Ahmed valves vs trabeculectomy combined with pars plana vitrectomy for neovascular glaucoma with vitreous hemorrhage

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ABSTRACT
Purpose: Vitreous hemorrhage is common in advanced neovascular glaucoma (NVG), which has poor visual prognosis. This study aimed to compare the efficacy of 23-G pars planar vitrectomy (PPV) combined with either Ahmed glaucoma valve (AGV) implantation or trabeculectomy after intravitreal ranibizumab (IVR) treatment for NVG with vitreous hemorrhage.

Methods: This retrospective, nonrandomized study included 33 eyes of 33 patients with NVG with vitreous hemorrhage. After IVR treatment for 3-7 days, 18 eyes underwent PPV + AGV (AGV group) and 15 underwent PPV + trabeculectomy (trabeculectomy group). The success criterion was a postoperative intraocular pressure (IOP) of 6-21 mm Hg, with or without antiglaucoma medication.

Results: Postoperative IOP decreased significantly in both groups, but the mean IOP after 12 months was significantly lower in the AGV group (16.92 ± 2.75 mm Hg) than the trabeculectomy group (21.50 ± 5.79 mm Hg; p = 0.018). The AGV group required fewer glaucoma medications than the trabeculectomy group. The cumulative probabilities of surgical success rates for the AGV and trabeculectomy groups at 12 months were 71.3% and 46.7%, respectively. No significant differences in postoperative complications were observed between the groups.

Conclusions: For NVG with vitreous hemorrhage, PPV with AGV implantation may reduce IOP more effectively than PPV with trabeculectomy.

Keywords: Ahmed glaucoma valve, Neovascular glaucoma, Ranibizumab, Trabeculectomy, Vitrectomy, Vitreous hemorrhage

Introduction

Neovascular glaucoma (NVG) is a severe form of glaucoma with devastating visual outcomes. Neovascular glaucoma usually occurs secondary to posterior segment ischemic diseases such as proliferative diabetic retinopathy, central retinal vein occlusion, and ocular ischemic syndrome, and is primarily caused by extensive ischemia and hypoxia of the retina. Early diagnosis and rapid implementation of the panretinal photocoagulation (PRP) procedure, which inhibits angiogenesis, is an effective measure for treating retinal ischemia (1). However, when NVG develops to the advanced stage, PRP cannot be performed because of media opacities, especially in cases of vitreous hemorrhage.

Advanced NVG is common in rural areas of China, where patients typically do not seek treatment until they experience unbearable ocular pain and poor vision due to extremely high intraocular pressure (IOP). In patients with NVG with vitreous hemorrhage, combination therapy involving pars plana vitrectomy (PPV) and PRP is required to manage the underlying disease, along with glaucoma surgery to control the IOP. However, filtering surgery, cyclophotocoagulation, and cyclocryotherapy only poorly control the IOP (2). Similarly, adjunctive treatment with antifibrosis drugs such as mitomycin C (MCC) and 5-fluorouracil trabeculectomy only yields modest improvements (3).

In recent years, anti-vascular endothelial growth factor (VEGF) antibodies and glaucoma drainage valves have been used in the treatment of NVG. Preoperative intravitreal bevacizumab or ranibizumab (humanized antibody fragments directed at VEGF-A) injections have been employed in patients with NVG to promote rapid iris neovascularization (NVI) regression, reduce IOP, and improve surgical success rates (4, 5). For example, ranibizumab has been successfully used for proliferative diabetic retinopathy in order to reduce intraocular bleeding during vitrectomy and facilitate glaucoma surgery (6, 7).

Ahmed glaucoma valve (AGV) implantation has shown promising success rates, comparable to those of conventional
Ahmed valves vs trabeculectomy combined with PPV

surgical modalities (8). When PPV combined with AGV implantation was used in the management of NVG with vitreous hemorrhage, the overall success rate reached 72.2% with or without antiglaucoma medication (9); however, few studies have investigated combination therapy involving the 3 above-mentioned methods (intravitreal anti-VEGF, PPV, and glaucoma surgery).

The purpose of this retrospective nonrandomized study was to compare efficacy between 23-G PPV combined with AGV implantation or trabeculectomy after intravitreal ranibizumab (IVR) treatment for the management of NVG with vitreous hemorrhage. We aimed to compare the surgical success rates and postoperative complications between the AGV and trabeculectomy groups.

Methods

Subjects

This study was approved by the Ethics Review Committee of Zhengzhou University and adhered to the Declaration of Helsinki. All patients received a detailed explanation of the study and provided written informed consent.

A total of 33 eyes of 33 patients with NVG and vitreous hemorrhage were recruited in this study. After IVR treatment for 3–7 days, 15 eyes underwent PPV + trabeculectomy (trabeculectomy group) between January and June 2014 and 18 eyes underwent PPV + AGV implantation (AGV group) between July 2014 and March 2015. The patients were not randomly assigned to the surgical groups. Additional procedures included endophotocoagulation, pars plana lensectomy (PPL), and IOL implantation.

Inclusion criteria were as follows: NVG with vitreous hemorrhage and an IOP of 30 mm Hg or greater despite maximum tolerated oral and topical antiglaucoma medical therapy, dense vitreous haze or hemorrhage, underlying retinal pathology (e.g., diabetic retinopathy and retinal vein occlusion), and visual acuity of light perception or better. Only one eye per patient was included. Exclusion criteria included age <18 years and previous cyclodestructive procedures, trabeculectomy groups.

The AGV group

A fornix-based conjunctival flap was created in the superotemporal or superonasal quadrant, and then the AGV (Model FP7; New World Medical Inc., Rancho Cucamonga, CA, USA) was implanted. The patency of the AGV tube was verified by irrigation with balanced salt solution. The plate was fixed to the sclera with 5-0 nylon sutures, 10 mm posterior to the limbus between the rectus muscles. A half-thickness limbus-based scleral flap was created with a 4 × 4 mm rectangle, and a 4 × 5 mm scleral flap was then extended posteriorly so that the tube could be entirely buried into the sclera. In order to decrease overfiltering following tube implantation, an additional puncture was made at the superotemporal limbus.

After injection of viscoelastic materials for anterior chamber maintenance, the anterior chamber was entered through the limbus under the scleral flap with a 23-G needle. The tube was cut to have a bevel-up appearance and placed in the anterior chamber parallel to the iris plane through the needle track. In 16 eyes, the tube was inserted into the anterior chamber. In 2 eyes with a shallow anterior chamber (the peripheral anterior synechia existed even though the lens had been removed), the tube was inserted into the posterior chamber from 3 mm after the limbus. Then, the scleral flap was sutured to cover the AGV tube. The conjunctiva and Tenon capsule were closed with 7-0 absorption sutures.

The trabeculectomy group

A fornix-based conjunctival flap was created. After creation of a 4 × 4 mm half-thickness scleral flap, small pieces of surgical sponge soaked in MCC (0.4 mg/mL) were placed under the conjunctival flap for 5 minutes. The eye was irrigated thoroughly with 200 mL of saline. Trabeculectomy was performed with a Kelly Descemet Membrane Punch (Inami, Tokyo, Japan), followed by peripheral iridectomy. The scleral and conjunctival flaps were sutured with 10-0 nylon sutures.

After surgery, all patients received a standard topical regimen, including TobraDex eyedrops (0.3% tobramycin + 0.1% dexamethasone; Alcon, Puurs, Belgium) for 4 weeks and tropicamide for 3 weeks. The aforementioned glaucoma medications were prescribed when the postoperative IOP was greater than 21 mm Hg, and their dose was subsequently adjusted according to the IOP level.
Outcome and analysis

Postoperative data regarding IOP, number of glaucoma medicines, BCVA, and complications were obtained at 1 day, 3 days, 1 week, 1 month, 3 months, 6 months, and 12 months. Criteria for success were defined before reviewing the data. Surgical success was defined as an IOP between 6 and 21 mm Hg with or without use of additional glaucoma medicines. Specifically, absolute success was defined as meeting this criterion without the use of medication, while relative success was defined as meeting this criterion with the use of medication. Failure was defined as an IOP >21 mm Hg despite the use of maximum tolerated medications, an IOP <6 mm Hg on 2 consecutive visits, further glaucoma surgery or removal of the implant, choroidal detachment requiring another surgical intervention, or loss of light perception.

Statistical analysis

The data were processed and statistically analyzed using SPSS version 19.0 (SPSS, Chicago, IL, USA). All the data were expressed as mean ± standard deviation (SD). A χ² or Fisher exact test was used for categorical variables. For comparisons between groups, an independent sample t test was used to evaluate differences in the averages between normally distributed data, while the Mann-Whitney U test was used for abnormally distributed data. Intraocular pressure levels were compared between the baseline and each follow-up point using one-way analysis of variance. For comparing glaucoma medications at various time points before and after surgery between the groups, the Wilcoxon signed-rank test was used. Success rates in the groups were compared using Kaplan-Meier survival curves and the log-rank test. As soon as an eye reached a failure endpoint, it was excluded from further analysis. Baseline and final logMAR BCVA were compared using the paired-samples t test. Fisher exact test was used to assess differences in complications. A p value of less than 0.05 was considered significant.

Results

A total of 33 eyes of 33 patients who met the inclusion criteria were analyzed in this study. Table I shows the baseline characteristics of the 2 groups. No significant differences in age, sex, number of eyes, mean IOP, mean logMAR BCVA, mean number of glaucoma medications, number of previous vitrectomies or laser (PRP) treatments at baseline, or follow-up times were observed between the groups.

Intraocular pressure and glaucoma medications

Compared with preoperative IOP, the IOP levels at all follow-up time points showed a statistically significant decrease in both the AGV (F = 107.283, p<0.01) and trabeculectomy groups (F = 60.293, p<0.01; Tab. II). The IOPs were not significantly different between the groups preoperatively, 3 days after IVR treatment, or 1 and 3 days postoperatively (p>0.05; Tab. II). However, at all follow-up time points from 1 week

| TABLE I - Demographic and preoperative data for the different study groups |
|-----------------------------|-----------------------------|-----------------------------|
|                            | AGV group (n = 18)          | Trabeculectomy group (n = 15) | p value |
| Age, y, mean ± SD           | 53.67 ± 15.56               | 49.33 ± 18.56                | 0.422   |
| Male/female                 | 10/8                        | 9/6                         | 0.797   |
| Right/left eye              | 12/6                        | 7/8                         | 0.247   |
| Intraocular pressure, mm Hg, mean ± SD | 49.83 ± 8.66 | 46.53 ± 9.68                | 0.309   |
| Number of glaucoma medications, mean ± SD | 3.39 ± 0.78 | 3.13 ± 0.83                | 0.370   |
| BCVA, logMAR, mean ± SD     | 2.18 ± 0.56                 | 2.15 ± 0.48                 | 0.897   |
| Previous vitrectomy         | 6                           | 5                           | 1       |
| Previous PRP               | 6                           | 5                           | 1       |
| Lens status                 |                             |                             |         |
| Phakic                      | 11                          | 8                           |         |
| Pseudophakic                | 6                           | 7                           |         |
| Aphakic                     | 1                           | 0                           |         |
| Etiology of neovascular glaucoma |                     |                             |         |
| Proliferative diabetic retinopathy | 12              | 11                          |         |
| Central retinal vein occlusion | 4                   | 4                           |         |
| Central retinal artery occlusion | 1                   | 0                           |         |
| Eales disease              | 1                           | 0                           |         |
| Follow-up time, mo, mean ± SD | 13.56 ± 3.31              | 14.6 ± 3.98                 | 0.417   |

AGV = Ahmed glaucoma valve; BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; PRP = panretinal photocoagulation.
after surgery, the IOPs were significantly higher in the trabeculectomy group than the AGV group (p<0.05).

Medication use for both groups decreased significantly after surgery at all follow-up time points compared with the preoperative amounts (p<0.05). Three eyes in the AGV group and 8 eyes in the trabeculectomy group needed glaucoma medications to maintain the IOP after surgery, and this difference was statistically significant (p = 0.026). Details of the number of postoperative medications at each point of visit in the 2 groups are listed in Table III.

**Surgical success rate**

The absolute cumulative probabilities of surgical success rates for the AGV and trabeculectomy groups at 3, 6, and 12 months were 83.3%, 77.8%, and 71.3% and 53.3%, 46.7%, and 46.7%, respectively. The relative cumulative probabilities of surgical success rates for the AGV and trabeculectomy groups at 3, 6, and 12 months were 83.3%, 77.8%, and 71.3% and 60.0%, 53.3%, and 46.7%, respectively. Although the absolute and relative surgical success rates in the AGV group were higher than the corresponding rates in the trabeculectomy group, these differences were not statistically significant (p = 0.110, log-rank test; p = 0.121, log-rank test). The reasons for postoperative failure according to the definition of surgical success are described in Table IV. Kaplan-Meier survival analysis for relative success is shown in Figure 1.

**Best-corrected visual acuity**

Best-corrected visual acuity improvement and worsening were defined as a difference of more than one Snellen line. At the final visit, the BCVA in the AGV and trabeculectomy groups had improved in 7 (38.9%) and 5 eyes (33.3%), remained stable in 8 (44.4%) and 6 eyes (40.0%), decreased in 1 (5.6%) and 2 eyes (13.3%), and decreased to loss of light perception in 2 eyes each (11.1% and 13.3%), respectively. The BCVA at the final visit was not significantly different from the baseline logMAR BCVA in either the AGV group (t = 1.068, p = 0.301) or the trabeculectomy group (t = 0.895, p = 0.386). Moreover, no significant difference in logMAR BCVA at the final visit was observed between the groups (t = -0.180, p = 0.858).

**Iris neovascularization**

All 33 eyes with NVI regressed significantly within 3 to 7 days after IVR treatment. The mean time interval between IVR treatment and the combined surgery in the AGV and trabeculectomy groups was 4.8 ± 1.4 days and 5.0 ± 1.1 days, respectively. No significant differences in NVI were observed between the groups (p = 0.696). Iris neovascularization reoccurred in 2 eyes (11.1%) in the AGV group and 3 eyes (20.0%) in the trabeculectomy group at the 3- to 5-month follow-up but disappeared when the patients received repeated IVR injections and PRP surgery.

**Complications**

No intraoperative complications were noted. As shown in Table V, postoperative complications included hyphema,
The main late postoperative complication in both groups was encapsulated bleb, which occurred in 2 eyes (11.1%) in the AGV group and 6 eyes (40.0%) in the trabeculectomy group. Two of the 6 eyes in the trabeculectomy group were provided AGV implants because the IOP was >30 mm Hg, despite the maximum permissible glaucoma medical therapy. Vision loss occurred in 2 eyes (11.1%) in the AGV group and 2 eyes (13.3%) in the trabeculectomy group. No statistically significant differences in the incidences of postoperative complications were observed between the groups.

**Discussion**

Despite advances in the surgical management of glaucoma, the treatment of NVG remains a challenge, especially when vitreous hemorrhage occurs (13). In this study, we found that by using a combination therapy of PPV, ranibizumab, and either AGV or trabeculectomy, a significant decrease in postoperative IOP was achieved in patients with NVG with vitreous hemorrhage. The mean IOP was significantly lower in the AGV group than in the trabeculectomy group at the 12-month follow-up. Surgical success rates were higher in the AGV group than those in the trabeculectomy group after 12 months. Moreover, fewer glaucoma medications were administered to the AGV group than the trabeculectomy group. Finally, no statistically significant differences in the incidence of postoperative complications were observed between the groups.

Aggressive surgery with multiple procedures and simultaneous trabeculectomy or a glaucoma drainage implant is often used in cases of NVG with vitreous hemorrhage; however, intraoperative bleeding and postoperative inflammation can limit its success. Therefore, VEGF inhibitors, such as ranibizumab, are increasingly used to reduce intraocular bleeding during these surgeries. Several studies have shown that IVR injection is a safe and successful method for NVG, leading to higher surgical success rates (14, 15). In this study, too, we found a statistically significant decrease in the IOP following IVR injection. Moreover, NVI regressed significantly in all eyes within 3-7 days after IVR injection. Our results corroborate the findings of a previous report that described the benefits of bevacizumab therapy in the treatment of NVG (16). Preoperative IVR treatment may suppress intraoperative bleeding and VEGF-mediated inflammation, thus ensuring the safety and stability of the subsequent combined surgery.

While IOP was significantly reduced after IVR treatment, it did not return to normal levels in our study. This is because the NVG in these patients had developed to the advanced stage, and the angles were closed by peripheral anterior synechiae. Therefore, IVR treatment should be followed by combined surgery to control IOP definitively. The purpose of vitrectomy is to eliminate intraocular hemorrhage and improve visual acuity as well as to facilitate the implementation of PRP (17). Panretinal photocoagulation reduces the production of angiogenesis factors from ischemic retinas and induces the regression of both shallow anterior chamber, choroidal detachment, AGV tube obstruction, vitreous hemorrhage, and encapsulated bleb. The most common complications in the early postoperative period were hyphema and a shallow anterior chamber. Hyphema occurred in 4 eyes each in the AGV group (22.2%) and trabeculectomy group (26.7%). A shallow anterior chamber was found in 2 eyes (11.1%) in the AGV group and 4 eyes (26.7%) in the trabeculectomy group. These cases were mild and recovered spontaneously without any surgical intervention during the first 5 postoperative days. Choroidal detachment occurred in 2 eyes (11.1%) in the AGV group and 1 eye (6.7%) in the trabeculectomy group. One of the 2 eyes in the AGV group and the 1 eye in the trabeculectomy group recovered after topical and systemic application of corticosteroids. For the other eye in the AGV group, gas tamponade was applied, and the choroidal detachment resolved during the next 7 postoperative days. Hypertension occurred in 1 eye in the AGV group because the AGV tube was obstructed by fibrin in the anterior chamber; this complication was resolved using recanalization. Vitreous hemorrhage occurred in 2 eyes (11.1%) in the AGV group and 2 eyes (13.3%) in the trabeculectomy group but recovered spontaneously without any surgical intervention.

The main late postoperative complication in both groups included vitreous hemorrhage, and encapsulated bleb. AGV tube obstruction, vitreous hemorrhage, and encapsulated bleb. Success criterion: postoperative intraocular pressure level between 6 and 21 mm Hg with or without antiglaucoma medications.

**TABLE V** - Postoperative complications in both groups

<table>
<thead>
<tr>
<th>Complication</th>
<th>AGV group (n = 18)</th>
<th>Trabeculectomy group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyphema</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Shallow anterior chamber</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Choroidal detachment</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>AGV tube obstruction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Encapsulated bleb</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

AGV = Ahmed glaucoma valve.
Anterior and posterior segment neovascularization in patients for a long period of time (17).

In this study, a PPL was used instead of ultrasonic emulsification cataract surgery for the following purposes: (1) to allow visualization for the PPV; (2) to reduce disturbance to the anterior chamber to protect the corneal endothelium (as elevated IOP is accompanied by corneal edema, and phacoemulsification can cause a more severe anterior chamber reaction); (3) to deepen the anterior chamber so that the AGV tube could be placed; and (4) to allow PRP to be applied to the ora serrata. Preservation of the anterior lens capsule keeps the anterior chamber intact, so that viscoelastic substances can be administered intraoperatively. This is because leakage from the scleral incision is likely after AGV tube implantation, resulting in early postoperative hypotony (low IOP). Administering viscoelastic agents intraoperatively can prevent leakage, limit anterior chamber bleeding, and reduce postoperative ocular hypotension (18). Therefore, in this study, the fact that hypotony only occurred in 1 of the 18 eyes in the AGV group is a satisfactory result.

Glaucoma surgery was performed after PPV in this study. Previous research has shown that when PPV and PRP are combined with trabeculectomy for the treatment of NVG with vitreous hemorrhage, the probability of success is 55.6% after 1 year and 18.5% after 2 years (19). Compared to trabeculectomy and cyclodestructive procedures (which can lead to severe hypotony and phthisis bulbi when performed excessively) (20, 21), glaucoma drainage implants show higher surgical success rates and fewer postoperative complications (22). Therefore, AGV implantation is now commonly advocated for the primary surgical treatment of refractory glaucoma.

In this study, IOP decreased significantly after both trabeculectomy and AGV implantation. However, the mean IOP was significantly lower in the AGV group than in the trabeculectomy group at the 12-month follow-up. Trabeculectomy is a complex joint surgery, often resulting in postoperative conjunctival scarring of the filtering bleb. In fact, from 1 week after the surgery onwards, IOPs were consistently lower in the AGV group than in the trabeculectomy group, which might be related to the scarring of the bleb that is prone to occur in trabeculectomy. This may also explain why trabeculectomy is less successful than AGV implantation. Other risk factors for surgical failure of trabeculectomy for NVG include younger age and previous vitrectomy (23).

In our study, we found that fewer glaucoma medications were administered to the AGV group than to the trabeculectomy group for appropriate postoperative IOP control. Moreover, the absolute and relative cumulative probabilities of surgical success rates were both higher in the AGV group than the trabeculectomy group after 12 months (71.3% vs 46.7%; 71.3% vs 46.7%, respectively). Together, these results imply that AGV implantation might contribute to the lowering of IOP more efficiently than trabeculectomy for treating NVG with vitreous hemorrhage. However, the difference in the surgical success rates between the groups was not statistically significant, although this may have been because of the small sample size and limited follow-up time.

With regard to postoperative visual acuity, our study shows that although PPV cleared the media opacities, there was no remarkable improvement in visual acuity in either group. This may be explained by the fact that the NVG in most of our cases had developed to the advanced stage (with underlying retinal disease and optic atrophy due to long-term hypertension), and the vision prognosis was therefore poor.

There were no intraoperative or severe postoperative complications. The latter included hyphema, shallow anterior chamber, choroidal detachment, AGV tube obstruction, vitreous hemorrhage, and encapsulated bleb; however, these complications were transient and resolved spontaneously or with simple medical interventions. Our results are similar to those observed in a previous 5-year follow-up study, which also found that the postoperative complications occurring after AGV implantation or trabeculectomy were transient and that the rates of late postoperative complications after both procedures were similar (23).

Conclusion

The results of our study suggest that for the management of NVG with vitreous hemorrhage, PPV combined with AGV implantation may be more efficient at lowering IOP than PPV combined with trabeculectomy. However, further research involving a larger sample size and longer follow-up is required to confirm our findings.

Disclosures

Financial support: No financial support was received for this submission.
Conflict of interest: None of the authors has conflict of interest with this submission.

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