We report results of a case series of preterm, extremely low-birth-weight infants, with zone-1, stage 3+ AP-ROP, treated successfully with intravitreal ranibizumab injection (LUCENTIS®; Novartis Inc.). 20 consecutive eyes of 10 preterm babies, 5 boys and 5 girls, with gestational age range from 27 to 32 weeks and gestation weight in range of 940 gms to 1200 gms, presented with zone-1, stage-3 ROP. They were treated with intravitreal ranibizumab injections at a dose of 0.3mg (60% of the normal adult dose) under sterile conditions given through the nasal pars plana of each eye. Improvement was seen in all eyes within 48 hours after the procedure and within next 1 week following the injections, the AP-ROP disappeared. After a period of 4-12 weeks, laser photocoagulation was performed in the peripheral retina. No adverse effects related to intravitreal ranibizumab were observed in any eye.

Aggressive posterior retinopathy of prematurity successfully treated with intravitreal ranibizumab and laser photocoagulation

Introduction:
Retinopathy of prematurity (ROP) is a disease that affects immature vasculature in the eyes of premature babies and is inversely related to gestation and birth weight. ROP has been divided into five stages. Stage-1 and 2 customarily get better on their own. However some eyes go on to Stage 3 ROP, which exists when disturbing new blood vessels grow out from the ridge in the retina toward the center of the eye, since premature baby has not had the time while in the womb to allow the blood vessels within the retina to grow all the way from the optic nerve in the back of the eye to the front of the eye. Aggressive posterior ROP (AP-ROP), sometimes referred to as Rush disease, is a rapidly progressive form of ROP. It is observed most commonly in zone I, but may also occur in posterior zone II. If untreated, it usually progresses to stage 5 ROP. The characteristic features of AP-ROP are its posterior location, prominence of plus disease.

ROP is emerging as a major cause of blindness, in developing countries. The incidence of ROP varies between 16-48% and 27-35% in infant weighing less than 1000g and 1500g respectively at birth.2 The incidence of ROP in neonatal intensive care units (NICUs) or referral to tertiary care hospital in India ranged from approximately 21 to 40%.3 The reasons this high prevalence rate can be higher rate of premature birth, lack of resources resulting in compromised neonatal care, leading to higher rates of severe ROP not only in extremely premature infants but also in larger, more mature infants.

Vascular endothelial growth factor (VEGF) is an important oxygen-regulated factor and its overexpression plays an important role in pathogenesis of ROP.4 The development of ROP is largely dependent on VEGF. When an infant is born prematurely the relatively hyperoxic environment the baby is introduced to shuts down the production of VEGF. Retinal maturation is delayed. Subsequently, at a time when intraocular VEGF levels would normally be declining late in the third trimester of pregnancy, abnormally high levels of VEGF are seen due to large areas of avascular retina and associated tissue hypoxia. The availability of FDA-approved drugs for anti-VEGF treatment renders it possible to treat such eyes off-label. The rationale for this treatment approach is that VEGF promotes retinal vascularization. Available drugs include pegaptanib sodium (Macugen®) for partial blockage of VEGF-A, or drugs such as ranibizumab (LUCENTIS®; Novartis inc.) and bevacizumab (Avastin®), which cause complete blockage of VEGF-A.

The studies, Pan-VEGF Blockade for the Treatment of Retinopathy of Prematurity (BLOCK-ROP) and Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP), have shown promise to potentially change the standard for treatment of ROP.

The purpose of BEAT-ROP was to determine whether injections into the vitreous of an anti-VEGF will reduce the incidence of blindness by suppressing the neovascular phase of ROP, compared to a control group receiving conventional laser therapy and to determine the safety and efficacy of intravitreal bevacizumab in the treatment of ROP. The result from BEAT-ROP showed significant efficacy of Intravitreal bevacizumab in treatment for zone-1 disease (P=0.003), in infants with stage 3+ retinopathy in comparisons with conventional laser therapy.5 Also, bevacizumab allowed continued vessel growth into the peripheral retina, whereas conventional laser therapy permanently destroyed vessels in the peripheral retina. Although question of right dose and safety of using intravitreal bevacizumab in this population still remains, nevertheless results of the BEAT-ROP trial
suggest that intravitreal bevacizumab monotherapy to be far safer and more effective than conventional laser for treating retinopathy of prematurity. These finding suggest that bevacizumab and other anti-VEGF drugs may signify a real advancement in treating this disease.

We report results of a case series of preterm, extremely low-birth-weight infant, with zone-1, stage 3+ AP-ROP, treated successfully with intravitreous ranibizumab injection (LUCENTIS®; Novartis Inc.), an anti-angiogenic, monoclonal antibody fragment, with strong binding to VEGF-A. A detailed search and analysis of content in medical databases like Medline, EMBASE, etc., failed to reveal mention of any case study, illustrating treatment of ROP, with Intravitreal ranibizumab. Few recent studies have shown that bevacizumab may be an effective alternative in the management of ROP. Since ranibizumab is derived from the same parent murine antibody as bevacizumab but is much smaller than the parent molecule and has better tissue penetration, encouraged us for experimenting Intravitreal ranibizumab in combination with laser, for treatment of ROP.

Report of a Case:
20 consecutive eyes of 10 preterm babies 5 boys and 5 girls, with gestational age range from 27 to 32 weeks and gestation weight in range of 940 gms to 1200 gms, presented with zone-1, stage-3 ROP with corneal haze, media hazy, and iris neovascularisation. The International Classification of Retinopathy of Prematurity Revisited1 was referred to define Zone I and to subdivide the severity of stage 3 into mild, moderate, or severe depending on the extent of extraretinal fibrovascular tissue infiltrating the vitreous. Subsequently infants with bilateral moderate or severe stage 3 ROP were included in study, excluding infants with any congenital systemic or ocular abnormality. Diagnosis of AP-ROP plus disease was confirmed. The tunica vasculosa lentis and hyaloid arteries were persistent.

All the eyes were treated with bilateral intravitreal injections of ranibizumab (0.3 mg/0.02 ml) followed by peripheral retinal laser photocoagulation. 10 babies (6 boys and 4 girls), received intravitreal injections of ranibizumab. After a period of 4-12 weeks, laser photocoagulation was performed in the peripheral retina with the following settings: spot size 300 microns, duration of 20 milliseconds with 100 milliseconds repeat interval.

Considering the severity of disease and based on recent use of anti-VEGF as intravitreal injections for ocular diseases caused by neovascularisation especially wet age-related macular degeneration (US Food and Drug Administration approved for ranibizumab in June 2006), off label use of ranibizumab intravitreal injection was considered. It was decided that intravitreal ranibizumab injections at a dose of 0.3mg (60%of the normal adult dose) under sterile conditions would be given through the nasal pars plana of each eye. The injections were administered using continuous cardiorespiratory monitor. A speculum for premature infants was placed between the lids. A drop of povidone–iodine (5%) ophthalmic solution was placed into the conjunctival sac for 1 minute (pre and post injection) with the excess removed by a sterile cotton tip applicator from the temporal lid margin. Toothed forceps was used to steady the eye as dose of ranibizumab (0.02ml [0.3mg]) was injected behind the lens, repeating same procedure for the other eye. Post procedure, ophthalmic antibiotic drop Moxifloxacin (Vigamox®) was prescribed for both eyes to begin immediately for the next 10 days at an interval of 4 hrs. Indirect ophthalmoscopy was utilized to look for any injury to the lens, to determine the presence of adequate blood flow through the central retinal artery, and to identify any retinal tears or vitreous hemorrhage immediately after the injection.

Improvement was seen within 48 hours after the procedure and within next 1 week following the injections, the AP-ROP disappeared. Extraretinal fibrovascular proliferation superior and inferior to the typical indentation toward the macula disappeared and retinal vessels continued their anterior...
growth into the previously avascular retina. Ophthalmic examinations revealed central and steady fixation without strabismus, round pupils could be fully dilated, clear corneas and lenses, and minimal or no myopia or anisometropia. No ocular complications, incidence of endophthalmitis or systemic thrombotic events, hypertension or gastrointestinal hemorrhages related to the intravitreal ranibizumab injections were observed.

Discussion

AP-ROP is an aggressive variant of ROP that has unique characteristics and can proliferate rapidly. Laser photocoagulation is still considered as initial treatment but thermal injury to the long posterior ciliary arteries in the horizontal meridian may result in anterior segment ischemia, the most devastating complication of ablative laser for threshold ROP. The choice of ranibizumab in our case study was deliberate, in order to try and minimize the possibility of systemic complications. The molecular weight of ranibizumab is 48 kd (provide greater retinal penetration) with intravitreal half-life of ~9 days and binding affinity of 0.14 nM. The shorter half-life of ~15 hours versus 20 days for bevacizumab, leads to reduced risk of systemic complications. In addition to this, Fc fragment of antibodies binds immune molecules such as complement factors but ranibizumab does not comprise Fc fragment, leading to a reduced risk of complement-mediated toxicity and eye inflammation. Similarly, the decision to give bilateral intravitreal injections was deliberate to avoid creating a case series of amblyopic eyes due to the unilateral visual deprivation caused by the inflammatory response, cataract, hemorrhage, or other complications after laser therapy.

Intravitreal injection of anti-VEGF agents in neonates offers potential advantages over laser treatment, as shown by BEAT-ROP study. These benefits include eliminating the direct effects of laser, which may include visual field loss secondary to retinal atrophy and myopia related to scleral weakening. Additionally, anti-VEGF therapy may offer a safer treatment option than blind external application of cryotherapy or laser photocoagulation in infants with rigid pupils or media too opaque for adequate visualization of the retina. Intravitreal injection can also cause regression of the proliferative component of ROP, leading to absorption of hemorrhage and improved visualization for subsequent laser therapy, if needed.

In our case series AP-ROP was successfully treated by ranibizumab and revealed the effectiveness of intravitreal injection of ranibizumab for treatment of severe stage 3 ROP in zone I. Appropriate controlled studies with long-term follow-up are warranted to determine the potential safety and benefit Anti-VEGF agent ranibizumab, which may potentially play an increasing role as primary and/or adjunctive therapy in the future as additional studies become available.

Reference:

3. Nazimul, Hussain; Rohit, Khanna; Anjli, Hussain; Trend of retinal diseases in developing countries, Expert Review of Ophthalmology, Volume 3, Number 1, February 2008 , pp. 43-50(8)

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Non Infectious Toxic Keratitis Following Bee Sting Injury –A Case Report

Introduction:
In our day to day clinical practice we come across various infective keratitis cases. Their management and prognosis depends on the clinical presentation. In this case report we present a different clinical scenario with an unusual presentation of keratitis.

Case report:
A 47-year-old gentleman, presented to ophthalmic casualty on 8th March 2011 with complains of defective vision, pain, redness & swelling in and around right eye - since 1 day. He gave a history of an insect (? bee) hitting the right eye on the previous day while driving his two wheeler. Following which he had severe foreign body sensation. He consulted a nearby ophthalmologist, who removed a foreign body from his right eye and topical antibiotics were prescribed. Thereafter the patient was asymptomatic. Next day he got up to notice significant diminution of vision in RE associated with severe pain, redness and swelling around the eye. For this complaint he consulted another ophthalmologist who referred him to our institute for further management.

On presentation patient was on topical antibiotics. There was no history suggestive of scraping / any other procedure.

UCVA RE – CF at 1 meter NIP NIG LE – 6/18 with refraction+1.75 DS 6/6 N.V + 2.50 J2.

Right eye presented with lid edema with normal margin & lashes, Conjunctival chemosis and congestion.

Corneal examination showed lack of lustre and transparency with corneal edema, dense radiating Descement’s folds and Striate Keratitis. With a circular 3x2.5 cm corneoscleral infiltrate at 3’o clock position.

On staining with fluorescein corneal Punctate Staining with epithelial defect over corneoscleral infiltrate was noted. Corneal sensation was intact.

AC- Details hazily seen, Pupil – RRR to D&C Reflex and lens appeared clear.

LE – Anterior segment examination was WNL.

Fundus examination: RE hazy view due to corneal edema, red glow seen . LE – WNL.

PROVISIONAL DIAGNOSIS:
On the basis of injury by insect & foreign body removal (probably sting) and typical clinical appearance a working diagnosis was made.

RE: Toxic keratitis with corneoscleral infiltrate S/P Bee sting injury

LE - simple hypermetropia, presbyopia

Address for correspondence - aneetajabbar@yahoo.com Cornea and Anterior segment services, Little Flower Hospital, Angamali.
Investigations: Routine blood investigations were WNL. Corneal scraping revealed no organism & negative culture report.

Patient was started on oral antihistaminics and analgesics. Topical prednisolone Acetate eye drops were started under antibiotic cover.

Supportive treatment in the form of topical cycloplegic and lubricant were given.

After 3 days: Pain & swelling subsided but defective vision persisted without any progression.

Lid edema has considerably reduced, conjunctiva showed mild congestion without chemosis. Corneal edema was decreased. Corneoscleral infiltrate was resolving with surrounding early scarring & epithelial defect reduced in size. At this time oral medication were stopped and patient was discharged on topical steroids, antibiotics & cycloplegic.

**After 1 week follow up:**

UCVA in RE has improved to 6/60.

O/E : RE Lids and conjunctiva were normal. Corneal edema has significantly reduced with scarring of corneoscleral infiltrate. Specular reflection showed presence of corneal guttae.

At this stage topical steroids were tapered and cycloplegic was stopped.

**After 3 weeks follow up:**

VA RE – 6/24

Refractive: +1.5 ds/+ 0.25 dc x 140- 6/6

O/E: Lids &Conjunctiva clear. Clear cornea with a marginal scar

**DISCUSSION:**

Corneal bee sting - an uncommon environmental eye injury. Though corneal or conjunctival bee sting represent localized form of reaction generalized reaction such as anaphylaxis may occur.

Complications due to ocular bee sting may involve the cornea, conjunctiva, anterior chamber, lens, optic nerve, or extraocular muscles.

Complication associated with bee sting injury may be due to the penetrating, immunological, or toxic effect of the stinger and its injected venom. Stinger, a modified ovipositor with a venom sac attached at the proximal end.

**Bee venom is a complex toxin consisting of:**

- Biologic amines - histamine, dopamine
- Nonenzymatic polypeptides toxins - melittin, apamin, mast-cell degranulating peptide, and minimine.
- High molecular weight enzymes - phospholipase A, phospholipase B, and hyaluronidase

Various clinical presentations which has been reported in literature includes:

- Periorbital edema, External ophthalmoplegia, Conjunctival chemosis & injection, Corneal edema, Striate keratopathy with radiating DM folds, Hyphaema, Iritis, iris depigmentation causing heterochromia iridis & Sector iridoplegia, Cataractous changes in lens & Subluxated lens, Optic nerve involvement in the form of papillitis, atrophy or papilloedema.

**MANAGEMENT:**

**ACUTE MEASURES INCLUDE:**

- Suppression of inflammation – topical steroids
- Prevention of secondary infection – topical antibiotics
- Oral antihistaminics – to counteract biogenic activity
- Severe iritis with hypopyon in AC – paracentesis
- Surgical removal of sting

Surgical removal of the retained bee stinger is still a matter of debate in the literature:

- Gilboa et al addressed two patients with corneal bee sting in whom the stingers remained protruding into the anterior chamber for 21 years and 28 years with no ocular manifestations.
- * Arcieri et al described a 12-year-old boy with a retained corneal stinger protruding into the anterior chamber resulted in a severe corneal inflammation.

**LONG TERM MANAGEMENT:**

- Refractive correction - astigmatism induced by corneal scar
- Penetrating keratoplasty:
- Corneal scar in visual axis
- Corneal decompensation
- Lens extraction: cataractous or subluxated lens

**Summary:**

Corneal bee stings with or without retained stinger, are rare causes of keratitis. Though it may present with violent clinical features, proper diagnosis and prompt management...
carries wonderful prognosis.

References:

Sonali Nagpure is working at Little Flower Hospital, Angamail.
Bilateral PION - A Case Report.

Introduction
Visual loss following general surgical procedures have been widely reported, the etiology being ischemic optic neuropathy. Both anterior and posterior ischemic optic neuropathy is described, the former being more common. This condition generally occurs in the perioperative period. We report a case of bilateral visual loss in a young male patient which occurred one month after a major cardiac surgical procedure. A brain MRI of the patient showed diffusion sequence restriction which confirmed the diagnosis of ischemic optic neuropathy.

CASE
A 48 year old male patient was referred to us with bilateral total loss of vision of 3 days duration. He apparently noticed decreased vision in the right eye on waking up in the morning which progressed to complete blindness by afternoon. The left eye was normal at that time but the next day similar loss of vision in the second eye. There was no history of transient visual obscuration or visual field defects prior. He gives history of DM of 5 years duration on treatment. He underwent cardiac bypass grafting with mitral valve repair surgery 1 month back. He was on Warfarin and antidiabetics. He was treated at a local hospital with intravenous methylprednisolone 1 gram iv for 3 days.

On examination the visual acuity was perception of light both eyes. The pupils were 5mm dilated and fixed. Rest of the anterior segment was within normal limits. Fundus examination was also normal. On the basis of clinical examination we made a provisional diagnosis of bilateral posterior ischemic optic neuropathy, possibly post surgical. The differential diagnosis we had in mind were bilateral ophthalmic artery occlusion, bilateral optic neuritis and bilateral occipital lobe infarction.

The patient underwent a FFA which showed normal A-V transit time. There was mild leakage from both the optic discs in the late frames. A brain MRI showed restricted diffusion from both the optic nerves suggestive of ischemia. MRA brain was normal. VEP showed inconsistent wave forms suggestive of bilateral optic pathway dysfunction. Routine blood and urine investigations were normal. With an ESR of 40mm / hour, ANA and CRP were non reactive. ECHO cardiogram showed left ventricular dysfunction.

Based on these findings we made a diagnosis of bilateral posterior ischemic optic neuropathy, possibly post surgical. In the followup period the vision improved to counting finger 1 metre and there was pallor of both optic discs.

Bilateral optic atrophy after PION
DISCUSSION

The incidence of post operative visual loss varies between 0.1 – 1.0 %, the cause being ischemia to the optic nerves. This manifests as anterior or posterior ischemic optic neuropathy. The term posterior ischemic optic neuropathy was first coined by Hayreh SS in 1981(15). This denotes ischemia to the retrobulbar optic nerve not supplied by the PCA. This is classified as arteritic (A-PION) ,non arteritic (NA-PION) and surgical( peri or post operative)3,4. The etiology of surgical PION is multifactorial . The main factors include severe and prolonged arterial hypotension, and hemodilution. This type of PION tends to cause bilateral massive vision loss and even complete blindness. The diagnosis of PION is one of exclusion based on normal fundus findings and no other ocular, orbital or neurological cause to explain the visual loss. Unlike NA-PION where spontaneous recovery and beneficial effect of systemic steroids is proven, the vision loss in surgical PION tends to be permanent and steroids are not effective5.

Patients generally experience vision loss as soon as they recover in the perioperative period. This patient had a rather delayed presentation. Hayreh SS has noted in one of his studies that a time lag of 2-3 weeks may occur2 .More over a brain MRI showed diffusion sequence restriction which classically occurs in ischemic stroke. We came across one similar case report describing diffusion restriction6.

REFERENCES


Dr Sandhya. A completed her DNB from Sankara Eye Centre, Coimbatore and Fellowship in Medical retina from Amrita Institute of Medical Sciences,Kochi. She is presently working for Comtrust Eye Hospital, Ottapalam.