



Smart-Eye

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Honourable Colleagues

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It gives me immense pleasure to bring out the first issue of EIZOC E-journal. In the last Executive meeting of the society at Tripura it was proposed by the honourable members to publish regularly an E Journal to bring forward the scientific talents that are in the members of the society. An annual journal is not suffice to meet the demands apart from being published at a considerable length of time.

This issue is a baby step. Our future articles shall be both more, both in numbers and category.

For any suggestions and feedback please feel free to communicate at editoreizoc@gmail.com.

Thanking You

Regards

Dr Sujoy Samanta

Editor.



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LATERAL TARSALE STRIP (LTS) COMBINED WITH LID EVERTING SUTURES FOR CORRECTION OF SENILE ENTROPION.

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Eyelid laxity combined with preseptal overriding of orbicularis oculi often leads to senile entropion. Various surgical procedures designed to correct this require unnecessary removal of central tarsal plate. It does not address the root cause of problem which is laxity of lateral canthal tendon. To correct this laxity, Anderson and Gordy designed the procedure of lateral tarsal strip.¹

The aim of our study is to evaluate the role of lateral tarsal strip procedure combined with lid everting sutures for correction of senile entropion.

Patients And Methods

Study Design

This is a retrospective, interventional study of patients who underwent LTS and lid everting sutures in the same sitting for senile entropion and who had completed 6 months follow-up. The demographic, clinical and operative data was analyzed. Detailed clinical examination was done in all the patients. Examination of the eyelids included evaluation of laxity - horizontal or vertical (medial canthal tendon laxity or lateral canthal tendon laxity), status of palpebral conjunctiva and lacrimal drainage system. Anatomical correction and functional reduction or relief from the main symptoms was considered as success. Exclusion criteria included follow-up duration of less than 6 months, previous lower eyelid blepharoplasty, previous conjunctival surgery other than chalazion removal, or cicatricial entropion.

Surgical Technique

Anesthesia: lidocaine 2% with epinephrine, 2-3 cc in

lateral canthal area and 2 cc for infraorbital nerve block.

Using straight artery forceps lateral canthus was crushed. Canthotomy was then performed using Stevens straight scissors. Inferior crux of lateral canthal tendon was located and cut for cantholysis. Protractors of lower lid attached to lower end of tarsal plate were cut 5 mm below lid margin. To make a strip of tarsal plate skin-orbicularis muscle and palpebral conjunctiva over the free part of tarsal plate were removed. Finally the conjunctiva over the lid margin was removed. Using 6-0 polyglactin sutures this strip was reattached to the periosteum over the lateral orbital rim at a higher position than previously. Skin and deeper layers were then closed using interrupted sutures.

Lid everting sutures were taken using 6-0 polyglactin (Vicryl). Sutures were passed from the conjunctival fornix and passed through sub-orbicularis plane to emerge just below lash line and tied. Three such sutures were taken. Mild ectropion at the end of surgery was aimed at.

Post operatively, oral antibiotics, NSAIDs, topical antibiotics and lubricants were prescribed. Skin sutures were removed on 7th day. Lid everting sutures were not removed.

Results

Fourteen eyelids of 10 patients were included in the study. All of the patients were males in the age group of 56 -80 years (mean age 66.16, SD + 5.9). Grade 3 entropion (lash touching eyeball in primary gaze) was noted in all the patients (100%). Symptoms of watering, redness and foreign body sensation were noted in 12 of 14 eyes (85.7%).

There was no intraoperative complication. No patient had postoperative eyelid retraction or scleral show, and there was no overcorrection or secondary ectropion in any of the patient.

One week after the surgery, all patients were free from symptoms of epiphora, redness and irritation (100%). Recurrence of entropion was not noted in any patient at the end of follow up.

Discussion

The tarsus forms the primary support or foundation for the eyelids. Although degeneration of the tarsus may promote eyelid laxity, the principle focus of weakness of the eyelids is at the lateral and medial canthal tendons.

Recurrence of entropion after various techniques is between 3.3 to 33%.^{2,3} With lateral tarsal strip alone the recurrence rate is 22%.² In a previously published study on combination of lateral tarsal strip and fornix sutures the recurrence rate was 1.6%.²

In our study recurrence was not noted in any patient and all of the symptomatic patients had resolution of symptoms.

The advantages of this procedure as felt by us were that

1. The surgery was directed to the site of pathology.
2. There was no disruption of meibomian gland function.
3. There was no notching of lid.
4. The surgery was simple.

The drawback of our study was that the follow up was limited to 6 months. Effort towards achieving longer follow up is ongoing.

Our study revealed that combination of lid everting sutures and lateral tarsal strip procedure was able to achieve 100% success rate both anatomically and symptomatically and hence it should be advocated for all cases of involutional entropion that are associated with eyelid laxity.

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Involutional entropion repair with fornix sutures and lateral tarsal strip procedure. Ophthal plast reconstr surg, 2001; 17(4):281-7.

3. Erb MH, Uzcategui N, Dresner SC. Efficacy and complications of the transconjunctival entropion repair for lower eyelid involutional entropion. Ophthalmology, 2006; 113(12): 2351-6.

Legend to Figures

Figure 1: Diagrammatic representation of surgical steps. A - Crushed lateral canthus. B - Lateral canthotomy using straight scissors.

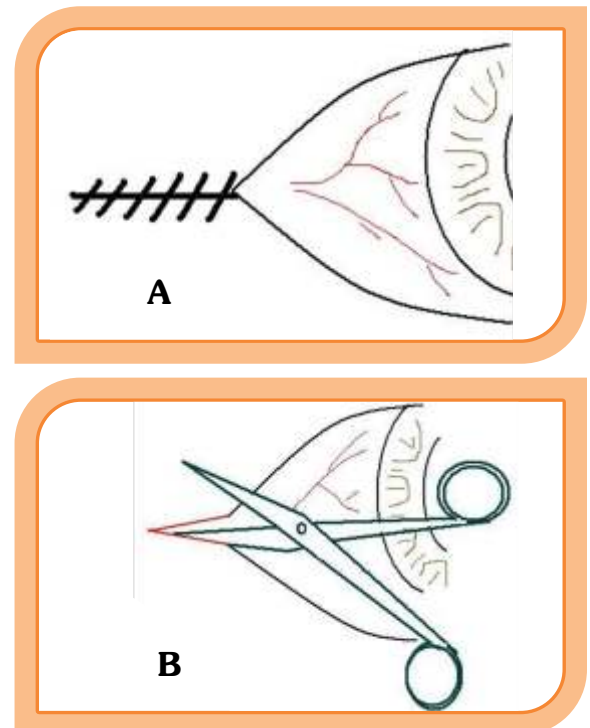
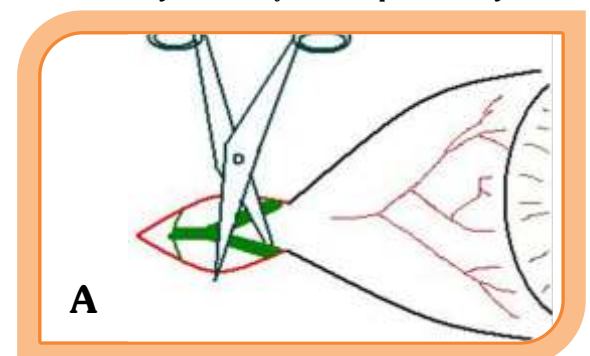


Figure 2: Diagrammatic representation of surgical steps. A - Cutting of lower crux of lateral canthal tendon. B - Fashioning a strip of tarsal plate by reflecting skin-orbicularis anteriorly and conjunctiva posteriorly.



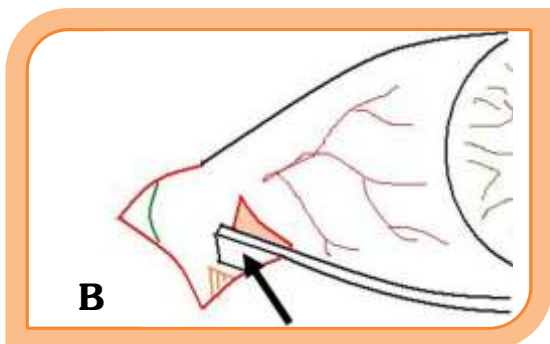


Figure 3: Diagrammatic representation of surgical steps. A - Passing 6-0 vicryl through periosteum over lateral orbital rim and through the lateral canthal tendon. B - Skin closure by interrupted sutures.

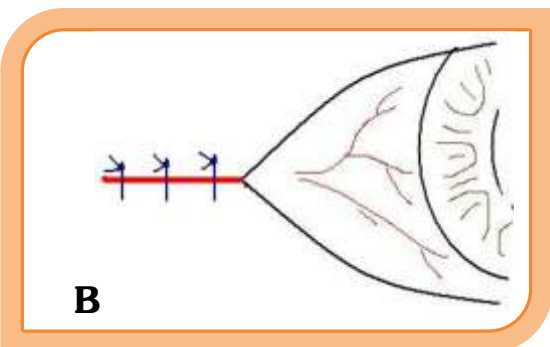
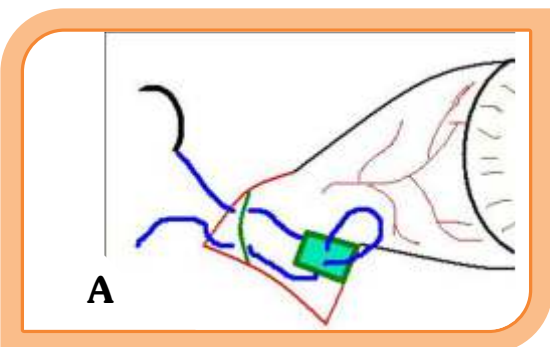


Figure 4: Preoperative photograph showing, A: - severe entropion of lower eyelid. B: - close up photograph of lower eyelid showing the totally hidden lashes.

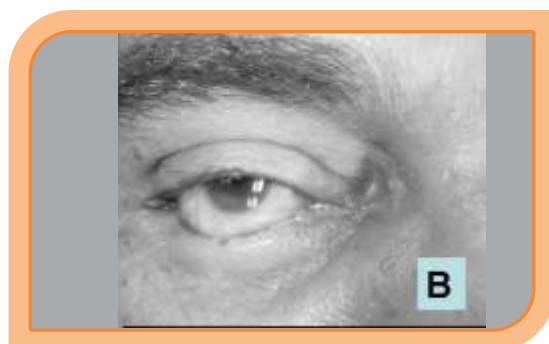
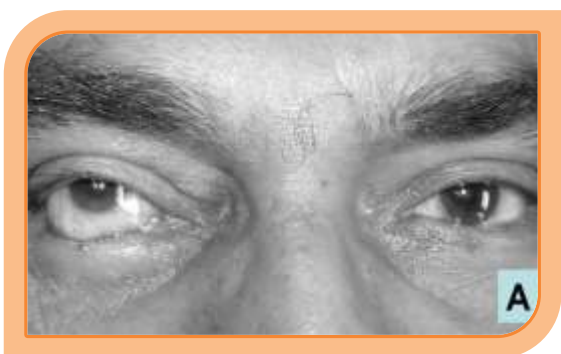
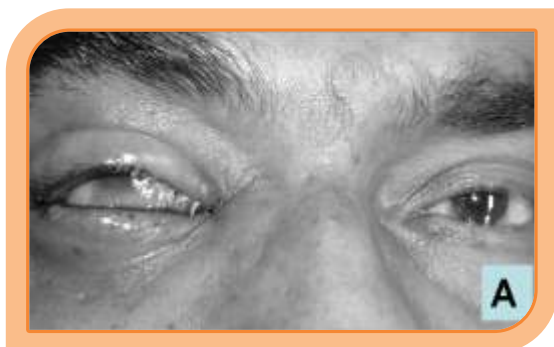


Figure 5: Postoperative photograph showing, A:- correction of the entropion. B: showing the barely visible incision site at lateral canthus.





RECENT ADVANCES IN GLAUCOMA PHARMACOTHERAPY

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ABSTRACT

Glaucoma is a chronic progressive heterogeneous group of neurodegenerative disease where both intraocular pressure (IOP) dependent and independent pathomechanisms lead to a irreversible optic neuropathy. Medical therapy is the first line of treatment in glaucoma management. Patient adherence and persistence to pharmacotherapy is a great barrier to its success because of the multiple factors including frequency of drop instillation with their different side effects. The field of glaucoma therapeutics has been advancing rapidly with an emphasis on compounds that are utilising the conventional aqueous outflow pathway through the trabecular meshwork (TM) and different novel drug delivery systems including gene therapy and stem cell therapy. Research is looking beyond IOP control to prevent or recovery the optic nerve and retinal ganglion cell (RGC) degeneration. This review highlights the recent advances in medical management of glaucoma.

Keywords: Glaucoma, Rho kinase inhibitor, gene therapy, stem cell therapy.

Background:

Glaucoma is a complex disease that requires lifelong individualised treatment. Though it is a multifactorial neurodegenerative disease, currently, the only known modifiable risk factor for glaucoma is intraocular pressure (IOP). Hence, it forms the mainstay target in contemporary glaucoma practice.[1] IOP reduction is considered as the primary efficacy endpoint in majority of the glaucoma clinical trials in the present day scenario. Maintaining functional vision and improving patient outcomes remains the goal in glaucoma therapeutics.

As a chronic and progressive disease, glaucoma poses a substantial burden to the health-care system. Management of glaucoma has direct medical costs (e.g, visits to providers, tests, medications, and surgery), direct non-medical costs (e.g, home health care, and transportation), and indirect costs (e.g, loss of productivity for both patient and caregiver). [2] So one unmet need is the challenge of adherence in patients receiving complex glaucoma treatment regimens.[3] Adherence is expected to be better for simple regimens.[4]

Most pharmacologic agents that lower IOP act by either reducing aqueous humor production or by increasing outflow / drainage of aqueous humor from the eye primarily through the uveoscleral pathway.[2,5] The trabecular meshwork tissue is diseased in glaucoma presenting increased resistance to aqueous outflow, and is therefore responsible for elevated IOP in POAG. [6,7] Current therapies do not target this conventional outflow pathway through TM (except miotics), leaving a potentially important modality for IOP reduction largely unused.[7]

So the search continues for drugs with novel mechanisms of action that could lead to better treatment, decreasing the need for multiple medications, thereby decreasing side effect profile and improving adherence and overall quality of life.

Aqueous Dynamics Review:

To understand new pharmacologic targets for IOP reduction, it is best to review normal aqueous humor dynamics. IOP is a complex homeostatic process, but it can be simplified by comparing the rate of aqueous humor formation inside the posterior chamber against the rate of aqueous humor exiting the anterior chamber.



Aqueous humor formation occurs in the ciliary epithelium lining the ciliary processes of the ciliary body and is created through a combination of passive diffusion and ultrafiltration, with the majority of aqueous derived from active secretion via selective transcellular movement of molecules mediated by protein transporters.[6] Once produced, aqueous makes its way from the posterior chamber to the anterior chamber and is traditionally believed to drain out of the eye through either the conventional pathway via the trabecular meshwork (TM) or the unconventional pathway via the uveoscleral route.[6]

Maintenance of stable IOP indicates adjustable control over inflow and outflow until compromised in the disease state.[8]

Outflow resistance has been classically associated with the juxtacanalicular portion of TM mediated through extracellular matrix, but resistance may also be mediated by the permeability of the endothelial cell lining of Schlemm's canal.[9,10]

Anatomically, the TM is comprised of a spongy connective tissue containing collagen and elastin fibers surrounded by endothelial-like trabecular cells, or trabeculocytes, which rest on a basement membrane. Cells of the TM have been reported to display smooth muscle-like properties including contractility, electromechanical characteristics, and expression of smooth muscle-specific actin and myosin, all of which may facilitate dynamic restructuring and result in disease as the cell population declines with age.[11,12]

Present strategies to slow the rate of glaucomatous progression all focus on lowering IOP, as other strategies such as neuroprotection have not met their clinical trial endpoints. At this time, IOP can be lowered by affecting inflow and outflow via pharmacologic agents (five current classes include prostaglandin analogs, beta-blockers, carbonic anhydrase inhibitors, sympathomimetics, and miotics), laser trabeculoplasty, and incisional surgery, which can be divided into standard filtration surgery or various newer minimally invasive procedures.[13-16] Among the topical medicines, only miotics, the cholinergic agonists (e.g, pilocarpine) indirectly targets aqueous humor draining through the trabecular meshwork / Schlemm's canal (the conventional outflow pathway). But cholinergic

agonists are not frequently used, as they may cause blurry vision and myopia and are subject to adherence challenges (they may be administered up to 4 times daily).[5,17,18] As a result, in practice, there is a lack of agents that target the conventional pathway.[17,18] Although several mechanisms for IOP-lowering are available, no treatment is available to repair or regenerate optic nerve damage in patients with glaucoma.

So current research is looking beyond lowering IOP, with a focus on protecting or regenerating the optic nerve, alongwith the novel targets to decrease inflow or increase outflow utilising both the conventional (through TM) and unconventional (through uveoscleral route) pathways.

Different Pharmacotherapies

- A. Topical medications
 - 1. Rho Kinase inhibitors
 - 2. Nitric Oxide donors
 - 3. Adenosine receptor agonists
 - 4. Prostanoid receptors agonists
 - 5. Small-interfering RNA
- B. Preservatives in topical formulations
- C. Neuroprotective medicines
- D. Drug delivery systems
- E. Gene therapy
- F. Stem cell therapy

Topical Formulations

Rho Kinase (ROCK) Inhibitors

The extracellular matrix (ECM) of the trabecular meshwork (TM) is composed of an intricate arrangement of fibronectin, laminin, proteoglycans, glycosaminoglycans, and matricellular proteins.[19] Trabecular meshwork and Schlemm canal (SC) endothelial cells have well-developed actin cytoskeletons. Cross-linked actin networks (CLANs) are found in glaucomatous TM cells and may contribute to increased outflow resistance.[20]

The Rho family consists of three small guanosine



triphosphate (GTP)-binding proteins (RhoA, RhoB, RhoC), which regulate aspects of cell shape, motility, proliferation, and apoptosis throughout the body.[21] On activation by binding to GTP, Rho activates its effector molecules (Rho kinase ROCK1 and 2), which signal downstream molecules to polymerize actin fibers.[22,23] In humans, ROCK1 and ROCK2 tend to be expressed in the majority of tissues, including human TM and ciliary muscle cells.[24] ROCKs (Rho-associated coiled-coil forming protein kinase) are serine/threonine kinases that regulate smooth muscle contraction.[25]

ROCK inhibitors act as selective inhibitors of the actin cytoskeleton contractile tone of smooth muscle in the trabecular meshwork. This results in increased aqueous outflow directly through the conventional pathway (TM), thereby lowering IOP.[26]

There are also animal studies indicating that ROCK inhibitors may improve optic nerve head blood supply, increase ganglion cell survival, and reduce scarring, serving in bleb modulation in glaucoma surgery.[27]

Ripasudil (K-115, Kowa Ltd, Nagoya, Japan) is the first Rho kinase inhibitor which has been approved in Japan since 2014 for ocular hypertension (OHT) and glaucoma therapy. Nearly 0.4% of drug is to be used as a twice daily application.[27,28] The drug displayed a favorable safety profile, and 50% of enrolled patients had only mild conjunctival hyperemia in Phase I and II of a clinical trial.[29,30]

Netarsudil (Rhopressa 0.02% ophthalmic solution; Aerie Pharmaceuticals Durham, NC), formerly known as AR-13324, is a once-daily dual inhibitor of ROCK and norepinephrine transporters (NET). Inhibition of NET provides persistent stimulation of β_2 -adrenergic receptors. It facilitates uveoscleral outflow in addition to the trabecular outflow and decreases the episcleral venous pressure and aqueous humor production by ciliary body.[31,32] Recent preclinical studies have also shown that netarsudil could have an antifibrotic effect on the TM.[32] Rhopressa was granted US Food and Drug Administration (FDA) approval on December 18, 2017.[33]

Roclatan, fixed-dose combinations of netarsudil 0.02% with latanoprost 0.005% for once daily night dosing, is in Phase III clinical trial.[34] In a 28-day study, once-

daily Roclatan provided greater IOP reductions than its individual components at the same concentrations.[33]

Although ROCK inhibitors seem very promising in the preliminary trials, many candidates have failed previously, as their selective inhibitory action is highly dose dependent. At higher concentrations, they tend to show unintended cross-reactivity with other protein kinase pathways, resulting in multitude of systemic side effects.[26]

Nitric Oxide Donors

There is increasing evidence that nitric oxide (NO) is a direct regulator of IOP and that dysfunction of the NO-Guanylate Cyclase (GC) pathway is associated with glaucoma incidence. NO has shown promise as a novel therapeutic with targeted effects that: 1) lower IOP; 2) increase ocular blood flow; and 3) confer neuroprotection.[35] Nitric oxide is an endogenous signaling molecule with a wide range of physiological functions including its well-known role as a mediator of smooth muscle relaxation and vasodilation. Generation of NO by nitric oxide synthases (NOS) leads to activation of soluble guanylate cyclase (sGC), resulting in increased levels of cyclic guanosine monophosphate (cGMP) and activation of protein kinase G. Resulting effects on cyclic nucleotide gated channels, protein kinases, and other molecules lead to actin cytoskeletal rearrangement and thus cell relaxation culminating in physiological outcomes.[36] In patients with POAG, markers for NO are decreased in aqueous humor, suggesting lower NO levels may contribute to increased IOP.[36] So Nitric oxide (NO) decreases IOP via relaxation of the TM and decreases in TM cell volume, reducing outflow resistance.[37,38,39] Nitric oxide also plays a role in the assembly and disassembly of inter-endothelial adherens junctions, which affects endothelial permeability.[40] Compounds that augment the NO signaling pathway or liberate NO, significantly enhance conventional outflow in rabbits, pigs, monkeys, and humans.[18,40,41]

Latanoprostene bunod 0.024% (BOL-303259 or LBN) is the first NO donating prostaglandin F₂ agonist that is metabolized in situ to latanoprost acid and butanediol mono-nitrate, an NO donating moiety. It combines 2 mechanisms and 2 targets into 1 molecule. It acts



through 2 distinct mechanisms of action to reduce IOP. It directly targets both aqueous humor outflow pathways, facilitating outflow through the trabecular meshwork / Schlemm's canal (via NO) and through the uveoscleral pathway (via latanoprost acid).[32,42]

In a phase 3 clinical trial, APOLLO, once daily LBN 0.024% provided more significant IOP reductions than twice daily timolol maleate 0.5% throughout the course of a 3-month long treatment ($P < 0.002$).[43] VOYAGER, LUNAR, JUPITAR studies have also proved the efficacy and safety of LBN.[44,45,46] Latanoprostene bunod (Vyzulta, Bausch and Lomb, Rochester, NY) was approved by the FDA on December 18, 2017.[32]

NCX 470 is an NO donating bimatoprost analog scheduled for a phase 2 study beginning in 2018 and lasting 1 year. In 3 preclinical models of glaucoma, NCX 470 seemed to be well-tolerated and more effective than equimolar bimatoprost in lowering IOP.[47]

NCX 667 (Nicox) is another NO donor shown to reduce IOP while being well-tolerated in both normotensive rabbits and laser-induced ocular hypertensive cynomolgus monkeys.[48]

Adenosine Receptor Agonists

Adenosine receptor agonists stimulate secretion of matrix metalloproteinases (MMPs) in the endothelial cells lining the trabecular meshwork. This causes cell volume shrinkage and extracellular matrix remodeling, which ultimately facilitates conventional aqueous outflow.[49]

Trabodenoson (INO-8875; Inotek) is a highly selective adenosine A1 receptor agonist that engenders an upregulation of protease A and matrix metalloproteinase-2 (MMP-2) in target cells. The proteases digest and remove hydrolyzed collagen type IV, a major component of the resistive ECM in the TM.[50,51,52] Treatment with trabodenoson does not affect the rate of aqueous humor production.[50] Phase II trials demonstrated a median IOP reduction of $6.5 \text{ mmHg} \pm 2.5$ (standard deviation) mmHg at 500 mcg dose twice daily by day 28 of trial. It demonstrated a favorable safety profile including an unremarkable electrocardiogram and the conjunctival hyperemias produced were generally mild and transient.[53] In its

first phase 3 trial, MATrX-1, trabodenoson failed to achieve its primary endpoint of superiority in IOP reduction compared with timolol.[54]

Can-Fite Biopharma (CF-101) is an adenosine receptor A3 agonist. Its IOP lowering effect was discovered during a clinical trial regarding dry eye syndrome. The safety and efficacy of orally administered CF-101 in patients with elevated IOP and primary open-angle glaucoma (POAG) is currently in Phase II trial stage.[55]

Prostanoid Receptors Agonists

Currently available prostaglandin analogs (PGAs) enhance aqueous outflow through the uveoscleral pathway and cause IOP lowering. Latanoprost and travoprost, act on prostanoid prostaglandin F receptor (FP receptor), a receptor for Prostaglandin F2 alpha (PGF2?). Bimatoprost is a synthetic PGF2? ethanolamide mimetic, termed prostamide F2?.

Other prostaglandin analogs (PGAs) currently in development, target the prostaglandin EP2 and EP4 receptors. Agonist sensitive EP receptors are present in TM cells and SC cells. EP1 and EP3 receptor activation increase cell stiffness, whereas EP2 and EP4 agonists dose-dependently decrease cell stiffness.[32] As TM and SC from glaucomatous eyes are stiffer than age-matched normal controls, EP2 and EP4 agonists became candidates for IOP lowering via decreasing cell stiffness and enhancing of outflow through the conventional drainage pathway.[56]

The selective EP4 receptor agonist 3,7-dithia-PGE1 reduced IOP and total outflow resistance in monkeys without affecting uveoscleral outflow or aqueous flow, indicating that the reduced total outflow resistance represented enhanced trabecular outflow.[56]

Omidenepag isopropyl (DE-117, Santen Pharmaceuticals) is an EP2 receptor agonist. In its phase 2a trials, the 0.002% dosage proved more effective than latanoprost 0.005% at week 1 and provided similar reduction in IOP to latanoprost through week 4. Conjunctival hyperemia, episcleral hyperemia, mild and transient photophobia, and eye pain were reported in 14.3% of patients in the trial, with no adverse events reported in the control eyes.[57] It



got its first global approval on 21 September, 2018 in Japan for use in open angle glaucoma and ocular hypertension.[58]

Sepetaprost (DE-126, Santen Pharmaceuticals), currently in phase 2b clinical trials, is an FP and EP3 receptor dual agonist. In a phase 2 clinical trial conducted to compare the safety, tolerability, and mean IOP reduction effects of sepetaprost versus latanoprost, sepetaprost achieved a greater reduction in mean diurnal IOP compared with latanoprost (7.2 mm Hg versus 6.6 mm Hg).[59]

Small-interfering RNA

Small interfering RNA (siRNA) functions through pairing with specific mRNA sequences and results in the mRNA's degradation. It is a potential therapeutic approach for many diseases caused by altered gene expression.

Bamosiran (SYL040012) (Sylentis, Spain) is a naked double-stranded small-interfering RNA. It acts through specific gene silencing and causes beta-2 adrenergic receptor blockade, thereby decreasing aqueous production by the ciliary body. Due to its preferential distribution in the ciliary body cells, undesirable beta-receptor blockade in bronchioles and alveoli is limited.[60]

Studies wherein the drug has been administered as a single dose or multiple divided doses of 600 mcg/ml/day, over 1 week period, with the contralateral eye serving as control, have demonstrated a favorable safety profile.[61]

Recent advances in preservatives in topical formulation

Most of the anti-glaucoma topical formulations cause ocular surface disorder either directly due to its inherent property or indirectly through the preservative, mostly benzalkonium chloride (BAK). This may ultimately cause problem with drug adherence and patients' compliance with therapy.

Reducing the frequency of instillations, with the use of fixed-dose combinations, can help improve tolerance, as it is a dose dependent toxicity.[62]

Purite which is a stabilized oxychloro complex (SOC), was introduced in the search of a less toxic preservative. It has a broad-spectrum antimicrobial activity even at

low concentrations (0.005%). Studies have shown that decreasing brimonidine concentration from 0.2% to 0.15% and replacing BAK with SOC improve drug tolerance, especially in irritated eyes.[63]

SofZia, another less toxic preservative, is an ionic buffer composed of boric acid, propylene glycol, sorbitol, and zinc chloride. It has been introduced as an alternative to BAK (0.015%) in some formulations of travoprost (Travatan Z, Alcon laboratories, Texas).[64] But it has shown limited effectiveness against *Staphylococcus aureus*. [65]

There are many preservative free single-dose unit preparations of different beta-blockers, pilocarpine, and prostaglandin analog tafluprost, available in the market. But these are less cost effective and have an increased risk of contamination.[66]

Timolol has become available in a new multi-dose drug dispensing container without preservative (TIMO-COMOD). This was realized by a built-in micropump. [67]

Neuroprotective Anti-glaucoma Advances

Glaucoma is a multifactorial optic neuropathy where IOP is one modifiable risk factor. But despite IOP control, visual field progression and RGC loss can happen. Thus emanates the need to find mechanisms and drugs that retard neuronal apoptosis and degeneration. Current research and clinical trials in neuroprotection are faced with many challenges. The slow progressive nature of the disease, variable worsening rates in different patients, outcome measure variability (mostly functional testing), and the need to test the new agent in patients who already have their IOP lowered attribute to the obstacles which one faces while designing these trials. An optimum way to distinguish change attributable to IOP lowering and that due to neuroprotection also remains unclear.[26,68]

Memantine is a selective N-methyl-d-aspartate receptor antagonist with a potential to prevent glutamate-induced excitotoxicity of RGCs. A randomized double-masked placebo-controlled clinical trial which was studying the neuroprotective effects of memantine failed to meet its primary endpoint. [69,70]

Low-pressure glaucoma treatment study, a randomized trial comparing the efficacy of 0.2%



brimonidine tartrate with 0.5% timolol maleate in preserving visual function in patients with low-pressure glaucoma, has suggested neuroprotective effect of brimonidine.[71]

Drug Delivery Systems

Nanoparticle on a scale 10-1000 nm serves as vehicles for drug delivery. They are bioinert, biodegradable, and mucoadhesive polymers which aid corneal penetration of the drug. Studies of carbonic anhydrase inhibitors, brimonidine, pilocarpine, using this delivery system has shown better drug permeability and stability compared to their commercially available counterparts.[72]

Silicone hydrogel soft contact lenses loaded with nanoparticles containing timolol, increasing the bioavailability potential by 50%, have been found to elute the drug for more than a month in animal models.[73] One big drawback while using hydrogels is that the drug elutes very quickly from the highly hydrated polymer networks as most IOP-lowering medications are water soluble.[26]

For patients with poor adherence to topical drop management and those with limited access to an ophthalmologist, drug delivery implants that provide sustained IOP management hold promise. The bimatoprost ring (Allergan) is a device that rests on the surface of the eye, under the eyelids, and releases bimatoprost for up to 6 months. Adverse events were consistent with bimatoprost exposure, and no unexpected ocular adverse events were observed. The ring was kept in place without clinician assistance in 88.5% of patients at 6 months.[74] Also in development by Allergan is a bimatoprost sustained-release (SR) biodegradable, intracameral implant (Bimatoprost SR, Allergan, Irvine, USA), currently in a phase 3 trial. Studies are needed to evaluate if this SR intracameral prostaglandin analog administration will increase the risk of endophthalmitis, uveitis, and cystoid macular edema.[75]

iDose (Glaukos) is another sustained release travoprost intra-ocular implant at the phase 2 clinical trial stage. To implant, the device is passed across the anterior chamber, and the anchor portion is advanced through the TM into scleral tissue where it is designed to elute therapeutic levels of medication for extended periods of time.[76]

The topical ophthalmic drug delivery device (TODDD) (Amorphex Therapeutics) is a soft, flexible device that floats on the tear film, completely concealed under the eyelid. It can be easily replaced by patients themselves and has the potential for carrying not only IOP management drugs, but also treatment for ocular allergies and other ocular disorders. The TODDD loaded with timolol has completed phase 2a clinical trials, where it demonstrated safety, comfort, retention, and uninterrupted efficacy in reducing IOP for 180 days.[77]

Gene Therapy in Glaucoma

The goal of gene therapy is to reprogram target cells to up-or downregulate a biochemical/physiological process by up - or downregulating production of a specific substance within specific cells.[78] Advances in the comprehension of the genetic basis of glaucoma have provided scope for the use of targeted gene therapy. Both viral and nonviral vectors are used to deliver genes to target tissue of interest such as trabecular meshwork, ciliary epithelium, ciliary body, and RGC. Gene therapy can be used to delete, replace/inactivate an aberrant gene, or introduce a new gene which helps in targeted therapeutic protein expression.[26]

There are adenoviral (AdV), adeno-associated viral (AAV), self-complementary adeno-associated viral (scAAV), herpes simplex viral (HSV), and retroviral vectors (RV) for genetic therapy, each having pros and cons depending on their properties and on the target tissue.[79,80]

Nonviral gene delivery, such as through naked small interfering RNAs (Si-RNA), can suppress targets in human TM cells.[81] Nanoparticles can provide noninvasive gene delivery to ocular tissues at greater efficacy than naked DNA.[82] Advantages of non-viral gene delivery include low immunogenicity, low mutagenicity, and a large capacity for packaging, but transfection is transient and inefficient. [83]

The rhoA and rho kinase pathway may be an effective target for gene therapy. This pathway modulates the actin cytoskeleton, cell adhesive interactions, ECM formation, and TM actomyosin contraction.[84]



Stem Cell Therapy

The goal of stem cell therapy is to replace or regenerate damaged and dead tissue. Trabecular meshwork and JCT cell counts are lower in medically untreated POAG eyes than in age-matched normals and decrease with age in both at essentially the same rate.[85 - 87] Thus, the resistance and consequential IOP increase are both greater in POAG eyes. Differentiated induced pluripotent stem cells (iPSCs) grown in TM cell culture medium could repopulate the cell depletion model. When transplanted, the TM-medium conditioned iPSCs became similar to TM cells in morphology and expression patterns, leading to the restoration of IOP homeostatic function.[88] In the future, iPSCs developed from patient-specific skin fibroblasts to avoid immune rejection phenomena could be a treatment option for older patients with more advanced glaucoma.

Conclusion

Research in glaucoma pharmacotherapy is continuously evolving for discovery of novel therapeutics with great mechanisms of action, with less side-effects that will increase patients' compliance and adherence to the treatment. In recent times, a galore of promising options exists for the development in glaucoma medical therapy. But the treating ophthalmologist need to plan a individualised approach depending on the type of glaucoma, underlying mechanisms, genetic make-up, comorbid conditions, and rate of progression.

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Conflicts of Interest

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ETIOLOGY & OUTCOME OF OPEN GLOBE OCULAR INJURIES

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ABSTRACT

Ocular open globe injuries are often disabling for both the victim and society, as most of these eyes may remain unsalvageable. Many initial variables have been identified which can help in predicting the final visual outcome in these eyes. Also, various prognostic tools have been validated by previous studies. This article aims to review all these factors.

Key words: ocular trauma, open globe injury, ocular trauma score

Introduction

Ocular injury is a frequent and often preventable cause of visual impairment. Although it comprises of only 2% of all ocular injuries, it accounts for over half a million cases of monocular blindness worldwide. In 1998, World Health Organization estimated the global incidence of open globe injuries (OGIs) to be 3.5 per 100,000 persons per year.

The primary aim in managing these eyes is to restore the structural integrity of the globe at the earliest by primary repair. For eyes that are beyond repair, a primary enucleation may be considered. In spite of improved micro-surgical facilities available now-a-days, the prognosis of most of these eyes remain grim.

Definitions of Ocular Trauma

Penetrating injury: Full-thickness corneo-scleral wound with no exit wound

Perforating injury: Full-thickness corneo-scleral wound with an exit wound

Intra-ocular foreign body (IOFB): Foreign object retained within the globe

Mechanisms of Injury

Various mechanisms of injury have been identified by

previous authors. In most of the articles, a sharp object (projectile objects eg. glass) has been reported to be the most common cause of injury, others being wooden/metal stick injuries, fist injury, pellet, fall etc.

There is a significantly higher incidence of OGIs in males, suggesting either more aggressive behavior or involvement in higher risk indoor and outdoor activities. Also, a correlation has been observed between the place of injury and gender. Street and work place related injuries are more common in males, where-as home-related injuries are seen more in females. The most common place of injury in pediatric age group is school.

Haavisto et al reported that, 36% of eye injuries caused by Pellet guns resulted in permanent impairment. In November 2016, American academy of Ophthalmology also recommended five safety tips to avoid toy related eye injuries.

In their study, Gupta et al found that injuries were more prevalent in pre-school and school age group, most of injuries occurred at home, majority of domestic injuries were caused by assault, wound size in accidental injuries was less as compared to those with assaults and no case of Sympathetic ophthalmitis was reported during follow-up.

Variables Affecting Final Visual Outcome

Previous studies have reported several preoperative factors associated with visual outcome of surgical repair in



OGIs, most significant being the presence or absence of RAPD, presenting VA, and size of wound. Other variables include: age, location of wound, lens damage, vitreous hemorrhage (VH), retinal detachment (RD), and presence of intraocular foreign body (IOFB). The outcome is significantly worse if the RAPD is present at the initial examination. Previous studies have shown that the presenting VA of less than 6/60 has significantly worse outcome as compared with an initial VA of more than 6/60.

Agarwal et al in their study reported an association of hyphema and adnexal injuries with poor visual outcome, however reports by Rahman et al and Agarwal et al did not corroborate this. Studies by Groessl et al, Pieramici et al, Rahman et al, and Williams et al have shown that visual outcome in cases where only single initial procedure was required is significantly better than those requiring more than one procedure.

Post traumatic endophthalmitis is most important complication of OGIs associated with worse final vision. Its incidence ranges from 4.9% to 54.2%. RD is also a major complication in OGIs, associated with worse visual outcome.

Ocular Trauma Score (OTS) and CART Model

Various systems have been reported to predict final visual outcome on the basis of pre identified presenting factors. In 2002, ocular trauma score (OTS) developed by Kuhn et al from eye injury registry. They listed initial poor VA, rupture, endophthalmitis, perforations, RD and APD as factors negatively affecting the final VA. OTS scores range from 1 (most severe injury and worst prognosis at 6 months follow-up) to 5 (least severe injury and least poor prognosis at 6 months). Each score is associated with a range of predicted post-injury visual acuities. It has a predictive accuracy of approximately 80%, which means that the OTS will be accurate 4 out of 5 times.

In 2008, Schmidt et al developed Classification And Regression Tree (CART) model to prospectively validate the VA prognosis in OGIs. Gupta et al found this useful in predicting the final visual outcome based on some initial factors. Scott R, Shah et al, and Unver et al reported usefulness of OTS in prognosticating final visual outcome in different types of ocular injuries. Wai Man et al reported that OTS has high prognostic accuracy to predict final visual outcome. However,

Calculation of the OTS

Initial Visual Factor	Raw Points
A. Initial Visual acuity category	NLP = 60 LP to HM = 70 1/200 to 19/200 = 80 20/200 to 20/50 = 90 ≥ 20/40 = 100
B. Globe Rupture	-23
C. Endophthalmitis	-17
D. Perforating Injury	-14
E. Retinal Detachment	-11
F. Afferent Pupillary Defect	-10

Probability of Visual Outcome

Raw Score Sum	OTS-Score Category	NLP %	LP/HM %	1/200-19/200 %	20/200-20/50 (%)	≥ 20/40 (%)
0-44	1	73	17	7	2	1
45-65	2	28	26	18	13	15
66-80	3	2	11	15	28	44
81-91	4	1	2	2	21	74
92-100	5	0	1	2	5	92

HM, hand movements; LP, light perception; NLP, No light perception; OTS, Ocular Trauma Score.

Knippers et al reported that both the OTS and CART models are accurate predictors of visual acuity outcomes after open globe injury.

Conclusion

Open globe injury present with management dilemmas to an ophthalmologist. The visual prognosis of such eyes is often difficult to assess. The OTS may help them in this regard. The initial visual acuity can be useful for non- ophthalmologists to help predict the final visual prognosis in OGIs.

Conflicts of interest: There are no conflicts of interest



PEARLS FOR MANAGEMENT OF OCULAR SURFACE DISORDER

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The most common patients a comprehensive ophthalmologist will likely take care of in his or her practice are those with ocular surface disease, including dry eyes and blepharitis. Proper management of these patients often depends on identifying the primary problems and addressing all the contributing factors.

Here are a few tips for making the proper diagnosis and treatment in patients with ocular surface disease:

1. Proper History taking : The patient's history can often help you make the proper diagnosis and, in turn, direct the proper management.

For instance, itching, in the inner canthal area, is almost always a sign of allergic disease. Likewise, it is well known that patients whose symptoms are predominantly due to aqueous tear deficiency will often have foreign body sensation, which is worse later in the day. Conversely, patients with predominantly meibomian gland disease are typically worse in the morning.

Fluctuating vision with worsening visual acuity after visually intensive activities is virtually diagnostic of an inadequate tear film.

2. Examine the patient before looking behind the slit lamp. To look for signs of rosacea, how frequently the patient blinks, as well as his or her eyelid positions. Lower lid laxity and floppy eyelid is often overlooked as the etiology of chronic surface disease.

3. Check corneal sensation. A neurotrophic cornea can be both the cause and the consequence of chronic ocular surface disease. Patients who are neurotrophic will typically demonstrate significant ocular surface staining but minimal symptoms. It is often overlooked as the etiology of dry eyes in longstanding diabetic patients. Punctal occlusion is a very effective first-line treatment for these patients.

4. Use vital dye staining : Fluorescein is the most

common dye to look for staining on the cornea. However, Rose Bengal and Lissamine Green are actually more sensitive than fluorescein and can be used to diagnose dry eye disease at an earlier stage by looking for staining in the conjunctiva with white light.

5. Zone of staining. Fluorescein staining that is more prominent in the superior cornea (which is typically covered by the upper eyelid) is almost never just due to dry eyes. Staining from dry eyes typically affects the interpalpebral zone. Therefore, one should have a high index of suspicion in patients whose staining is more prominent superiorly.

Upper eyelid should be everted to check for floppiness and/or changes on the palpebral conjunctiva. Likewise, superior limbic keratoconjunctivitis should be considered by checking for staining and redundancy of the superior conjunctiva.

Contact lens-induced limbal stem cell deficiency will typically present with staining in a whorl pattern starting in the superior cornea and limbus.

6. Emphasize and provide clear instructions on lid hygiene. As we are pressed for time, there is a tendency to jump to medical therapies without adequately emphasizing or instructing patients with blepharitis on lid hygiene. One strategy that is helpful is to make an illustrated handout that clearly demonstrates and explains your preferred technique.

7. Early use of anti-inflammatory therapy. Inflammation plays a role in every form of ocular surface disease. In patients with obvious signs of inflammation, it is best to begin anti-inflammatory therapy early such as a short course of mild steroid such as loteprednol and start topical cyclosporine drops concomitantly.

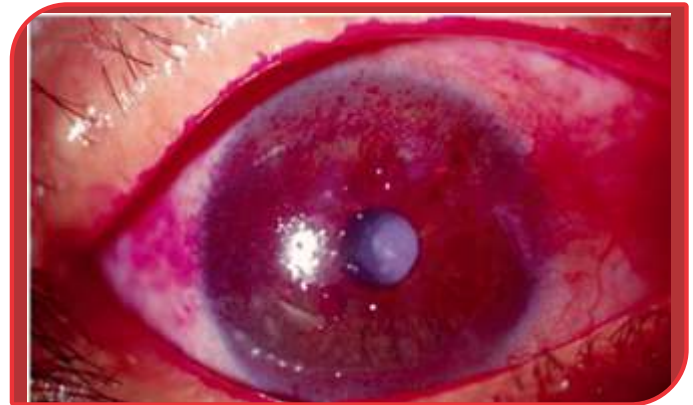
Punctal occlusion in the presence of inflammation will often exacerbate the patient's signs and symptoms in the

short run, given that it will keep more inflammatory mediators on the ocular surface. Therefore, it is better to control the inflammation first.

8. Minimize preservative toxicity. Patients with ocular surface disease are much more sensitive to preservatives, particularly benzalkonium chloride (BAK). In addition to using non-preserved topical lubricants, when prescribing antibiotics, steroids or glaucoma medications, preservative free preparations are preferred.

9. Use tetracycline based drugs at lower doses. There is enough evidence to indicate that medications such as doxycycline can be effective for the management of meibomian gland disease at a lower dose. Although more expensive, doxycycline can be prescribed at 20 mg twice a day. If not affordable to the patient, then 50 mg twice a day generic version is also an option.

10. Manage patient expectations and be persistent. Obviously, ocular surface diseases such as dry eyes and blepharitis are chronic conditions that, at best, can be controlled but rarely cured. Managing patient expectations is critical, given the tendency for patients to expect immediate improvement.



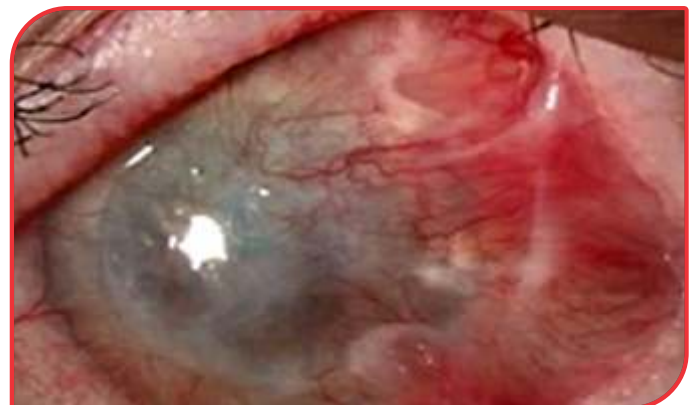
Rose Bengal Staining in Severe Dry Eye



Superficial Punctate Keratitis



Yellow Horner Trantas dots



Stevens-Johnson Syndrome



CLINICO-SOCIAL STUDY OF LOW VISION AID TREATMENT AND ITS BENEFITS IN IMPROVING QUALITY OF LIFE AMONG PATIENTS IN PATNA

Dr. Ashwini

1. Introduction:

2. Aim

3. Material and methods:

- Places: Mahavir Netralayakankarbagh Patna and Renu Eye Center (Dr Pranav Ranjan Clinic) Boring Road Patna
- Patients: 36 patients with low vision
- Period: Dec 2018 to April 2019
- History, Clinical examination and relevant lab investigation
- Process: Visual acuity : Snellens chart for distance; Near vision chart, Colour vision with ishihara charts, ocular movements, Slit lamp examination;
- Newer instruments: Mono-ocular and Binocular telescopes for distance vision; and for near vision- Hand held magnifiers, illuminated and non-illuminated, pocket magnifiers, dome magnifiers, half eye magnifiers, cutaways
- Treatment: Different kinds of magnifiers were given for visual correction and improvement, M training for the patients with peripheral vision loss, Notex to recognize currency

4. Result: Most patients were satisfied;

Problems	Numbers
Retinitis Pigmentosa	3
Coloboma	1
Nystagmus	4
Staghart disease	6
Corneal opacity	4
Diabetic retinopathy	4
Ambylopia	1
Psuedophakia	3
Galucoma	3
High Myopia	3
Center Serous Retinopathy	4
Total:	36



Improvement in Visual Acuity:

- PL-PR to 6/60 - 8
 - Counting fingers to 6/60- 6
 - Counting fingers to 6/36- 3;
 - Counting fingers to 6/18: 3
 - 6/60 to 6/36 -9
 - No improvement: 4
 - Total:
 - Improvement in quality of life: reading newspaper, doing home and office work, 1 child able to read black board and give exams, improvement in walking independently through M training, handling money, improvement in household and cooking chores, including cutting vegetables, identifying spices and condiments.
- 5. Conclusion:** Proper diagnosis, treatment and rehabilitation helps in improving vision as well as quality of life. The management of low vision needs both visual correction and rehabilitation which may take several months of practice at home and in daily life.
- 6. Discussion:** Low vision correction is a worthwhile investment of time and resources
- 7. References**

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