MALAYSIAN SOCIETY OF OPHTHALMOLOGY

MANAGEMENT OF NEOVASCULAR GLAUCOMA

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INTRODUCTION

Neovascular glaucoma (NVG) is a devastating and aggressive secondary glaucoma that has been associated with poor visual prognosis. The core purpose of treatment is to lower intraocular pressure (IOP) and preserve the patient's visual function. It is a sequela of many ocular ischemic conditions, most of which are associated with retinal ischemia. Due to the underlying systemic and ocular pathologies, which cause NVG to present late, treatment has been challenging. Understanding the pathogenesis of NVG allows the treating doctors to diagnose the disease as early as possible to provide the best opportunity to maintain vision. The advent of anti-vascular endothelial growth factor (VEGF) in recent years has, however, resulted in a paradigm shift in the management of NVG.

In 1963, Weiss and colleagues proposed the term NVG which has been universally accepted. NVG can be divided into the following three stages: rubeosis iridis, secondary open angle glaucoma and secondary closed angle glaucoma. Posterior segment ischemia drives neovascularization of iris (NVI) and drainage angle (NVA), causing the formation of fibrovascular membrane which eventually obstructs the trabecular meshwork and contracts to produce synechial angle closure with peripheral anterior synechiae.

The most common conditions associated with NVG are proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO) and ocular ischemic syndrome. The list of other causes is extensive; however, the majority are associated with retinal ischemia and hypoxia.

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MANAGEMENT OF NVG

The management of NVG involves addressing key factors which are:

1. ***Visual potential,***
2. ***Aetiology,***
3. ***Neovascularization caused by ischemic drive,***
4. ***IOP***

Reducing elevated IOP and treating the underlying diseases that led to the ischemic insult causing anterior segment neovascularization is the mainstay of treatment.

1. VISUAL POTENTIAL

Patients with poor visual potential are usually those with severe underlying eye disease at presentation. The optic discs are usually pale and visual acuity is hand movements or worse. There is usually presence of a relative afferent papillary defect. Indications for treatment in this group of patients are usually pain associated with inflammation or high intraocular pressure. The primary goal of treatment in this stage is pain control. Medical therapy includes topical atropine 1% and steroids. If corneal decompensation occurs, use a bandage contact lens. Cyclodestructive procedures are performed if medical therapy fails to provide symptomatic relief. With cyclocryotherapy, the IOP-lowering effect is achieved by destroying secretory ciliary epithelium and/or reducing blood flow to the ciliary body. It is indicated as a last resort only if relief of pain is the main goal. In a large series, 34% of eyes achieved IOP of less than 25 mm Hg; however, 34% of eyes became phthisical and 57% of eyes lost all light perception. Other complications include sympathetic ophthalmia and anterior segment ischemia. The use of long term expensive topical antiglaucoma is usually not indicated in an eye with poor visual potential due to cost and undesirable side effects.

In an eye with good to moderate visual potential, the management strategies are elaborated below.

2. AETIOLOGY

Identifying the underlying aetiology for the neovascular drive is fundamental for the management of NVG. Among conditions that underlie it are CRVO, advanced stage PDR, ocular ischaemic syndrome and others. All require systemic workup and appropriate intervention to prevent further complications. As this article is focusing on management, the investigations to be carried out are beyond the scope of this article.

3. TREATMENT OF NEOVASCULARIZATION AND ITS UNDERLYING DISEASES

The main principal in treating anterior segment neovascularization is to reduce the ischemic drive. In many cases, panretinal photocoagulation (PRP) is essential to achieve this ischemic reduction in the long term. The mechanism of how PRP works is relatively unclear. PRP may reduce the oxygen demand by destroying the outer photoreceptor-retinal pigment epithelium complex which accounts for most of the total retinal oxygen consumption. With this, choroidal oxygen may diffuse into the inner retina, thus decreasing the inner retinal

hypoxia and stimulus for the release of angiogenic factors.

Adequate PRP treatment is essential. Studies have revealed that laser spots of 1200-1600 can regress NVI in 74% of patients. PRP has been indicated as the first line treatment of NVG secondary to PDR. In ischaemic CRVO, presence of more than 2 clock hours of NVI and/or any NVA warrants a prompt PRP to aid in regression of the new vessels according to CVOS.

In many cases where adequate PRP is not possible, in view of cloudy media like corneal edema, hyphaema, or vitreous haemorrhage, other retinal ablation modalities should be considered like panretinal cryotherapy and transscleral retinal diode laser photocoagulation. A surgical option for peripheral retinal ablation is pars plana vitrectomy with endolaser photocoagulation and cataract extraction if necessary. When synechial angle closure has already occurred, it is considered the late stage and the management becomes more challenging. In these cases, glaucoma filtration surgery is recommended of which PRP should be performed, if possible, prior to the surgery, so as to prevent failure of the surgery.

Anti VEGF agents

The role of anti-angiogenic agents has provided a significant impact in treatment of anterior segment neovascularization and in improvement of survival of glaucoma drainage surgery when used as an adjunct. Administration of intravitreal bevacizumab (IVB) with a dose of 1.25mg/0.05 ml

used as an adjunct. Administration of intravitreal bevacizumab (IVB) with a dose of 1.25mg/0.05 ml induces rapid resolution of new vessels and decreases IOP when used alone or in combination with PRP. Duration of suppression of neovascularization is three to six weeks with bevacizumab, which provides an opportunity for adequate PRP during that time. Systematic review of the efficacy and safety of IVB in the treatment of NVG establishes bevacizumab is well tolerated, effectively stabilizes INV activity, and controls IOP in patients with INV when used alone and at an early-stage of NVG. Although NVG outcomes improve with bevacizumab, regression of neovascularization is often temporary and recurrence is possible unlike PRP which provides a more permanent reduction of ischemic angiogenic stimulus. IOP has been postulated to be under control without surgical intervention if bevacizumab is administered prior to peripheral anterior synechiae and angle closure.

Caution is needed when considering intravitreal injections of anti VEGF in an eye with active neovascularisation and very high IOP. The complications which can occur include hyphaema, vitreous incarceration through injection site and tractional retinal detachment in presence of proliferative diabetic retinopathy. The role of intracameral injections of antiVEGF has yet to be established although several clinicians advocate this. Currently, there are no reported adverse effects from this method of delivery although its efficacy is debatable as the ischaemic drive is from the posterior segment.

4. TREATMENT OF ELEVATED IOP AND INFLAMMATION

A) Medical

Controlling IOP is essential to prevent further optic nerve damage, decrease associated pain and possibly improve corneal edema resulting from elevated IOP. Medical management of NVG is most effective when the angles of the anterior chamber are open. However, the angle can relentlessly close until PRP is performed. If the angles are closed due to synechiae, medical therapy can only be of temporary measures. Topical administrations of agents used to lower IOP by reducing aqueous production are beta-blockers, carbonic anhydrase inhibitors, and alpha-adrenergic agonists (which also increases aqueous humor outflow). Prostaglandin analogs may be less effective as presence of synechiae may obstruct the uveoscleral outflow of aqueous humor and potentially increase inflammation. Miotics are generally contraindicated as well in view of exacerbating inflammation, worsening angle closure from synechiae and decreasing uveoscleral outflow of aqueous humor.

Topical corticosteroids like prednisolone acetate are useful to reduce inflammation. Usage of topical cycloplegic agents like atropine can prevent worsening of synechiae and at the same time, relieve pain.

B) Surgical

As long as there is useful vision potential of hand movement or better, surgical intervention is indicated when medical therapy has failed to control IOP or when synechial angle closure from neovascularization of angles has occurred. PRP is necessary prior to surgical intervention if possible, to reduce extent of NVA/NVI, and hence reduce risks of surgical failure.

Trabeculectomy is useful in cases of quieter eyes with less inflammation, requiring a lower IOP goal. Success of trabeculectomy in NVG is limited by severe inflammation, high incidence of intraoperative hemorrhage and post-operative progression of fibrovascular membrane. Presence of active neovascularization may lead to early bleb failure through conjunctival scarring at the filtration site. Application of mitomycin C has been shown to be more effective than 5-fluorouracil in routine trabeculectomies. A retrospective cohort study found that prognostic factors for failure of trabeculectomy with mitomycin C for NVG were younger age and previous vitrectomy.

Adjunctive use of anti-VEGF alongside trabeculectomy, either intraoperatively or post-operatively, is also an option. In a short case series, the use of intracameral bevacizumab prior to trabeculectomy with MMC improved NVG. The postoperative inhibition of angiogenesis after glaucoma surgery has also been described. Possible routes of bevacizumab administration are subconjunctival application during trabeculectomy, postoperative needling, or intravitreal injection during a filtrating procedure. Favorable outcomes have also been reported with use of IVB into NVG eyes with silicone oil in after vitrectomy for advanced diabetic retinopathy.

The usage of glaucoma drainage devices has shown promising results in treatment of refractory NVG when conventional filtration surgery fails or is not possible due to excessive conjunctival scarring. The success rate is less dependent on control of inflammation and the failure of filtering bleb. Hence, these devices can be placed in eyes of active inflammation. In usage of Molteno implants in 60 eyes with NVG, success rate was only 10% at five years. In 36 eyes of NVG, the success rate of using Baerveldt implants was 80% at the first year, but only 56% at 18 months. Ahmed valve implants may also be used in treatment of refractory NVG.

CONCLUSION

NVG remains a therapeutic challenge as it is a devastating ocular disease, which is associated with poor visual prognosis. In managing NVG, it is essential to treat the underlying cause of the disease, neovascularization, and elevated IOP. However, successful management of the disease may be difficult once IOP is elevated. Understanding its pathogenesis and detecting neovascularization early with prompt, aggressive treatment to reduce retinal hypoxia and retard the angiogenic cascade, may prevent blindness in this disease. Long-term outcomes with latest approaches in management are lacking from recent literature.

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