Effect of Preoperative Intravitreal Bevacizumab on the Success of Trabeculectomy with Mitomycin C in Neovascular Glaucoma.

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Abstract
Background: To assess the effect of preoperative Intravitreal Bevacizumab on the success of Trabeculectomy with Mitomycin C in neovascular glaucoma.

Methods: In this case control study 21 eyes of 21 patients with neovascular glaucoma irrespective of the primary pathology were selected. All of them were given Intravitreal Bevacizumab one to two weeks prior to a conventional primary trabeculectomy with Mitomycin C. All eyes were then followed after 01 month for the surgical outcome of success, which was an IOP of less than 21 mmHg without medication with a functioning bleb. Intravitreal Bevacizumab was given in a dose of 1.25mg/.05ml using a 29 gauge insulin syringe, approximately one to two weeks prior to a planned primary trabeculectomy. The trabeculectomy procedures were all performed under local anesthesia (facial and peribulbar block). A fornix based conjunctival flap was lifted and a 4mm x 2mm rectangular sclera flap raised and Mitomycin C, in a concentration of 0.5mg/ml applied beneath the scleral and conjunctival flaps using a soaked sponge for 4 to 5 minutes and later washed with 20 ml Ringer’s Lactate solution. A sclerotomy was then fashioned measuring 1.5mm x 1mm and a peripheral iridectomy performed. The scleral flap was sutured back using two 10/0 nylon stitches at the two corners. The conjunctival flap was also then sutured with 10/0 nylon. All the patients were followed up regularly and their IOP assessed at 01 month. The mean IOP was then calculated for all the patients as a measure of success of following this treatment protocol.

Results: Majority (61.9%) were females. Mean age at presentation was 52.6 ±8.7 years. Mean preoperative IOP was 37.2 ±8.8 mmHg and mean postoperative IOP at one month was 15.2 ±3.7 mmHg. There was no or minimal hemorrhage peroperatively. Hypotony was seen in 25%.

Conclusion: Intravitreal Bevacizumab prior to trabeculectomy with MMC in neovascular glaucoma is a safe and successful option.

Introduction
Neovascular glaucoma (NVG) is a severe form of secondary glaucoma characterized by proliferation of fibro vascular tissue in the anterior chamber angle.1 NVG can present through either a secondary open-angle or secondary closed-angle mechanism depending on the extent of neovascularization. It can be a potentially blinding and painful condition.1 It is almost always caused by retinal ischemia. Neovascular glaucoma is usually refractory to medical therapy alone. Surgical approaches to managing this complicated form of glaucoma have evolved over the past few decades while often still resulting in a guarded visual prognosis and failed surgical results. Trabeculectomy has often been performed to treat this condition but the results have been variable even with Mitomycin C (an antimetabolite) as an adjunct. The new vessels on the iris are a major concern in the failure of these procedures. In light of the association of vascular endothelial growth factor (VEGF) with retinal ischemia, and its role in new vessel formation, the advent of anti-VEGF drugs is proving to be a welcome addition in the treatment strategy for this potentially devastating condition.2-5

Patients and Methods
In this case control study, performed at Department of Ophthalmology Holy Family Hospital and a private eye surgery hospital, between December 2013 to April 2015, 21 eyes of 21 patients with NVG, irrespective of the primary pathology were selected. All of them were given Intravitreal Bevacizumab one to two weeks prior to a conventional primary trabeculectomy with
Mitomycin C. All eyes were then followed after 01 month for the surgical outcome of success, which was an IOP of less than 21 mmHg without medication with a functioning bleb. Intravitreal Bevacizumab was given in a dose of 1.25mg/.05ml using a 29 gauge insulin syringe after following necessary disinfection and sterilization protocols approximately one to two weeks prior to a planned primary trabeculectomy. The trabeculectomy procedures were all performed under local anesthesia (facial and peribulbar block). A fornix based conjunctival flap was lifted and a 4mm x 2mm rectangular sclera flap raised and Mitomycin C, in a concentration of 0.5mg/ml applied beneath the scleral and conjunctival flaps using a soaked sponge for 4 to 5 minutes and later washed with 20ml Ringer’s Lactate solution. A sclerotomy was then fashioned measuring 1.5mm x 1mm and a peripheral iridectomy performed. The scleral flap was sutured back using two 10/0 nylon stitches at the two corners. The conjunctival flap was also then sutured with 10/0 nylon. All the patients were followed up regularly and their IOP assessed at 01 month. The mean IOP was then calculated for all the patients as a measure of success of following this treatment protocol. Patients with uncontrolled diabetes or hypertension, retinal detachment, fresh or non-resolving organized vitreous hemorrhage, hyphema or with history of previous trabeculectomy or cyclo-cryo / laser ablation were excluded from the study.

Results

The 21 eyes that were included in the study all belonged to different individuals. 13 (61.9 %) of them were females and 8 (38.1 %) were males (Table-1). Mean age at presentation was 52.6 (± 8.7) years. Mean preoperative IOP was 37.2 (± 8.8) mmHg and mean postoperative IOP at one month was 15.2 (± 3.7) mmHg (Table-2). There was no or minimal hemorrhage peroperatively. Some of the eyes had hypotony during the initial few days. Other than that there were no significant postoperative complications.

Table 1: Distribution of Patients According to Gender (n=21)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>8</td>
<td>38.1%</td>
</tr>
<tr>
<td>Females (%)</td>
<td>13</td>
<td>61.9%</td>
</tr>
<tr>
<td>Total (%)</td>
<td>21</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2: Pre-op/Post-op Intraocular pressure (n=21)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean</th>
<th>S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.6</td>
<td>8.7</td>
</tr>
<tr>
<td>Pre-op IOP (mmHg)</td>
<td>37.2</td>
<td>8.8</td>
</tr>
<tr>
<td>Post-op IOP (mmHg)</td>
<td>15.2</td>
<td>3.7</td>
</tr>
</tbody>
</table>

p-value = 0.004*

*p-value <0.05 is significant

Discussion

The cause of NVG except for certain rare cases is always retinal ischemia. Retinal ischemia triggers a cascade of events beginning with an inadequate oxygen supply to the retina cells leading to the release of various angiogenic factors including VEGF and interleukin-6. Normally VEGF levels are in equilibrium with pigment epithelium-derived growth factor (PEDF), an antiangiogenic factor. When the equilibrium between VEGF and PEDF is shifted in favor of VEGF, this promotes activation, proliferation, and migration of endothelial cells, leading to neovascularization of the anterior segment. 4, 7 Diagnosis of NVG is primarily clinical. The earliest signs of NVG are tiny tufts of new vessels at the margin of the pupil and engorgement of major arterial circle of the iris. Whereas normal vessels tend to lie in the stroma and are radial in orientation, neovascular vessels appear on the surface of the iris and take on an irregular pattern.5, 12 As the vessels migrate towards the angle, one can see very fine arborized vessels on gonioscopy, which cross over the scleral spur onto the trabecular meshwork. Normal vessels typically remain behind the scleral spur. 6, 13 The walls of these vessels have increased permeability due to the absence of tight intercellular junctions, which are prone to vascular leakage and variable amounts of cellular inflammation. 6, 7 When new blood vessels appear within the anterior chamber angle, aqueous outflow can be compromised with extension of these new vessels across the scleral spur and subsequent obstruction of the trabecular meshwork. The new blood vessels are usually accompanied by a fibrous membrane, and contraction of this membrane results in formation of peripheral anterior synechiae and progressive angle closure.

Treatment of neovascular glaucoma has always posed a considerable challenge. Whichever treatment modality is chosen, the mainstay of management remains panretinal photocoagulation (PRP). Treatment of underlying systemic disease may improve neovascularization of the iris. Since elevated IOP is in part due to compromised trabecular meshwork function, aqueous suppressants (beta blockers, alpha-agonists, carbonic anhydrase inhibitors) are likely to have higher efficacy. Prostaglandins may be effective but may also exacerbate ocular inflammation. Miotic agents or any other medications acting on aqueous outflow are usually ineffective if the angle is already closed. Osmotic agents may be used to clear the cornea for treatment or diagnosis. Adjunctive treatment with topical steroids may control inflammation to improve
outcome of subsequent surgery whereas cycloplegics may aid in patient comfort and improve visibility for PRP.

In eyes with vision better than 20/400, most glaucoma specialists prefer filtering surgery or aqueous shunts versus cyclophotocoagulation. Regardless of the surgical procedure chosen, preoperative panretinal photocoagulation should be performed whenever possible. The presence of florid neovascularization poses a significant risk for intraoperative and postoperative hemorrhage, either extra or intraocular. Also, the increased permeability of these fragile vessels predisposes the eye to severe postoperative inflammation.

While trabeculectomy offers the advantage of achieving lower postoperative IOP compared to aqueous shunts, failure to adequately resolve neovascularization may ultimately lead to bleb failure through conjunctival scarring at the filtration site. Aqueous shunts bear the advantage of avoiding the necessity of surgical iridectomy, thereby decreasing the risk of intraoperative hemorrhage. In addition, aqueous shunts are more likely to tolerate intraoperative and postoperative bleeding and massive fibrin reaction in carrying out their function. However, glaucoma filtration shunts are very expensive and associated with a cumbersome technique with its own list of possible complications.

The advent of anti-VEGF agents has led to their use in the form of intravitreal injections. The duration of suppression of iris and angle neovascularization lasts approximately 3-6 weeks with anti-VEGF injections, thereby creating a window of opportunity to allow procedures like PRP and trabeculectomy to be carried out adequately.

Treating neovascular glaucoma has always been difficult especially with trabeculectomy because of the bleeding and inflammation frequently associated with neovascularisation which enhances the chances of postoperative scarring beneath the bleb resulting in early failure. Our study shows that the mean postoperative IOP at one month was 15.2 (± 3.7) mmHg without any medication which was significantly lower from the mean preoperative IOP of 37.2 (±8.8) mmHg with maximum possible medical therapy (p < 0.05). This is consistent with the studies carried out by Kitnarong et al., Wakabayashi et al. and Saito et al. Alkawas et al. in a very similar case series also reported similar success rate. Peroperative bleeding was very minimal in all the cases which confirmed the findings of previous reports. No significant postoperative complications, apart from hypotony in 07 eyes during the first few days, were encountered in any of the cases. The initial hypotony (IOP less than 5mmHg) which resolves within the first 3 to 5 days is frequently observed and may in fact be considered as a routine occurrence in the convalescent course of trabeculectomy.

Conclusion

Using Intravitreal Bevacizumab prior to trabeculectomy with Mitomycin C in neovascular glaucoma is a safe and successful option.

References