Combination of Trabeculectomy and Primary Pars Plana Vitrectomy in the Successful Treatment of Angle-Closure Glaucoma with BEST1 Mutations: Self-Controlled Case Series

Yuxin Fang · Xiaoming Duan · Lin Chen · Jie Shi · Jie Liu · Yunxiao Sun · Jin Wang · Yang Li · Xin Tang

ABSTRACT

Introduction: This study aimed to illustrate the efficacy of the combination of lens extraction, trabeculectomy, and anterior vitrectomy in patients with secondary angle-closure glaucoma (ACG) with autosomal recessive bestrophinopathy or Best vitelliform macular dystrophy.

Methods: This is a retrospective self-controlled case series study. Five patients undergoing a single trabeculectomy in one eye and triple surgery in the other eye were enrolled. All patients underwent a complete ophthalmic examination that included best-corrected visual acuity (BCVA), intraocular pressure (IOP), ultrasound biomicroscopy, and static gonioscopy. Multimodal fundus imaging was performed, including color fundus photography, fundus autofluorescence, and optical coherence tomography. Genetic testing was also analyzed.

Results: Among the 10 eyes, the mean IOP was 31.4 ± 4.7 mmHg before surgery. The mean axial length (AL) was 21.53 mm and the anterior chamber depth (ACD) was 2.31 mm. There were no statistically significant differences in preoperative IOP, BCVA, ACD, and AL between the two groups (all P > 0.05). The mean follow-up time was 64.0 months. All five eyes with a single trabeculectomy developed malignant glaucoma (MG). No complications were found in the other five eyes with triple surgery, and the anterior chamber was deepened and stable after surgery until the last visit. The mean IOP at the last visit was normalized to 16 mmHg without using any medications.

Conclusions: Triple surgery is superior to single trabeculectomy for patients with ACG and BEST1 mutation, effectively bypassing MG complications. The vitreous may play a vital role in the mechanism of ACG in those patients and the high incidence of MG after filtering surgery.

Keywords: Angle-closure glaucoma; Anterior vitrectomy; Autosomal recessive bestrophinopathy; Malignant glaucoma; Trabeculectomy

Yuxin Fang and Xiaoming Duan contributed equally to the work presented here and should therefore be regarded as equivalent authors.
Autosomal recessive bestrophinopathy (ARB), with homozygous or compound heterozygous sequence variants in BEST1, was first recognized by Burgess et al. [1] in 2008, with a high risk of angle-closure glaucoma (ACG). Angle closure with or without glaucoma was reported to affect around 29–71.4% of patients with ARB, the rate of which was much higher in Chinese patients [1–4]. The cause behind the simultaneous occurrence of ACG in BEST1-associated retinopathy, referred to as bestrophinopathies [5], including ARB and Best vitelliform macular dystrophy (BVMD), had not yet been elucidated.

Yttrium–aluminum–garnet laser peripheral iridotomy alone was not enough to reduce intraocular pressure (IOP) in patients with ARB with narrow anterior chamber [2]. Most reports agreed that a cataract extraction also failed to open the anterior chamber angle to a sufficient degree so that IOP was still high [2, 6, 7], despite a single case with controlled IOP, but required continued use of two topical medications after lens extraction [8]. Zhong et al. [9] observed that all eight of their cases of ACG with ARB (15 eyes) developed persistent shallow anterior chamber after trabeculectomy. ARB generally manifests in the first two decades of life; some patients are even younger than 18 years of age (children-onset disease) [2, 4]. The onset of glaucoma in ARB tends to be younger than in primary ACG. Younger age, being refractory to IOP control, 100% penetrance of malignant glaucoma (MG) after trabeculectomy, and possible dysgenesis of the anterior segment make it a huge challenge to find optimal therapeutic regimens for patients with ARB with refractory glaucoma.

Tongren Eye Center is one of the largest and best-known eye centers in China, with a number of experienced consultants from all fields of ophthalmology, which attracts patients with refractory and rare eye diseases from all over the country. Glaucoma is one of the strongest subspecialties in Tongren. Through our experience, we found that the combination of lens extraction, trabeculectomy, and anterior vitrectomy is
an appropriate choice in the surgical management of ACG in patients with ARB. Nineteen patients with ACG as well as ARB or BVMD treated by a glaucoma specialist (Xin Tang) in our hospital were extracted from January 2014 to November 2021. Among those patients, nine were referred from the local hospital or junior doctors from our hospital, primarily because of the presence of MG after filtering surgery. The other 10 patients without any surgical history visited us first mainly because of uncontrolled IOP and underwent the following treatment in our department. Therefore, some patients experienced two different surgeries, trabeculectomy alone and combination surgery, in two separate eyes, respectively.

The purpose of the study is to compare the surgical outcome of two different surgeries in each patient. We also showed additional surgical options in the management of MG after trabeculectomy. This study aimed to illustrate the efficacy of a combination of lens extraction, trabeculectomy, and anterior vitrectomy in refractory glaucoma with BEST1 mutation in Asian patients in a tertiary institute.

METHODS

This is a retrospective, self-controlled case series study recruiting patients with ACG and BEST1 mutation who underwent single trabeculectomy in one eye and a combination of phacoemulsification, intraocular lens (IOL) implantation–trabeculectomy–anterior pars plana vitrectomy (triple surgery) in the other eye from January 2014 to November 2021 at Beijing Tongren Eye Center. All patients underwent a complete ophthalmic examination that included best-corrected visual acuity (BCVA), IOP, slit-lamp biomicroscopy, and ultrasound biomicroscopy (UBM, MD-300L, MEDA Co., Tianjin, China). The axial length (AL) was measured by IOLMaster (Carl Zeiss Meditec AG, Jena, Germany). The IOP, BCVA, and anterior chamber depth (ACD) were analyzed at preoperative, postoperative, and last visits. Multimodal fundus imaging was also performed, including color fundus photography, fundus autofluorescence (AF), and optical coherence tomography (OCT).

Patients provided their written informed consent for all procedures, which were approved by the Ethics Committees of the Beijing Tongren Eye Center and adhered to the Declaration of Helsinki.

The clinical diagnostic criteria for ARB were bilateral multifocal vitelliform lesions with subretinal fluid or intraretinal cystoid edema, abnormal electro-oculography (EOG) (Arden ratio below 1.5), and an autosomal recessive or sporadic mode of inheritance [1]. BVMD was diagnosed on the basis of the following criteria: juvenile-to-adult onset; bilateral or unilateral macular lesions showing vitelliform, vitelliruptive, pseudohypopyon or atrophic and cicatricial changes; abnormal EOG with Arden ratio below 1.5; at least one family member had typical vitelliform lesions [10].

Surgery Procedures

Three patients (patients 1, 2, and 5) underwent trabeculectomy with mitomycin C (MMC) at our hospital and the other two patients (patients 3 and 4) at other local hospitals. A fornix-based conjunctival flap was prepared in the superotemporal or superonasal quadrant, and a trapezoidal half-thickness limbus-based scleral flap with $4 \times 3 \text{ mm}$ in area was created. MMC of 0.4 mg/ml was placed under the conjunctiva and scleral flap for 3–4 min and then washed off with balanced saline solution. MMC of 0.4 mg/ml was applied for 3 min in two eyes at other local hospitals, according to medical records. After incision of a small trabecular tissue and peripheral iridectomy, the scleral flap was closed with two releasable sutures with confirmation of maintenance of the anterior chamber. Finally, the conjunctiva was closed with interrupted 10–0 nylon sutures.

The triple surgery was performed by the same glaucoma specialist (Xin Tang). After MMC was applied, phacoemulsification and IOL implantation were performed. Then, viscoelastic was used for goniosynechialysis to deepen the peripheral anterior chamber. After the incision of the trabecular tissue and peripheral
Iridectomy, the scleral flap was temporally closed. Therefore, a two-port (for infusion and cutter) 23-gauge vitrectomy was performed using a trocar and cannula system. After complete anterior vitrectomy, especially surrounding the peripheral iridectomy area, the iris notch was enlarged with a vitrectomy cutter to create direct communication between the anterior and posterior chambers. A round posterior capsulectomy was also constructed. The subsequent procedures were the same as in the trabeculectomy, as mentioned above.

**Success Criteria for Surgery and Follow-up Outcomes**

The criteria for surgery success were defined as postoperative IOP less than 21 mmHg with or without antiglaucoma medication but without additional further glaucoma surgery. The follow-up outcomes were collected, including pre- and postoperative (last visit) IOP, visual acuity, anterior chamber depth, number of glaucoma medications, fundus photographs, and OCT. The follow-up time was also recorded.

**Genetic Analyses**

Peripheral blood samples were taken from patients 2–5 for genetic analysis. Genomic DNA was extracted using a genomic DNA extraction and purification kit (Vigorous Whole Blood Genomic DNA Extraction Kit; Vigorous, Beijing, China), following the manufacturer’s protocol. All exons and flanking splicing sites of the BEST1 gene were amplified by polymerase chain reaction (PCR). The primer sequences and related information are available on request. PCR assays were carried out using standard reaction mixtures and purified amplified fragments were sequenced using an ABI Prism 373A DNA sequencer (Applied Biosystems, Foster City, CA, USA).

**Statistical Analysis**

For statistical analyses, we applied a statistical software package (SPSS version 24.0 IBM-SPSS, Chicago, IL). We first described the distribution of the main parameters by calculating their median or means and standard deviations. Wilcoxon signed-rank test was used to compare all ocular parameters between two eyes in different surgical approaches, and also used to analyze the difference in IOP, BCVA, ACD, cup to disc ratio between preoperative and postoperative visits. A P value less than 0.05 was considered statistically significant.
RESULTS

Five patients (three women and two men), including four (patients 1, 2, 3, 5) diagnosed with ARB and one (patient 4) diagnosed with BVMD, with bilateral secondary ACG undergoing triple surgery in one eye and single trabeculectomy in the other eye as self-control were identified. The mean age was 33 years (range 17–46 years) when the first trabeculectomy was performed. The initial ocular manifestations were elevated IOP and shallow anterior chamber in all patients, but only patient 2 complained of visual impairment in his childhood. Three patients (patients 1, 2, and 4) were suspected of having bestrophinopathy at first presentation, and two patients (patients 1 and 2) in our hospital refused to undergo the triple surgery in the first eye. All patients showed bilateral subretinal yellowish deposits within the posterior pole corresponding to hyperautofluorescence on AF. On OCT, subretinal fluid was present in all eyes (Fig. 1). Other signs of subretinal hyperreflectivity consistent with vitelliform material and cystoid macular edema changes can also be found.

Table 1 shows the clinical features of both eyes with two different surgical procedures in each patient. Uncontrolled IOP with maximum antiglaucoma medications or progression of visual field defects during follow-up were detected in all eyes before surgery. The mean IOP with full medications was 31.4 ± 4.7 mmHg (median 30.0 mmHg), ranging from 26 to 40 mmHg. Narrow anterior chamber angles with grade III–IV using Scheie classification were observed before operation in all patients (no data in two eyes with trabeculectomy in other hospitals). The mean AL was 21.53 ± 0.69 mm (median 21.84 mm), and the ACD was 2.31 ± 0.24 mm (median 2.36 mm). According to the cup-to-disc ratio and visual field testing, all eyes except the right eye of patient 4 showed glaucomatous visual defects varying from nasal step, arcuate defect, and very advanced stage tunnel vision. On comparison of those features in the eyes with single trabeculectomy and triple surgery, there were no statistically significant differences in preoperative IOP (median 31 mmHg vs. 29 mmHg), BCVA (median 0.70 logMAR vs. 0.40 logMAR), ACD (median 2.53 mm vs. 2.21 mm), AL (median 21.81 mm vs. 21.93 mm), and the ratio of cup to disc (median 0.8 vs. 0.4) (all P > 0.05).

For all patients, single trabeculectomy was performed for the first time in one eye following triple surgery in the other eye. The median interval time between both eyes in each patient was 64 months (range 2–79 months). The mean follow-up time was 64.0 ± 21.4 months (range 31–87 months). The surgical outcome is shown in Table 2. After single trabeculectomy, all five eyes (100%) developed postoperative persistent shallow or flat anterior chamber within 1 week after surgery, even despite potent cycloplegic, topical, and systemic corticosteroids (Fig. 2a). Aqueous misdirection was suspected, and the diagnosis was confirmed on UBM in two patients who underwent trabeculectomy in other hospitals (Fig. 2b). The range of IOP after trabeculectomy was 18–54 mmHg with a median of 26 mmHg, which is not significantly different compared to preoperative IOP (Z = −0.405, P = 0.686). To treat MG, all eyes received additional operations, phacoemulsification–IOL implantation–anterior PPV, ending with successful anterior chamber reformation (Fig. 2c). The mean ACD at the last visit was 3.47 mm (median 3.40 mm). The median interval between those two operations in the eye with initial trabeculectomy was 6 months (range 1 week to 10 months). The IOP reduction from presentation (31 mmHg) to the last follow-up (16 mmHg) was statistically significant (Z = −2.023, P = 0.043), with antiglaucomatous medication controlled only in patient 4.

Triple surgery was achieved in the other eyes for all patients. No complications were found, and the anterior chamber was deepened (2.21 mm vs. 3.71 mm; Z = −1.826, P = 0.068), but without reaching statistical significance because of the small sample. The anterior chamber was stable after surgery until the last visit (Fig. 2d–f). The median follow-up time (from the time when triple surgery was performed) was 8 months. The mean IOP at the last visit was normalized to 16 mmHg, significantly lower than the preoperative IOP (Z = −2.023,
Table 1  Clinical features of both eyes with different surgery procedures in patients with ARB or BVMD

| Patient | Age, years/gender | Trabeculectomy | Phaco + IOL-trabeculectomy–anterior PPV |
|---------|-------------------|----------------|---------------------------------------|
|         | Eye IOP, mmHg     | Pre-op BCVA    | Pre-op ACD (mm) | Axial length (mm) | C/D ratio | Interval time*, months | Eye Pre-op IOP, mmHg | Pre-op BCVA | Pre-op ACD (mm) | Axial length (mm) | Pre-op visual field | C/D ratio |
| 1       | OS 28             | 1.0            | 2.59            | 21.81            | Arcuate defect | 0.8 | 79 | OD 27 | 0.25 | 2.36 | 22.08 | Tunnel vision | 1.0 |
| 2       | OS 31             | 0.2            | 2.47            | 22.24            | Nasal step | 0.4 | 6  | OD 26 | 0.1  | 2.20 | 22.02 | Arcuate defect | 0.4 |
| 3       | OS 35             | 0.2            | –               | 21.87            | Tunnel vision | 0.8 | 72 | OD 29 | 0.2  | 2.21 | 21.93 | Nasal step | 0.3 |
| 4       | OD 29             | 0.1            | –               | 20.51            | Within normal limit | 0.4 | 64 | OS 31 | 0.2  | 1.87 | 20.23 | Arcuate defect | 0.4 |
| 5       | OD 38             | 0.1            | –               | 21.16            | Tunnel vision | 0.9 | 2  | OS 40 | 0.05 | 2.50 | 21.45 | Tunnel vision | 0.9 |

ARB autosomal recessive bestrophinopathy, BVMD best vitelliform macular dystrophy, Pre-op preoperative, IOP intraocular pressure, BCVA best-corrected visual acuity, ACD anterior chamber depth, C/D ratio cup to disc ratio, Phaco + IOL–trabeculectomy–anterior PPV phacoemulsification, intraocular lens implantation–trabeculectomy–anterior pars plana vitrectomy

*Interval time between trabeculectomy performed in one eye and Phaco + IOL–trabeculectomy–anterior PPV performed in the other eye
| Patient | Trabeculectomy and additional PPV | Phaco + IOL–trabeculectomy–anterior PPV |
|---------|----------------------------------|----------------------------------------|
|         | Pre-op LPI IOP, mmHg | Post-visit IOP, mmHg | Last-visit BCVA | Last-visit ACD | Last-visit visual field | Follow-up time | Pre-op LPI IOP, mmHg | Post-visit IOP, mmHg | Last-visit BCVA | Last-visit ACD | Last-visit visual field | Follow-up time |
| 1       | No 30 Atropine, IOP-lowering drugs, 1 week | 16.6 1.0 3.44 Arcuate defect | 87 Yes 10 15.5 0.2 3.52 Tunnel vision | 8 |
| 2       | Yes 26 Atropine, 6 months | 17 0.2 – Tunnel vision | 60 Yes 10 19 0.1 – Arcuate defect | 54 |
| 3       | No 18 Atropine, IOP-lowering drugs, 10 months | 13 0.3 3.74 Tunnel vision | 78 Yes 17 16 0.3 3.85 Nasal step | 5 |
| 4       | Yes 54 Atropine, IOP-lowering drugs, 7 months | 16 0.5 3.33 Within normal limit | 64 Yes 10 15 0.4 3.86 Arcuate defect | 2 |
| 5       | No 26 Atropine, 12 days | 14 0.05 3.36 Tunnel vision | 31 No 14 13 0.05 3.57 Tunnel vision | 28 |

*Follow-up time between first presentation and last visit
†Follow-up time between Phaco + IOL–trabeculectomy–anterior PPV and last visit

Pre-op preoperative, LPI laser peripheral iridotomy, Post-Trab post-trabeculectomy, IOP intraocular pressure, MG malignant glaucoma, PPV pars plana vitrectomy, BCVA best-corrected visual acuity, ACD anterior chamber depth, C/D ratio cup to disc ratio, Post-op postoperative, Phaco + IOL–trabeculectomy–anterior PPV phacoemulsification, intraocular lens implantation–trabeculectomy–anterior pars plana vitrectomy.
Without using antiglaucomatous or cycloplegic medication, the BCVA was maintained in all eyes regardless of surgical procedures (both $P > 0.05$) and improved in both eyes of patient 4 owing to cataract removal. No significant visual field progression was detected. At the last visit, there was no significant difference in IOP, BCVA, and ACD between the two eyes with different surgical approaches (all $P > 0.05$).

Except for patient 1 who refused to undergo genetic analyses, four patients were found to carry mutations in the *BEST1* gene (Table 3). All mutations have been previously reported. Two heterozygous mutations and one homozygous mutation were identified in three ARB patients. One heterozygous mutation was identified in the patient with BVMD; her mother, brother, and daughter had the same mutation.

**DISCUSSION**

To the best of our knowledge, this is the first self-controlled series comparing the surgical outcome of triple surgery, Phaco + IOL implantation–trabeculectomy–anterior PPV, and trabeculectomy alone as a control, in the
| Patient no. | Diagnosis   | BEST1 mutation | Amino acid change | homozygous/heterozygous mutations | Reported or not | Fundus appearance | FAF          | OCT         |
|------------|-------------|----------------|-------------------|-----------------------------------|-----------------|-------------------|--------------|-------------|
| 1          | ARB         | –              | –                 | –                                 | –               | Bilateral multifocal vitelliform deposits | Hyper-AF lesions | N           | Y           |
| 2          | ARB         | c.103G>A       | p.E35K            | Heterozygous                      | Reported        | Right multifocal vitelliform deposits Left foveal RPE hyperplasia and scar | Hyper-AF lesions | Y           | Y           |
| 3          | ARB         | c.119T>C       | p.L40P            | Heterozygous                      | Reported        | Bilateral multifocal vitelliform deposits | Hyper-AF lesions | Y           | Y           |
| 4          | BVMD        | c.241G>A       | p.V81M            | Heterozygous                      | Reported        | Bilateral foveal vitelliform deposits | Hyper-AF lesions | N           | Y           |
| 5          | ARB         | c.604C>T       | p.R202W           | Homozygous                        | Reported        | Bilateral macular diffuse yellowish deposits | Hypo-AF lesions | Y           | Y           |

ARB: autosomal recessive bestrophinopathy, BVMD: best vitelliform macular dystrophy, RPE: retinal pigment epithelium, FAF: fundus autofluorescence, OCT: optical coherent tomography, CME: cystoid macular edema, SRF: subretinal fluid
same patients with ARB or BVMD. Little information was provided on the best strategy for these types of patients. Our paper clearly shows that triple surgery ultimately yielded excellent results in lowering IOP, maintaining the visual function, deepening the anterior chamber, avoiding MG complications without additional topical medication or additional surgery, and can also remain functional for up to 54 months. The high incidence of MG after trabeculectomy alone was confirmed again in the present study, which was also shown by Zhong et al. [9]. The aforementioned authors concluded that filtration surgery should be avoided in these patients. However, our study provides strong evidence that the combined initial vitrectomy was applicable to bypass the complication of MG after filtration surgery. Consequently, trabeculectomy might not be absolutely contraindicated but a safe and effective method to reduce IOP in patients with ACG with ARB.

Recently, Low et al. [6] first presented a favorable outcome bilaterally after primary PPV and posterior chamber drainage tube implantation in a 23-year-old woman with BEST1 mutation, who achieved normalized IOP, stable vision, avoiding the complication of MG, and even reversal of disc cupping in one eye during the 5-year follow-up. Shi et al. [7] also reported a unique case of a 26-year-old woman diagnosed with ARB and ACG without any improvement of the anterior structure by combined phacoemulsification, intraocular lens implantation, and goniosynechialysis, but benefited from additional low-dose transscleral cyclophotocoagulation (TCP) that ends with a lower IOP and a deepened anterior chamber in both eyes. The authors analyzed the reason for success: anterior vitreous liquefaction generated by post-TCP inflammation subsequently decreased vitreous integrity, absorbed the force from choroidal expansion, and increased flow conductivity through the vitreous cavity [7]. It indicated that the vitreous is intimately involved in the pathogenesis of the shallow anterior chamber in those patients. In addition to the younger age, solid and liquefied vitreous presumably induce high posterior pressure, which is also confirmed during the surgery (personal perspective). The forward force potentially accelerates the development of narrow anterior chamber and even complete angle closure. This assumption is strengthened by our observation of 100% surgical success rate after triple surgery, while 100% penetration to MG after trabeculectomy alone inevitably increases the pressure gradient between the anterior and posterior segments. It is hereby especially emphasized that removal of the anterior vitreous is an indispensable procedure for patients with ACG and BEST1 mutation.

Malignant glaucoma is a serious complication after glaucoma filtering surgery, often with elevated IOP, but may also present with normal IOP, given the presence of an alternative aqueous outflow pathway. Although the exact mechanism of MG is not fully understood and may be multifactorial, the principle of management was clear: eliminate the pressure gradient between anatomic compartments and introduce communication between the posterior and anterior segments of the eye. The role of choroidal expansion has also been described [11]. In the present study, all five eyes with MG after trabeculectomy alone did not respond to medical management, including antiglaucoma medications and strong cycloplegics. It is reported that 14–50% of MG can be resolved with only medical therapy [12, 13]. The resolution of MG was finally achieved by the following surgery of phacoemulsification–IOL implantation–anterior PPV with successful lowering IOP and reforming of the anterior chamber. Our results provided an effective treatment algorithm for refractory MG in patients with BEST1 mutation. It showed that vitrectomy was required in those cases, potentially relieving the peripheral vitreous pressure, restoring the orientation of the ciliary body, and deepening the anterior chamber. Even the five eyes that experienced MG after trabeculectomy and following secondary surgery also achieved a good outcome compared to the other eyes that succeeded by triple surgery for the first time. A combined approach to simultaneously address all conditions would be advantageous to patients in terms of reduced costs and potentially faster visual recovery.

A single case (PPV + glaucoma drainage implant) without lens extraction shown by Low
et al. [6] achieved a good outcome. However, clear lens/cataract extraction and IOL implantation were performed in all eyes in the present study. Removing the lens may largely deepen the anterior chamber and potentially reopen the angle, which is definitely beneficial to maintain the physiologic trabecular aqueous outflow since the filtering pathway is possibly no longer functional during their subsequent long life. We also encountered a case with a very early phase of ACG (not shown in this study) that underwent phacoemulsification, IOL implantation–goniosynechialysis–anterior PPV (without trabeculectomy), ending with deep anterior chamber and normal IOP. However, the therapeutic role of lens/cataract extraction in patients with ACG and BEST1 mutation needs to be clarified in future studies.

Young patients with angle closure are very rare [14]. Recently, Gao et al. [15] reviewed a large number of Chinese patients with ACG from 15-year records in a single center. The etiologies other than primary ACG could be identified in a large number of cases (67.4%). More comprehensive examinations are needed, especially fundus examinations, to exclude any secondary causes. Even with patients with ACG older than 40 years, especially combined with a fundus lesion such as “macular edema” in OCT, the differential diagnosis of ARB or BVMD with age-related macular degeneration and choriorretinitis can be challenging. Genetic analysis should be performed in suspect cases.

The application of mitomycin C during trabeculectomy remains the gold standard for glaucoma surgery, especially in China, since Asian patients appear to have a greater scarring response and are more susceptible to bleb failure compared to Caucasian patients [16]. The dose and duration of mitomycin C of 0.4 mg/ml and 2–3 min is very common in China [17]. Increasing the exposure time of mitomycin C can be adapted for younger patients who are known to have a greater wound healing capacity. In general, the surgical outcome can be influenced by the dose of mitomycin C, with higher rates of hypotony after higher concentration or/and duration. However, this complication was not found in any of our patients. Compared to our study, Zhong et al. applied a lower concentration of mitomycin C and a shorter exposure time which may indicate that the failure of single trabeculectomy in patients with ARB may not be related to mitomycin C dosing.

Limitations of our study should be discussed. First of all, there were two patients who underwent trabeculectomy at other local hospitals, so one may be concerned that the surgical outcome is influenced by the different levels of glaucoma specialists. However, trabeculectomy was also performed at the local tertiary eye center on these two patients, and according to the medical record, surgical procedures, including mitomycin C dose, were also similar to those of our hospital. Previous studies showed that the results of trabeculectomy performed by residents or trainees can also have a high success rate [18, 19]. We believed that the failure after single trabeculectomy in patients with ARB may not be affected by the different surgeons. Second, there was a possibility of bias between two eyes in each patient since trabeculectomy was always performed first in the eyes with usually earlier onset of ACG than in the other eyes, even though there were no significant differences in all ocular parameters between those two groups. Third, the follow-up time of patients was variable, and only two patients had a long-term follow-up after triple surgery. Long-term observations in those eyes with triple surgery should be addressed. Fourth, the EOG was not performed on all patients. However, multimodal imaging and genetic analysis can also support the diagnosis. The clinical diagnosis of ARB was also confirmed in one patient without genetic testing by a panel of retinal specialists. Fifth, the number of cases was relatively small. The condition in which the secondary ACG and ARB combined is very rare. In addition to that, the strict criteria that met the self-controlled study design also limited the number of enrollees. Sixth, the natural retrospective designs lead to a lack of preoperative and postoperative anterior segment photographs of the anterior chamber.
CONCLUSIONS

This self-controlled series study clearly showed that triple surgery is superior to single trabeculectomy for patients with ACG and BEST1 mutation in terms of IOP control, maintenance of visual function, and deepened anterior chamber, effectively bypassing the complication of MG. The role of the vitreous is complicated in the mechanism of ACG and the high incidence of MG after filtering surgery, together with the younger age, short AL, and shallow anterior chamber. Trabeculectomy was not a contraindication but is strongly recommended in combination with removal of the anterior vitreous in the management of patients with ACG with BEST1 mutation. MG can be successfully managed by appropriate and timely interventions.

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Author Contributions. Xin Tang contributed to the conception and design of the study. Material preparation, data collection, and analysis were performed by Yuxin Fang, Xiaoming Duan, Lin Chen, Jie Shi (genetic testing), and Yang Li. Parts of imaging were supplied by Jie Liu, Yunxiao Sun, and Jin Wang. The first draft of the manuscript was written by Yuxin Fang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosures. Yuxin Fang, Xiaoming Duan, Lin Chen, Jie Shi, Jie Liu, Yunxiao Sun, Jin Wang, Yang Li and Xin Tang confirm that they have no competing interests to declare.

Compliance with Ethics Guidelines. This study was carried out in accordance with the principles of the Declaration of Helsinki. The approval was granted by the Ethics Committee of the Beijing Tongren Eye Center. Informed consent was obtained from all individual participants included in the study.

Data Availability. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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