



Outcomes of Adjunctive Intracameral Bevacizumab with Ahmed Glaucoma Valve Implantation in Neovascular Glaucoma

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ABSTRACT

Background To compare surgical outcomes of Ahmed glaucoma valve (AGV) surgery with or without concurrent intracameral bevacizumab in neovascular glaucoma.

Methods:

All patients that underwent AGV by a single surgeon from 2021-2024 were identified from the hospital operation theatre database. Those that had received adjunctive intraoperative intracameral bevacizumab along with AGV (group1) were compared with those that underwent AGV surgery alone (group2). Success was defined as IOP <21mm Hg with (qualified success) or without (complete success) glaucoma medications. Data was collected for identifying the time of onset of hypertensive phase after surgery and the final outcomes in terms of additional procedure required in that eye.

Results:

Of 35 patients (M: F=29:6) with intractable neovascular glaucoma that underwent AGV, 15 received concurrent bevacizumab injections along with drainage implant surgery. The IOP at final follow up did not vary between the two groups, p=0.8. Hypertensive phase was seen in 8 (n=5 in group1 and n=3 in group2) eyes with the mean time of onset of hypertensive phase (>6 weeks) being longer in eyes receiving adjunctive bevacizumab injection, (p=0.03). Additional retinal surgeries like vitrectomy for vitreous haemorrhage, pan retinal photocoagulation (PRP) and repeat bevacizumab were required in 8 eyes in group 2 and 2 eyes in group 1, p=0.03.

Conclusion:

Though there was no statistical difference in the number of eyes developing hypertensive phase, the onset was delayed for >6 weeks in eyes receiving adjunctive bevacizumab with AGV surgery. Additional retinal surgeries were greater in NVG eyes undergoing AGV alone though the final outcome did not vary with concurrent bevacizumab.

Keywords: Neovascular glaucoma; vascular endothelial growth factor; bevacizumab; Ahmed glaucoma valve; glaucoma drainage devices.

INTRODUCTION

Glaucoma drainage devices have revolutionised glaucoma filtering surgeries by improving surgical outcomes in refractory glaucoma.^[1] Ahmed glaucoma valve surgery is most commonly preferred surgery for refractory glaucoma among the valved implants.^[2-5] Common reasons for failure after drainage devices include inflammation or excessive fibrosis around the plate.^[3] Its success in neovascular glaucoma has been reported to range from 60-70% in several studies. Failure in neovascular glaucoma is due to ongoing ischemic process in the eye which can cause angiogenesis and resultant increased

failure rates due to vascularisation of the bleb by new vessels.^[4-5] There is evidence supporting the role of vascular endothelial growth factor (VEGF) in ocular neovascularisation including NVG. Attempts to reduce vascularisation in routine filtering surgeries include use of anti-metabolites like Mitomycin-C.^[6] Yet, such attempts in AGV surgery are very scarce. Ma et al reported the use of bevacizumab in AGV surgery and reported good outcomes in terms of IOP control by its direct effect on wound modulation by inhibiting angiogenesis and decrease in influx of pro-inflammatory cytokines through vessels at the bleb surface.^[7] This should theoretically obviate the hypertensive phase in the postoperative course which is caused due to encapsulation or wound healing response in all AGV surgeries. Yet these studies have looked at intravitreal or sub-conjunctival routes of bevacizumab injection either prior to or after glaucoma surgery. Studies reporting the adjunctive use of bevacizumab by different routes also fail to reflect the real success or failure rate in terms of need for additional surgeries/procedures after surgery or its outcome on the hypertensive phase after AGV surgery. We therefore attempted to evaluate the role of adjunctive intracameral bevacizumab with AGV implantation in cases of refractory neovascular glaucoma prior to vitreoretinal intervention.

METHODS

All patients that underwent AGV by a single surgeon from 2021-2024 were identified from the hospital operation theatre database. Data that were retrieved from the database included demographic details like age, sex, laterality, diagnosis, best corrected visual acuity, gonioscopy done before surgery, dilated fundus evaluation, highest preoperative intraocular pressure on treatment, intraocular pressure on day 1, day 7, 4 weeks and thereafter every 3 months for 12 months, number of medications pre and post surgery, need for additional interventions, complications, final visual acuity and final follow up period.

Patients were excluded from the study in the presence of prior AGV surgery, prior cyclophotocoagulation and those with neovascular glaucoma due to intraocular tumors. Those that had received adjunctive intraoperative intracameral bevacizumab along with AGV (group1) were compared with those that underwent AGV surgery alone (group2). Details of reason stating need for intraoperative bevacizumab was noted, if available on the hospital records.

Surgical technique

Ahmed glaucoma valve surgery was performed by a fornix based supero-temporal conjunctival flap and using AGV model (FP7 or FP8, New World Medical, Rancho Cucamonga, LA, USA). The plate was fixed using 10-0 prolene suture 8mm from the limbus. The tube was inserted through a 24 gauge needle scleral track into the anterior chamber after priming with 1-2ml of balanced salt solution and trimming to ensure that 1.5-2mm was placed in the anterior chamber. In those receiving bevacizumab injections, intracameral bevacizumab (0.1mL, 2.5mg) was injected into the anterior chamber via a 26 gauge side port entry before tube insertion. The tube was fixed using 10-0 prolene sutures and was covered with a partial thickness corneal patch graft (prepared from rejected corneas available which were deemed unsuitable for penetrating keratoplasty by the hospital eye bank repository) which was secured using 10- nylon or fibrin glue. The conjunctiva was closed using continuous 8-0 vicryl sutures.

Postoperatively, all patients were initiated on prednisolone acetate 1% and cycloplegics which were gradually tapered over 4 weeks. Postoperative visits were scheduled at day 1, day 7, 1 month and thereafter every 3 months. Patients were referred to retina services for appropriate retinal intervention as and when required for PRP, additional bevacizumab injections or other treatments after dilated fundus evaluation at each visit from 1 month postoperatively. The number of retinal interventions post surgery was noted.

Success was defined as IOP <21mm Hg with (qualified success) or without (complete success) glaucoma medications. with failure defined as IOP >21 or <5 mmHg despite maximum medical treatment on two consecutive follow-up visits after 3 months with encapsulated bleb with or without significant visually threatening complications (like endophthalmitis, suprachoroidal haemorrhage or IOP), the need for additional surgery to control IOP or sight threatening complications, as listed above. The need for retinal intervention was not classified as failure unless the basic disease for NVG (like PDR, CRVO) had not progressed. Data was collected for identifying the time of onset of hypertensive phase after surgery and the final outcomes in terms of additional procedure required in that eye.

STATISTICS

All analysis was done using the Stata version (Stata Corp, Version 12, CA, USA). Continuous data is presented as mean \pm SD while categorical variables were compared using chi-square or Fisher exact statistics. Variables between groups (group 1:AGV+bevacizumab, group2-AGV alone) were compared using unpaired t test or Mann-Whitney U test while pre and postoperative variables were compared using paired t test or Wilcoxon sign rank test. Kaplan-Meier survival curves or log rank test was used to assess success rates with patients censored at the time they were lost to follow up.

RESULTS

Demographic variables of the 35 patients included in analyses were summarised in Table 1. Of 35 patients (M: F=29:6) with intractable neovascular glaucoma that underwent AGV, 15 received concurrent bevacizumab injections along with drainage implant surgery.

Table 1: Demographic and clinical variables in eyes with neovascular glaucoma that underwent Ahmed glaucoma valve (AGV) surgery with concurrent bevacizumab (group 1) or AGV alone (group2).

Variables	Group 1 (n=15)	Group 2 (n=20)	P value
Age	44±20.3	39±21.5	0.4
Male: Females	17:4	12:2	0.6
Number of preoperative Medications	4±2.1	3±2.4	0.1
Success	13	12	0.6
Failure	5	5	0.8

Of 15 in group 1, 5 had closed angles, 7 had open angles while gonioscopy could not be performed in 3 eyes due to hazy cornea (n=2) or hyphema (n=1). In group 2, 7 each had closed or open angles while 6 were not possible due to corneal edema.

Preoperative vision varied widely from perception of light (n=4), hand movements close to face (n=2), finger counting close to face (n=8) to 20/30 and was <20/400 in 24 eyes, >20/400 and <20/100 in 9 eyes, better than 20/100 in 6 eyes and better than 20/40 in 4 eyes. The mean preoperative IOP in all eyes reduced significantly from 32±9.9mm Hg to 15±5.8mm Hg postoperatively, p<0.001.

Of all 35 eyes, 5 were diagnosed developmental glaucoma status post previous filtering surgeries with neovascularisation, 14 were pure NVG due to central retinal vein occlusion (CRVO) or proliferative diabetic retinopathy (PDR), 7 were status post vitreoretinal surgery, 3 had secondary neovascular glaucoma after penetrating keratoplasty, 4 post trauma, 1 post inflammatory, 1 pseudoexfoliation with vascular occlusive disease and 1 spontaneous hyphema due to juvenile xanthogranuloma.

Postoperatively, the IOP at day 1, day 7, 3months and 6months reduced significantly in all eyes, **Table 2**. The IOP at final follow up did not vary between the two groups, p=0.8 (**Table 2**).

Table 2: Intraocular pressure in eyes that underwent Ahmed glaucoma valve (AGV) surgery with concurrent intracameral bevacizumab (Group 1) versus those with AGV alone (Group 2).

Intraocular pressure	Group 1 (n=15)	Group 2 (n=20)	P value
Immediate postoperative	9±1.6	14±1.8	0.1
3 months	21±2.8	18±2.09	0.5
6 months	22±3.1	17±3.2	0.3
12 months	17±2.8	14±1.5	0.3
Final follow up	16±1.3	14±1.8	0.2
Number of postoperative Medications	0.5±0.2	0.2±0.7	0.2

Hypertensive phase was seen in 8 (n=5 in group1 and n=3 in group2) eyes ranging from 6 weeks (n=3), 10 weeks (n=1), 2 months(n=2), 3 months (n=2). Twenty five eyes (13 in group1+12 in group2) did not experience any hypertensive phase with final visual acuity better than 20/40 in 7 eyes. The mean time of onset of hypertensive phase was longer in eyes receiving adjunctive bevacizumab injection, (all eyes >6 weeks, range 6 weeks-6months, compared to eyes receiving AGV alone with all eyes developing raised IOP<4months), (p=0.03). The mean number of medicines reduced from 4±2.1 and 3±2.4 to 0.5±0.9 and 0.2±0.5 in group 1 and 2 respectively, p=0.1.

Postoperative vision ranged from perception of light in 10 eyes, <20/400 in 23, <20/100 in 7 and better than 20/100 in 9 with vision better than 20/40 in 7 eyes. Of 17, 8 were vision >20/200. Of 21 in group2, 7 eyes had vision >20/200.

Additional procedure required after AGV surgery included superficial keratectomy for band shaped keratopathy (n=1), graft rejection (n=1), ozurdex injection (n=1) for persistent macular oedema and vitrectomy for vitreous haemorrhage (n=1) 8 months post AGV surgery. AGV related complications included extrusion of the implant in 2 eyes which required conjunctival resuturing and AGV explantation, choroidal detachment requiring choroidal drainage, and one NVI with tube blockage. One eye with implant extrusion developed corneal ulcer due to prolonged steroids at 2 years with eventual atrophic bulbi due to irregular follow up despite intensive antibiotic regime. One developed with history of repeated vitreoretinal surgery (5 times) for diabetic retinopathy with cataract (including bevacizumab injections, pars plana vitrectomy twice, cataract surgery with intraocular injections of antibiotics, band buckle surgery) developed corneal

decompensation 1.4 years after AGV despite tube placed away from the cornea. The visual acuity dropped from 20/80 at 1.4 year follow up to 20/200 at 2 year follow up on hypertonic saline drops.

Additional retinal surgeries like vitrectomy for vitreous haemorrhage, add pan retinal photocoagulation (PRP) and repeat bevacizumab were required in 8 eyes in group 2 and 2 eyes in group 1, $p=0.03$. Four eyes were classified as failure ($n=3$ in group 2 and 1 in group 1) due to hypotony ($n=2$), raised IOP >21 mm Hg at 6 months and 9 months ($n=2$).

DISCUSSION

We did not find any difference in survival rates or success in terms of IOP control in this study in eyes receiving adjunctive intracameral bevacizumab with AGV surgery in refractory NVG. Though there was no statistical difference in the number of eyes developing hypertensive phase, the onset was delayed for >6 weeks in eyes receiving adjunctive bevacizumab. Additional retinal surgeries were greater in eyes undergoing AGV alone though the final outcome did not vary between the two groups. These observations suggest the possible role of reducing VEGF levels with adjunctive bevacizumab in delaying hypertensive phase >6 weeks and reducing the need for retinal interventions due to concomitant reduction in VEGF levels, albeit even with an anterior route of administration.

Neovascular glaucoma represents one of the most severe forms of refractory secondary glaucoma resistant to conventional methods like trabeculectomy, cyclophotocoagulation or other filtering procedures.^[1-3, 8-10] AGV has gained increasing popularity for IOP control in this condition due to its success rates in refractory glaucoma post trabeculectomy or repeat surgeries with scarred conjunctiva. While success rates of drainage implants are reported to be comparable to trabeculectomy, its use in neovascular glaucoma is understandable due to high failure rate of routine or modulated trabeculectomy in refractory NVG.^[3-5,10]

Failure rates are definitely higher as compared to controls in refractory NVG with success rates ranging from 60-70% at 1 year in most studies.^[3-5,10] WuDunn et al found higher likelihood for failure in 34 NVG patients.^[11] Netland et al also reported similar results with NVG eyes at greater risk of surgical failure after AGV compared with controls.^[4] Yalvac and his colleagues reported a 63% success rate of AGV at 1 year in NVG patients.^[2]

Ongoing ischemia and role of VEGF has been proved to be main determinants of failure after routine filtering surgeries in refractory NVG.^[1-2,9-10] Yet failure rates or need for medicines post surgery is still a problem with drainage devices also which mandates the need for alternate surgical methods for improving surgery rates with implants. This study found similar survival rates with bevacizumab injection in refractory NVG. Li et al reported NVG as a major risk factor for failure in 55 eyes with refractory NVG (70%) compared to non-NVG group (92% survival at 1 year).^[12] Ma et al reported a greater drop in IOP in eyes receiving adjunctive bevacizumab injection.^[7] Zhou et al reported a slight better outcome of eyes receiving intravitreal bevacizumab before AGV surgery; yet the authors used Mitomycin-C during AGV surgery in all eyes which may be a confounding factor.^[13] They have also not reported the need for additional surgeries after AGV which may be an important determinant of final outcome in such eyes. Other studies using similar or alternate postoperative sub-conjunctival routes of administration have used different implants or different versions (S2 model) of AGV.^[11-18]

Our study did not find any difference in final IOP or success rates with intracameral bevacizumab with AGV surgery. This may be due to different modes of bevacizumab injection, more stringent criteria of defining success and failure.

Need for further retinal interventions as per discretion of retina service review was not classified as failure unless associated with progression of primary disease causing NVG (ex PDR) after surgery which implied failure of AGV surgery per se. This study found fewer retinal interventions and medications in group 1 as compared to the other group. Kim et al reported elevated VEGF levels in aqueous humour of eyes undergoing AGV in the group of patients whose surgeries failed suggesting that preoperative use of anti-VEGF agents can improve surgical outcomes in NVG. Several studies have shown an increase in levels of VEGF in the vitreous and aqueous humor in NVG.^[1,16] Further, increased inflammation and bleeding from new vessels at the angle or anterior segment may result in postoperative inflammation, hyphema and fibrinous reaction with resultant failure of the surgery. These facts have prompted surgeons to combine intravitreal injections of Bevacizumab 1 –2 weeks before AGV surgery thereby serving as a priming factor for future AGV surgical outcomes. Several studies report better surgical outcomes and survival rates of 70% at 1 year with intravitreal or intracameral use of bevacizumab.^[11-18] Our study reporting similar outcomes on intracameral adjunctive use of bevacizumab obviates the waiting time need for priming the eye for AGV surgery achieving IOP control and concomitantly reducing the need for retinal interventions post surgery due to reduction in VEGF load in the anterior segment.

A single injection of bevacizumab has a vitreous half life of 4.32 days in a rabbit eye with aqueous half life of about 6.86 days. In humans, the vitreous half life is estimated to be about 9.8 days.^[19] This action lasts for 4-6 weeks after which very minimal levels (11.17ng) are detected in the vitreous or aqueous (4.5 ng). This effect may vary depending on route of administration and dose of bevacizumab used though minimal benefit is obtained after increasing the concentration beyond

2.5 mg. An intravitreal injection has been reported to last an average of 58 days in an eye with NVG and open angles.^[16-17] A single intracameral injection may also work similar to intravitreal injection which has been supported by other studies evaluating outcomes of other filtering surgeries in refractory NVG.^[16]

Most of the eyes in this study were refractory NVG with presumed high levels of ischemic factors in the AC (anterior chamber). So presumably bevacizumab injection reduced the load of ischemic factors in the AC leading to lesser need for retinal interventions postoperatively. This possibly is due to regression of neovascular processes and inflammatory components leading to better surgical outcomes. We are however unsure if this can be accepted as standard of care for all NVG eyes since the final outcomes in terms of IOP or visual acuity were not different between groups. Earlier studies have reported that bevacizumab injection induces regression of neovascularisation causing IOP lowering in patients with open angles with surgery required in eyes with angle closure in late stage disease.^[11-15] In our study, patients with NVG almost all eyes presented at advanced stages during the course of their disease, missing the narrow therapeutic window for mandating the need for glaucoma surgery. However, we should be conscious that the effect of bevacizumab is short; persistence of retinal ischemia could induce recurrence, and it is likely that neovascularisation recurred and repeated bevacizumab injections or PRP is necessary. Though this study showed fewer rates of retinal interventions in neovascular glaucoma, such results are difficult to extend to other refractory glaucoma with increased VEGF, for uveitic glaucoma.

This study did not find any difference in the number of eyes developing hypertensive phase in either group though it presented significantly later in eyes receiving bevacizumab injection. The hypertensive phase is secondary to formation of fibrous tissue around the AGV plate seen at 6 weeks onwards. It may be possible that anti-VEGF injections reduce the ischemic load in the AC which may in turn help reduce the load of inflammatory mediators leading to prolonging of the hypertensive phase. While this is presumptive, it needs to be seen if use of anti-VEGF actually helps in obviating hypertensive phase in implant surgery.

In conclusion, concurrent AGV with intracameral bevacizumab may be a useful technique for reducing the overall number of interventions in patients with refractory neovascular glaucoma with useful vision due to immediate reduction in VEGF levels in the anterior chamber. Though success rates are similar, it may help prolong the hypertensive phase in eyes with a severe neovascular process at an advanced stage of presentation.

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