5 Failed eyes in the UG Group

Patient number Age Sex (※)	**Cause of failure**	**Type of UG**	**Steroid responder**	**POAG or OH in the fellow eye**
2, 74M (1475)	a reduction of IOP<20%	Sarcoidosis	＋	UD
3, 69F (1004)	IOP≧22	Sarcoidosis	－	UD
11, 59M (198)	IOP≧22	Sarcoidosis	－	POAG
14, 54F (1287)	IOP≧22	PSS	＋	OH
20, 39F (478)	IOP≧22	Sarcoidosis	＋	UD
33, 43M (2440)	IOP≧22	PSS	UD	OH
39, 34M (2503)	Plate exposure	UD	UD	OH

UG = uveitic glaucoma; POAG = primary open-angle glaucoma; OH = ocular hypertension; IOP = intraocular pressure; UD = undetermined; PSS = Posner-Schlossman syndrome

※ Period (days) between the date of surgery and when determined as failure