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Neovascular Glaucoma – A Review

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Abstract

Neovascular glaucoma (NVG) is a severely blinding disease with high intraocular pressure (IOP) resistant to treatment. The main problem in NVG is the release of vascular endothelial growth factor (VEGF) due to retinal ischemia caused by the underlying disease. Both the underlying disease and intraocular pressure should be treated in management of patients with NVG. The purpose of this review is to discuss etiology, pathogenesis, clinic classification and management of NVG. The main purpose in NVG management is to prevent the development of NVG by treating the underlying cause mainly proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO) and ocular ischemic syndrome (OIS). If NVG has developed, then it will be necessary to both treat the underlying etiology and high intraocular pressure. Panretinal photocoagulation (PRP) and anti -VEGF drugs are important in the treatment of NVG. Anti-glaucomatous drugs that reduce the production of aqueous are used in medical treatment in the control of IOP. Medical treatment may be insufficient in the control of IOP. Surgical methods will be required when IOP is not controlled by medical therapy. Fibrosis that develop after trabeculectomy and tube shunt surgeries reduces the success of surgery. Applying preoperative anti-VEGF may increase the rate of surgical success. Cyclodestructive procedures should be preferred when other surgical methods fail and patients with poor visual prognosis.

Review Article

INTRODUCTION

Neovascular glaucoma (NVG) is a severely blinding disease with high intraocular pressure (IOP) resistant to treatment. The main problem in NVG is the release of vascular endothelial growth factor (VEGF) due to retinal ischemia caused by the underlying disease. Both the underlying disease and intraocular pressure should be treated in management of patients with neovascular glaucoma. The purpose of this review is to discuss etiology, pathogenesis, clinic classification and management of NVG.

Etiology

The 3 most common causes of NVG are PDR, CRVO and OIS. One of the 2 most common causes of NVG is PDR [1-6]. 22% of PDR would develop NVG. Cataract surgery and pars plana vitrectomy (PPV) trigger the development of NVG in PDR patients [7]. Risk of NVG increases with presence of rubeosis iridis (RI) before PPV, chronic retinal detachment present and higher HbA1c levels after PPV and aphakia after cataract surgery in PDR [8-10]. Risk of NVG decreases with intraocular silicone oil [11].

One of the 2 most common causes of NVG is CRVO [1-6]. NVG does not develop in non-ischemic CRVO. About 40-45% of ischemic CRVO would develop NVG and most often occurs in the first 2 months [12,13]. But NVG can develop up to 2 years. Therefore, patients with CRVO should be followed up at regular intervals for 2 years.

OIS is third most common cause of NVG [14]. Since ocular perfusion pressure decreases in OIS, anterior and posterior segment ischemia occur. As a result, RI and NVG occur. Even if angle closure is occurred, IOP may be low or normal in patients with OIS, because of low ocular perfusion.

Less common causes of NVG are ocular radiation, ocular tumours, chronic uveitis, retinal vasculitis, Coat's disease, Eales' disease, peripheral retinal detachment, X-linked retinoschisis, cryoglobulinemia and Churg-Strauss syndrome [12].

Pathogenesis

Retinal ischemia is the main cause of NVG. Angiogenic factors, mainly VEGF, are secreted due to retinal ischemia. Secreted VEGF reaches the anterior chamber from the posterior segment and VEGF causes RI and NVG [15,16].

Clinical classification

NVG has 3 stages clinically.

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1. Rubeozis iridis: At this stage, neovascularization is seen at the pupil edge, iris surface, iridotomy edge and angle. Iris and angle should be carefully examined at high magnification. Otherwise, neovascularization can be overlooked. Especially in CRVO, neovascularization may be found at angle without pupil edge and iris surface. Therefore gonioscopy should be done at every control before the pupil is dilated. IOP may be normal at this stage. RI may regress with treatment.
2. Open angle glaucoma stage: At this stage, there is intense neovascularization at angle. Neovascularization at an angle creates the fibrovascular membrane and closes the trabeculum. IOP begins to rise at this stage. If patients untreat at this stage, synechial angle closure occur.
3. Angle closure glaucoma stage: If neovascularization continues, the peripheral iris is pulled towards the trabeculum by contracting the fibrovascular membrane and the angle closes progressively. Gonioscopy shows that synechia and angle closure. IOP is very high at this stage. Therefore, untreated or delayed treatment patients has glaucomatous optic atrophy.

Management of NVG

If NVG is not managed properly, it may cause irreversible vision loss and painful eyes. So management of NVG is very important. The main purpose of NVG management is to prevent the development of NVG. Therefore, the underlying cause mainly PDR, CRVO and OIS should be treated properly. When NVG develop, it should be treated in terms of the underlying etiology and high intraocular pressure. So visual function can be maintained and pain can be reduced.

Treating underlying causes

The most common 3 causes of NVG are PDR, CRVO and OIS. The main pathology causing NVG in these 3 diseases is retinal ischemia. Fundus fluorescein angiography is a very important imaging method in determining retinal ischemia [17]. The development of NVG can be prevented with the treatment of these 3 diseases. The management of these 3 diseases is described to prevent the development of NVG.

Prevention of NVG development in PDR; PRP is the most effective treatment for preventing NVG in PDR patients [18]. The pupil, iris and angle should be examined carefully in patients with diabetic retinopathy at each control. If neovascularization is detected, PRP should be applied. Combined treatment of the anti-VEGF with PRP provides a longer-term preservation of the angle in NVG [19].

Prevention of NVG development in CRVO; NVG does not develop in nonischemic CRVO. But there is a high risk of developing NVG in ischemic CRVO. Routine prophylactic PRP is not recommended in ischemic CRVO. However, in studies, it is recommended that patients with ischemic CRVO be followed closely and PRP is performed if RI is detected in at least 2 hours [20].

Prevention of NVG development in OIS; Management of patients with OIS is difficult and requires a multidisciplinary approach. These patients should be examined by neurology and cardiology. Because the main problem in these patients is the underlying carotid artery stenosis. In OIS, the only cause of RI is not retinal ischemia. Uveal ischemia plays a role in the pathogenesis of RI [14,21]. These patients benefit from carotid endarterectomy surgery. RI may be regressed after surgery [14]. Low or normal intraocular pressure before surgery may increase after surgery. Because the ciliary circulation increases after this surgery, there may be an increase in IOP [22]. Although PRP is controversial in OIS, PRP can be performed if pronounced retinal ischemia is detected in FFA [23].

Medical management of NVG

Anti-glaucomatous, anti-inflammatory and anti-VEGF drugs are included in the medical treatment of NVG.

Anti-glaucomatous drugs: Anti-glaucomatous drugs that decrease aqueous production should be preferred to reduce IOP in NVG. Topical beta blockers, alpha-2 agonists and carbonic anhydrase inhibitors reduce aqueous production. Oral carbonic anhydrase inhibitors can also be used. Hyperosmolar drugs such as mannitol can be used to reduce IOP. The use of topical prostaglandin analogs should be avoided as it increases ocular inflammation. Miotics can increase inflammation and ciliary spasm. Therefore miotics are contraindicated in NVG.

Anti- inflammatory drugs: Topical steroids and cycloplegic agents should be used to reduce ocular inflammation and pain.

Anti-VEGF can be applied intracameral or intravitreal or both simultaneously. In many studies, intravitreal and intracameral were administered at the same dose [26-28]. Anti-VEGF can be applied alone or with PRP. The effectiveness of anti-VEGF is temporary [29]. Therefore, it is recommended to combine anti-VEGF with PRP. Advised

approach is that if the fundus is visible, anti-VEGF should be combined with PRP. If the fundus is not visible due to the media opacity, only anti-VEGF should be performed.

The effect of anti-VEGF drugs is quite fast. When RI begins to regress 2 weeks after PRP is applied, RI regress within the 2nd day after intravitreal anti-VEGF. It has also been reported to reduce intraocular pressure, inflammation and pain in the open angle glaucoma stage after intravitreal anti-VEGF [30].

Surgical management of NVG

NVG may be resistant to medical treatment**.** Surgical methods will be required when IOP is not controlled by medical drugs. Trabeculectomy, tube shunts and cycloablation are surgical options for neovascular glaucoma surgery. Which surgical method to choose depends on the patient (underlying disorder, value of intraocular pressure, degree of inflammation, stage of NVG, stage of glaucomatous optic neuropathy and visual potential) Surgical success rate in PDR is higher than CRVO and OIS.

Trabeculectomy: Intraoperative mitomycin C (MMC) use in trabeculectomy surgery reduces bleb failure caused by subconjunctical scar. In NVG the success rate of trabeculectomy with MMC is 62.6% at 1 year and 51.7% at 5 years [31]. The success rate after the application of preoperative anti-VEGF has been reported as 95% [32]. Preoperative reduction of inflammation and regression of RI increases surgical success. Therefore it is recommended to apply preoperative anti-VEGF and PRP. Preoperative anti-VEGF should be planned within 1 week from surgery. Anti-VEGF can be applied intraoperatively and postoperatively as well as preoperative for treatment of failing blebs. The route of administration may be intravitreal, anterior chamber or subconjunctival [33-37].

Tube Shunts: Tube shunts are preferred primarily recently in neovascular glaucoma surgery due to bleb failure in trabeculectomy surgery [38]. But there is no clear scientific evidence as to which trabeculectomy and tube shunts will be the primary method. Molteno implant, Baerveldt implant and Ahmed glaucoma valve implant used in neovascular glaucoma surgery and success rates were not statistically significant between them [39]. Preoperative anti-VEGF is recommended in tube shunt surgeries as well as preoperative in trabeculectomy surgery. The success rate after the application of preoperative anti-VEGF has been reported as 95% at 1 year [40]. The main problem after tube shunt surgeries are the blockage of internal fistula and external filtration site and fibrous encapsulation. Microstent EX-PRESS shunt was also used in neovascular glaucoma surgery. But the success rate is very low [41].

Cyclodestructive Procedures: Cyclodestruction is an ablation of the ciliary body. Cyclodestructive procedures are cryotherapy, endoscopic laser coagulation and transscleral diode laser photocoagulation. These procedures reduce the production of aqueous by destroying the ciliary epithelial cells. Cyclodestructive procedures should be preferred when other surgical methods fail and patients with poor visual prognosis. These procedures can be repeated to reduce intraocular pressure, if necessary.

If IOP cannot be controlled by medical and surgical treatment, enucleation or retrobulbar alcohol injection may be required in painful and invisible eyes.

CONCLUSION

NVG is a serious disease with a poor visual prognosis. The main purpose in NVG management is to prevent the development of NVG by treating the underlying. If NVG has developed, then it will be necessary to both treat the underlying etiology and high IOP. Medical treatment may be insufficient in the control of IOP. Trabeculectomy, tube shunts, and cycloablation are among the surgical options according to the clinical features of the patient. Fibrosis that develops after trabeculectomy and tube shunt surgeries reduces the success of surgery. Applying preoperative anti-VEGF may increase the rate of surgical success. Cyclodestructive procedures should be preferred when other surgical methods fail and patients with poor visual prognosis.

Conflict of interest

The authors declare that they have no conflict of interest.

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