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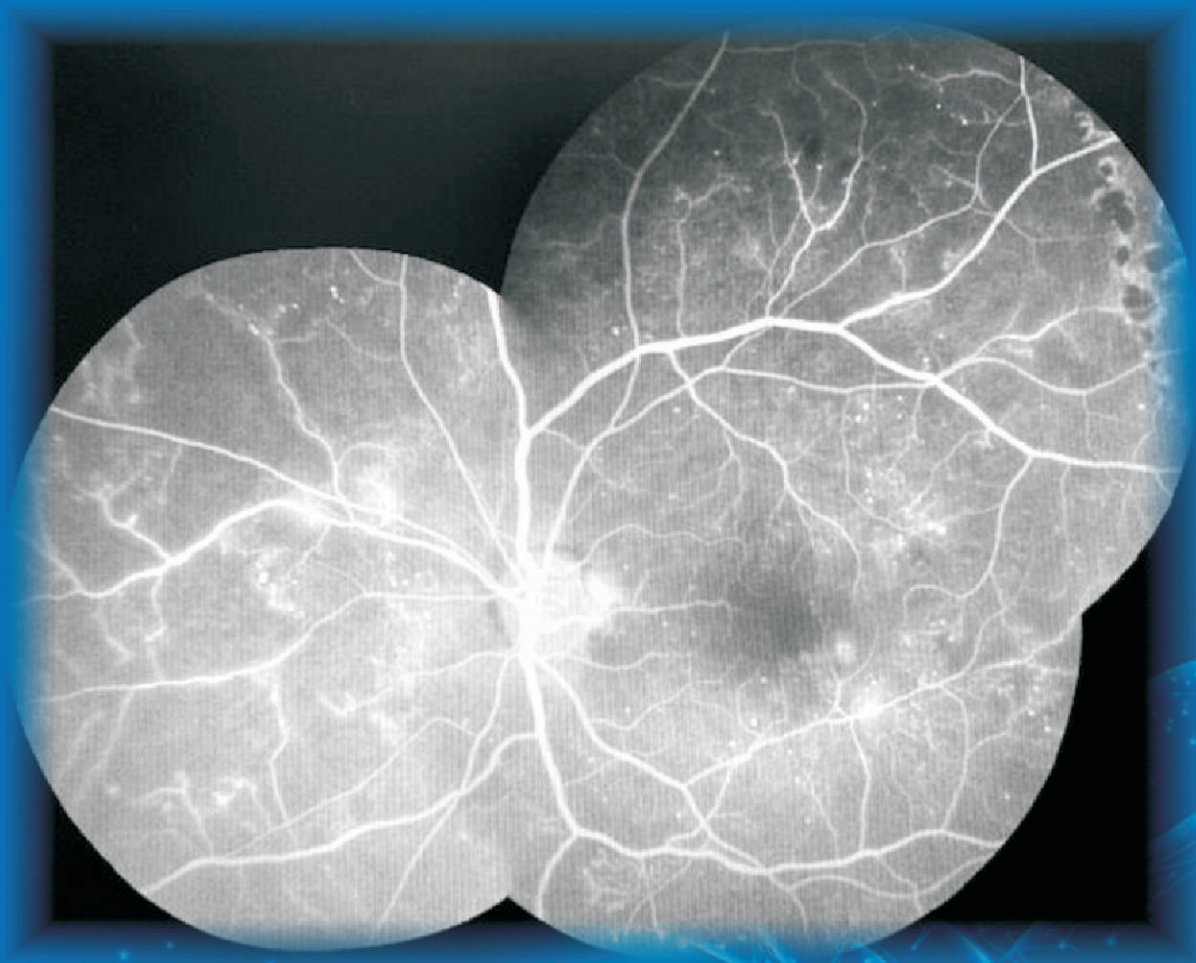

The Scientific Journal of U.P. Ophthalmological Society

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Cover Photo

Superficial plexus in BRVO (OCTA)

Courtesy : Dr Mohit Khattri, Kanpur

"It is not the strongest of species that survived,nor the most intelligent, but the ones most responsive to change"

-Charles Darwin

The above words of wisdom and worldly fact is befitting for the world of ophthalmology and the people involved in revolutionizing working and treatment methods since Ophthalmology has been a very dynamically developing branch.

I am grateful to be able to interact with all the exceptional professionals through this medium and I wish to share some of my thoughts with all of you.Members of our society have made a lot of progress in clinical and academic fields in the regional, national, and international scene. But reality is that much more progress is necessary to remain at par with the contemporary world of ophthalmology.

The recent mushrooming of private medical colleges is encouraging but also worrisome in context of the commercial viewpoint and substandard services both in terms of teaching and treatment. The ophthalmology branch being a high-tech branch requiring regular upgradations. The department is mostly under equipped. hence the central medical governing bodies should adopt a stricter approach before granting permission to such institutions.

The covid 19 pandemic has severely burdened health services to the patients but more so patients with ophthalmic diseases requiring regular follow up and evaluation and it was highly unfortunate that many patients turned blind due to unavailability of access to ophthalmic services.

It should be of utmost importance on the part of our ruling government to prioritize and actively promote sanctioning of economic,infrastructural, and human resources for purpose of establishment of eye care facilities for preventable blindness specially eye banking and corneal transplantation, so that the incidence of preventable blindness can be reduced in our country.

Another major concern is the increment of diabetes worldwide and in our own country. International diabetes federation report 2017 estimated 425 million diabetics in the world which is expected to increase to 629 million by the year of 2045. And every fifth diabetic will be Indian making India diabetic capital of world. As perNational diabetes and Diabetic Retinopathy survey 2015-2019 among population aged ≥ 50 years,Prevalence of diabetic retinopathy (DR) among diabetics is 16.9%, diabetic maculopathy7.0%, sight threatening DR 3.6%.Given these alarming rates it should be a major concern for the policy makers of our country to propose diabetic control measures,easy access to medications and ophthalmic fundus screening for early detection and laser for treatment of diabetic retinopathies.

Key issues of present day are reaching out to our young friends, familiarizing with the amazing, advanced technology and unprecedented explosion of information and knowledge. And our society must keep ourselves updated with this world of evolving health care facilities.

Wishing you all a fruitful reading experience.

Dr. Shrikant, MS
President, UPSOS
Former Professor & Head, Regional Institute of Ophthalmology
Institute of Medical Science BHU, Varanasi
Presently Prof. & Head Department of Ophthalmology
Heritage Institute of Medical Sciences, Varanasi

Sanctity of Research

Dear Friends,

Research is the search for knowledge/new information / innovation without any prejudices and with an open mind meant to bring a change in presently available knowledge in the subject. It is to be performed in all spheres of life for upliftment of current practice and methodologies and to peep into oblivion. The ultimate goal is to comes out with pearls and ideas to promote and incorporate the new invention for the welfare of mankind.

The research is cultivated with deep thoughts, in depth knowledge, meticulous planning and brain storming sessions to find out theses imperative question:

1. What am I looking for?
2. What's my goal to achieve?
3. How will this research help us?
4. Am I ethical in my work?
5. Am I principally correct while working on it?

The research in present scenario is questionable and the criterion under which the works are being done are unjustified. When we look around and see in the society a sense prevails that the sanctity of research is in danger.

So, What went wrong?

1. We hardly thrive about the purpose of research.
2. Unethical practices and malpractice dominate.
3. Manipulatory data and methodologies destroy the facts.
4. People become impatient to get quick results biased as per their thoughts.
5. The sponsors of the study might dominate on the results
6. Ethical clearance and proper consent lacking
7. Worst scenario are due to fake news in media just for the sake of gaining name and fame.

People don't aim at publishing in indexed journals rather fake news and trivial work done without any evidence find space in media which is highlighted as per the stature and contacts of the individuals that is put in a way to sensationalize resulting to impact the masses.

Is it not the high time to introspect?

Should we not peep into our soul and stir our conscience to find out the facts?

Should we not take the pen in our own hands rather than mouse doing the cut, copy and paste job?

Presenting the new edition of the journal in front of you with aim of presenting the real subject by various researchers of repute. Thanks to President Dr Shrikant, Secretary DrMohita Sharma, CSC Dr

Deepak Mishra and whole editorial board along with executive body members for their constant support.

Wishing you safe and healthy new year 2022.

Dr Shalini Mohan

MBBS (Gold Medalist), MS, DNB, MNAMS, FCGP

Editor, UP Journal of Ophthalmology

Associate Professor of Ophthalmology

Chief Glaucoma, Cornea Services & Eye bank, GSVM Medical College, Kanpur (UP)

Central Zone Incharge : Glaucoma Society of India

Ex Senior Resident Dr. R.P. Centre, AIIMS, New Delhi

Ex Consultant, Sir Ganga Ram Hospital, New Delhi.

Good News

As per the Guidelines on Safe Ophthalmology Practices in Covid-19 Scenario issued on 28th December 2020 by Ministry of Health and Family Welfare, Government of India,

'Collection/retrieval of eye balls/Corneas from home settings is allowed with all precautions being taken to prevent spread of infection to retrieval technicians and to the recipient of corneas. Corneas may be utilised for therapeutic as well as optical purposes'

The document can be accessed on following link:

https://aios.us5.list-manage.com/track/click?u=5b1666c401fa04c2eac1d0763&id=88f9574df7&e=5403adef5e

The staff manning these entry points should ensure appropriate personal protection as entailed in guidelines already issued. (available at:

https://www.mohfw.gov.in/pdf/AdditionalguidelinesonrationaluseofPersonalProtectiveEquipmentsettingapproachforHealthfunctionariesworkinginnonCOVIDareas.pdf

In case of a suspect or confirmed case in the premises, the protocols for attending to suspect or confirmed case and disinfection available at:

https://www.mohfw.gov.in/pdf/GuidelinesonpreventivemeasurestocontainspreadofCOVID1 9inworkplacesettings.pdf

Dear all

Welcome to post COVID era !! In an era where almost everything came to a standstill the UP Journal of Ophthalmology continued to come out and impart scientific knowledge to all its members. This journal signified that life can never stop and scientific upgradation is a continuous process.

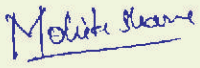
Now that we are back to the era of physical exchange of knowledge, the importance of journal becomes even more as the changing times brought in new types of diseases which need solutions. In this journal these have been well covered in the gorm of articlrs on mental health (a very important challenge in currebt times) and on mucormycosis (something which took us by surprise and needed a brushing up of our current knowledge and new insights into the management of this disease.

Some chronic diseases like glaucoma and diabetic retinopathy were ignored during the epidemic times due to less hospital visits. These need special attention now and the review on glaucoma in this journal well covers that.

As a State society UPSOS is committed to imparting scientific knowledge. On behalf of the whole executive committee my Congratulations to the editor Dr Shalini Mohan and the editorial team for theit continued efforts on this front.

The lockdown and less work during COVID times initiated some new studies from our state. Literature also shows increase in number of good publications. Let us take this initiation phase into acceleration phase and promote more scientific writing and research activities in our State for more academic upgradation.

Stay safe, stay healthy and stay updated in your knowledge



Dr Mohita Sharma

General Secretary, UPSOS

Rajesh Sinha , MD, DNB, FIACLE, FRCS
Professor of Ophthalmology Cornea, Lens and Refractive Surgery Services
Dr R. P. Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi
e-mail : sinharaj1@gmail.com

Dear Friends,

It gives me immense pleasure to write the Guest Editorial for this issue of the UP journal of Ophthalmology and I feel truly honoured. The effort that is being done in this direction is truly commendable and this journal will definitely fulfil its job of disseminating the up-to-date knowledge in the field of ophthalmology.

As I could figure out, this journal has some of the best articles that can be published for the benefit of the readers. The original article involves a burning topic which every cornea surgeon would love to read and update his information regarding the role of anti-VEGF in tackling corneal neovascularization to prevent the occurrence of corneal graft rejection and improve graft survival. The role of anti-VEGF in corneal neovascularization is truly controversial and it is essential to understand the benefits and limitations of ant-VEGF in this direction. In this issue we have a couple of wonderful review articles which provide insight towards systemic health in general that can have an impact on eye health. Glaucoma is a silent killer which can have relationship with systemic diseases and also with the medications needed to treat these systemic conditions. It is also very essential to emphasize the need to understand the mental health and psychology of a patient reporting to an ophthalmologist. This is again not only essential to understand the seriousness of the disorder in such patients but also to enhance the drug compliance and to improve the efficacy of treatment. Rho kinase inhibitors are becoming popular these days not only to improve the corneal endothelial function but also to enhance the efficacy of treatment of glaucoma. Earlier it was not available in Indian market but of late the Indian pharmaceutical companies have started manufacturing this drug and it is a very good addition to our armamentarium.

The COVID pandemic and the Mucor mycosis resulting due to this had a huge impact on the well being of the mankind. Things are improving now and we hope that it will keep on improving so that the year 2022 brings relief for everyone.

The ophthalmic fraternity has been badly affected by the pandemic but in spite of all these, the academic activities have continued online to update each other with the latest in our subjects. This journal is also a great step in this direction and I am sure that the efforts made by the editorial team led by the Editor Dr Shalini Mohan will be of great value in the betterment of scientific knowledge amongst our peers thereby improving the quality of patient care.

I congratulate the whole team of UP state Ophthalmological Society for the excellent work that they are doing and wish all the members a very safe, healthy, prosperous and happy 2022.

Best regards

Rajesh Sinha
Hon. Secretary, ISCKRS
Professor of Ophthalmology
Dr R. P. Centre for Ophthalmic Sciences, AIIMS, New Delhi

Ten Years of Intravitreal Bevacizumab : Systemic and Ocular Safety Review at Tertiary Care Centre.

Sanjeev Gupta, MS

Professor, Department of Ophthalmology, KGMU Lucknow, UP, India

Introduction :

The first Anti-VEGF which was approved and available for clinical use was Bevacizumab, which was first marketed in 2004 for treatment of colon carcinoma.[1] Later it was realized that this treatment improved the wet Age Related Macular Degeneration (ARMD) in those who had both the diseases and thus systemic Bevacizumab was used for some time for the treatment of wet ARMD.[2] Soon after, ophthalmologists began injecting bevacizumab directly into the vitreous cavity as an off-label use in the treatment of wet AMD.[3] Since then intravitreal Bevacizumab has been used in various other retinal disorders and is now as an established treatment option for wet ARMD, macular edema due to retinal vein occlusion, diabetic retinopathy, uveitis and other diseases. [4]

Safety of intravitreal Bevacizumab has been challenged as it has not passed the rigorous approval process of USFDA for use as an intravitreal injection for the treatment of retinal diseases. However numerous case series and clinical trials over the period of time have established its safety as an intravitreal injection except for few adverse events as reported in literature.[5] Bevacizumab may continue to be a choice for patients and ophthalmologists in coming future because of being equally safe, effective and very cost effective than the contemporary molecules in spite of being "Unlicenced" for ophthalmic use till the exorbitant prices of the "Approved" anti-VEGF molecules are brought down at par to the dosing of Bevacizumab.[6]

Here we are reporting the retrospective analysis of safety of intravitreal anti-VEGF in cases which received intravitreal Bevacizumab for various indications in our institute during the course of 10 years.

Materials and Methods :

Medical records of consecutive subjects who had received intravitreal anti-VEGF during last 10 years for various indications and had completed at least6 weeks of post intervention follow up were retrieved and analysed for the adverse events and comorbid conditions. The institutional ethical committee was intimated for the same and the confidentiality of the subjects was maintained as per the declaration of Helsinki.

As per the protocol, the subjects who require intravitreal anti-VEGF were registered for the day care procedure and the procedure was done in an operation room under aseptic conditions. A fresh vial of Bevacizumab (Inj. Avastin®100mg/4 ml) was utilized for all the subjects planned on a single day and the injection was withdrawn separately for each subject using an insulin syringe with 30g needle. The subjects receivedo.05ml injection Bevacizumab (25mg/ml) + 0.05ml injection Dexamethasone (4mg/ml) under topical anesthesia with aseptic precautions after paracentesis (approximately 0.1ml) done through a self-sealing needle track at the limbus. After all the subjects planned for that day had received the injection, the vial was discarded. The subjects were prescribed eye drop moxifloxacin 4 times a day starting immediately after the procedure as no eye patching was done. The subjects were evaluate on day 1, 14, and at 6 weeks for the therapeutic benefits and any adverse events.

The variables retrieved and included in the study included the demographic details, clinical details regarding the eye condition and the systemic comorbidities as mentioned in the table

1. The details of adverse events post intervention were retrieved for a period of follow up till 6 weeks. The adverse events related to eye conditions were grouped as expected/mild (Non sight threatening) and severe (Sight threatening).

Results :

The average age of the 773 subjects included in the study was 53.1 years (Range 0.1-91 years, Median 55, SD 15.4) and there were 227 (29.4%) female vs 546 (70.6%) males. The premorbid conditions which were seen in the available records are described in the.

The majority of premorbid systemic condition werediabetes mellitus, hypertension and insomnia. Ocular comorbidity was seen in form of cataract in 271 (35.00%) subjects. There were 175 (22.7%) individuals with history of tobacco use in any form past or present.

Looking at the indications of the intravitreal anti-VEGF the most common was diabetic retinopathy (NPDR, n=183, 23.67% and PDR, n=171, 22.12%). The indication in NPDR was macular edema as seen on Optical Coherence Tomography and in PDR it was a preparatory step when proceeding for pars plana vitrectomy. This procedure was done in 115 (14.87%) and 93 (12.3%) subjects for retinal vein occlusion associated macular edema and wet ARMD respectively. Three eyes of neonates with ROP received intravitreal anti-VEGF for aggressive posterior ROP and rigidity of the pupils.

Table 1

Summary of demographics and baseline characteristics of the study population (n=22).								
Characteristic	Value							773
Age (years)	77 (61-90)		53.1 (0.1-91)	55	15.4			
Females	15 (68.2)		227					
Tobacco usea								
Never used tobacco		8	281	36.36364				
Ever used tobacco		2	70	9.090909				
Current tobacco user		3	105	13.63636				
Information not available		9	316	40.90909				
			773					
Medical history								
Cataract		20	271	35.00				
Arterial hypertension			217	28.07				
Insomnia		6	211	27.27				
Hypercholesterolemia		5	176	22.73				
Prostatic benign hyperplasia		5	176	22.73				
Hypothyroidism		5	176	22.73				
Arrhythmia		4	141	18.18				
Diabetes mellitus			554	71.67				
Right bundle branch block		3	105	13.64				
Depression		3	105	13.64				

There was total 337 adverse events noted in the study population over the observation period of 6 weeks which transforms to 47.34 events per 100 injections. Out of these adverse events 315 were of non-serious nature and 51 were sight threatening .

The most common AE was conjunctival haemorrhage which resolved in 2-week time with no added intervention. The serious and sight threatening AE were endophthalmitis (n=2, 0.25%) and cataract formation (n=21, 2.7%). The two cases which had endophthalmitis were with deranged renal functions and were on haemodialysis. The subjects with post injection cataract formation were supposedly needle injury to the crystalline lens during the intravitreal injection or paracentesis.

Discussion :

The purpose of the analysis was to evaluate and report the adverse events associated with the intravitreal Bevacizumab

Eye disease for which Anti-VEGF was given	n	(%)
Age Related Macular Degeneration	93	12.03
Branch Retinal Vein Occlusion	91	11.77
Capillary hemangioma of optic nerve head withmacular edema	3	0.39
Central retinal vein occlusion	24	3.10
Central serous chorioretinopathy	9	1.16
Eale's Disease	91	11.77
Macular edema	40	5.17
Non-proliferative diabetic retinopathy	183	23.67
Neovascular glaucoma	11	1.42
Pars Planitis	15	1.94
proliferative diabetic retinopathy	171	22.12
Pseudophakic CME	3	0.39
Retinopathy of Prematurity	3	0.39
subretinal neovascular membrane	24	3.10
Toxiplasmosis SRNVM	9	1.16
Traumatic subretinal bleed	3	0.39

wherein the drug was aspirated from a fresh single vial using multiple punctures on a single day.

Injection bevacizumab is commonly used by ophthalmologists widely over the world as acost-effective substitute to "Approved" anti-VEGF molecules. This practice will continue till the "approved" molecules are available at a comparable price,unfortunately this does not appear to be a possibility in coming future. Thus, it is of importance to investigate and innovate safe practices for use of multidose vials to keep this affordable and effective option available for patients. This

Table 2 : Adverse events as seen in the subjects included in the study

Outcome	Frequency	AE rate per 100 injections
Total	366	47.34799483
seriousness category		
Non sight threatning	315	40.75032342
Sight threatning	51	6.59767141
Eye inflammation/Endophthalmitis	2	0.258732212
Conjunctival hemorrhage	182.428	23.6
Conjunctival hyperemia	34.785	4.5
Eye pain	27.828	3.6
Conjunctivitis	20.871	2.7
Cataract/nuclear cataractc	20.871	2.7
Ocular hypertension	13.914	1.8
Systemic reactions	0	0
Hypertension	20.871	2.7
Headache	13.914	1.8

requirement is even more relevant for a country like India as majority of individuals have to afford the treatment out of their pocket as less than 20% population has insurance cover.[7]

Bevacizumab as an intravitreal injection to treat retinal diseases got a setback in 2016 when the Drug Controller General India issued an advisory, banning the use of Bevacizumab (inj. Avastin) as intravitreal injection after reports of few cases of eye infection following its use appeared. Though this ban was revoked 2 months after a committee recommended that there is enough evidence that this drug is very useful and cost effective when compared to the "approved"drugs.[8] A guideline has been published by the joint committee of AIOS and VRSI indicating the management of DME. Since then, the ophthalmologists are less keen to use Bevacizumab for their patients because of the apprehension of being on the wrong side of the law.[8]

Our study has looked at the adverse effects as seen up to 6 weeks after the intravitreal injection of Bevacizumab 1.25 mg in a large subset of patients with a wide age spectrum and indications. Though we have not evaluated the efficacy of this procedure as there is enough conclusive evidence (over 2500 publications) and hence that was not the immediate need. However, the outcomes of our study demonstrate that the multidose vial of Bevacizumab can be used safely in multiple subjects with adverse events attributable mainly to the injection technique rather than the use of single source for multiple subjects. There were two cases of endophthalmitis (incidence rate of 0.25 per 100 injections) in subjects who were having compromised renal functions and were on haemodialysis, which itself has been reported to be a risk for endophthalmitis with[10] or without concurrent intraocular procedure.[11] Thus, the cause of endophthalmitis may not be the injection itself. There was an accelerated cataract formation in 21 subjects (incidence rate of 2.1 per 100 injections) within 6 weeks of the injection and this commonly occurs due to direct needle injury to the crystalline lens and cannot be attributed to the multidose vial use.

Thus, the present study shows that a single vial of injection Bevacizumab (Injection Avastin, 100mg/4ml) can be used in more than 1 patient on a single day and multiple punctures using aseptic technique and the practice is safe. Further comparative prospective studies may be conducted for head-to-head comparison of multidose vial vs single dose vials of available biosimilars so that the cost effectiveness of the multidose vial is available for future patients and ophthalmologists do not have any hesitation with support of robust scientific evidence supporting this practice.

References :

1. Cohen MH, Gootenberg J, Keegan P, Pazdur R (March 2007). "FDA drug approval summary: bevacizumab plus FOLFOX4 as second-line treatment of colorectal cancer". The Oncologist. 12 (3): 356–61.
2. Moshfeghi AA, Rosenfeld PJ, Puliafito CA, Michels S, Marcus EN, Lenchus JD, Venkatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration:

twenty-four-week results of an uncontrolled open-label clinical study. Ophthalmology. 2006 Nov;113(11):2002.e1-12.
3. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. Ophthalmic Surg Lasers Imaging. 2005 Jul-Aug;36(4):331-5.
4. Afarid M, SadegiSarvestani A, Rahat F, Azimi A. Intravitreal Injection of Bevacizumab: Review of our previous Experience. Iran J Pharm Res. 2018;17(3):1093-1098.
5. Van der Reis MI, La Heij EC, De Jong-Hesse Y, Ringens PJ, Hendrikse F, Schouten JS. A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections. Retina. 2011 Sep;31(8):1449-69.
6. Raftery J, Clegg A, Jones J, Tan SC, Lotery A. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness. Br J Ophthalmol. 2007;91(9):1244-1246.
7. Chandwani, Rajesh. (2021). Stakeholders in the Indian Healthcare Sector. Vikalpa: The Journal for Decision Makers. 46. 65-70.
8. Narayanan, Raja Commentary, Indian Journal of Ophthalmology: June 2020 - Volume 68 - Issue 6 - p 1102
9. http://www.aios-scientificcommittee.org/wp-content/uploads/2020/02/AIOS-Guidelines-on-DME_10-02-2020.pdf
10. Smith KG, Ihle BU, Heriot WJ, Becker GJ. Metastatic endophthalmitis in dialysis patients. Am J Nephrol. 1995;15(1):78-81.
11. Kim SH, Yu MH, Lee JH, Kim SW, Rah SH. Endophthalmitis after Cataract Surgery in Korea: A Nationwide Study Evaluating Incidence and Risk Factors in a Korean Population. Yonsei Med J. 2019 May;60(5):467-473.

Safety Outcomes of Brolucizumab in Neovascular Age-Related Macular Degeneration Results from the IRIS Registry and Komodo Healthcare Map

Arshad M. Khanani, MD, MA[1,2]; Marco A. Zarbin, MD, PhD[3]; Mark R. Barakat, MD[4]; et al Thomas A. Albini, MD[5]; Peter K. Kaiser, MD[6]; Guru prasad B, MBBS, MD[7]; Neetu Agashivala, B Pharmacy, MS[7]; Justin S. Yu, Pharm D, MS[7]; Charles C. Wykoff, MD, PhD[8,9]; Mathew W. MacCumber, MD, PhD[10,11]

Author Affiliations Article Information

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Key Points

Question What are the incidence rates and risk factors for intraocular inflammation (IOI) and/or retinal vascular occlusion (RO) after brolucizumab treatment for neovascular age-related macular degeneration (AMD) in clinical practice?

Findings In this cohort study of patient eyes with neovascular AMD treated with brolucizumab, the incidence rate for any form of IOI and/or RO was approximately 2.4%. A history of IOI and/or RO was a key risk factor for IOI and/or RO after brolucizumab treatment initiation.

Meaning These early findings explore potential risk factors for inflammation-associated adverse events that may occur following real-world treatment with brolucizumab.

Specular Microscopy for General Ophthalmologists

Aakash Sharma, MS; **Mohit Khattri,** MS
Regency Hospital, Kanpur

Abstract :

Specular microscopy, invented in the later half of the 20th century, has regained gained importance as an essential diagnostic tool for prognosticating the outcome after phaco emulsification and at times even plays a crucial role in deciding which procedure to choose.

Keywords :

Specular microscopy, endothelium, cataract, phaco emulsification

Specular in Latin means having the properties of a mirror. David Maurice invented the specular microscope in 1968, the principles of which are utilized in modern clinical microscopes. In 2001, Eye Bank Association of America adopted endothelial cell density as a medical standard, and specular microscopy gained popularity. It is due to the difference between refractive indices of endothelial cells and aqueous humor that 0.22% of the incident light is reflected.[1]

Figure1: Representative image of a specular microscope

Specular microscopy is a non-invasive photographic technique that provides a high magnification view of light reflected from the endothelium. According to the orientation, machines can be horizontal-for clinical use or upright for ex-vivo corneal bank use. Furthermore, clinical microscopes can be contact or non-contact. In contact microscopes, due to applanation, the corneal surface is flattened, and hence a more magnified image is obtained since the surface area of the specular reflex depends on the curvature of the reflecting surface. The non- contact ones use auto-focussing [Examples: Konan Noncon Robo (Konan Medical, Japan), CEM-530 (Nidek, Japan), Tomey EM-3000 and EM-4000 (Tomey, United States), Topcon SP-2000P and Topcon SP-3000P (Topcon Corp, United States)]. There are various methods for analysing a specular image, but irrespective of those, accuracy depends mainly on the quality of the image obtained.

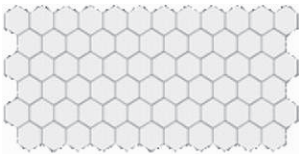


Figure 2a: Normal Endothelial Cell Density (ECD)

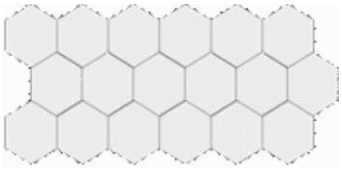


Figure 2b: Low ECD

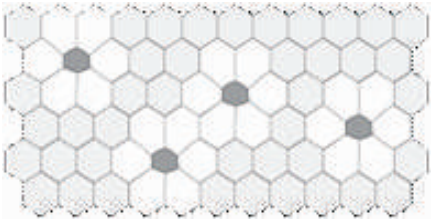


Figure 2c : Polymegathism

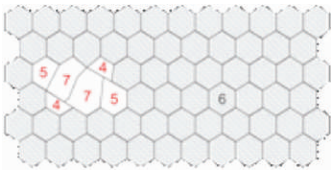


Figure 2d : Pleomorphism

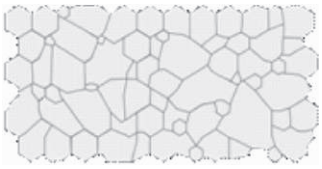


Figure 2e : Normal ECD with Polymegathism and Pleomorphism

(https://www.konanmedical.com/cellchek/specular-fundamentals)

Endothelial Cell Density **(ECD)** or Cell Density **(CD)** reduces with age due to physiological increase in corneal dimensions

and senescence. Normally it is around 5000-6000 cells/mm^2 at birth, but gradually reduces to around 3500 cells/mm^2 by the age of 5 years, 3000 cells/mm^2 in the late teens and 2500 cells/mm^2 in late adulthood. The average cell size is 150-350 µm^2 depicted by **AVG** in the report. [2]

Normal endothelial cells are hexagonal. The endothelial monolayer of cells is arrested in the G1 phase and do not regenerate. Thus, to cover for cell loss, they increase in size; this is known as **polymegathism** and is measured by the coefficient of variance (**CV**). CV is the most sensitive indicator for endothelial dysfunction, and normally it is less than 0.30. Normally the percentage of hexagonal cells is more than 60%; however, a deviation of cells from their hexagonal morphology above this level is termed as **pleomorphism** depicted by **'6A'** in the report.

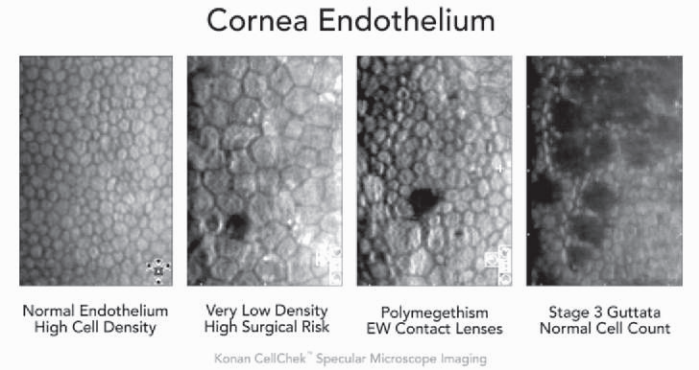


Figure 3 : Corneal endothelium in health and disease

Applications :

1. Early diagnosis of Fuch's Endothelial Dystrophy.
2. In certain eyes before cataract surgery
   a) Previous trauma
   b) Pseudoexfoliation
   c) Recurrent uveitis
   d) Corneal edema in contralateral eye
   e) Clear graft with operable cataract
   f) Glaucomatous eye with cataract
   g) Subluxated lens, choosing the IOL
   I) Posterior polymorphous dystrophy (PPMD)
   i) ICE syndrome,
   j) Congenital glaucoma
3. Evaluation of donor endothelium
4. Contact lenses and phakic IOLs

It is helpful for endothelial disorders- primary or secondary

Customization of the Cataract Surgery in a patient with low endothelial count-

A standard phacoemulsification procedure with controlled fluidics has a very low risk for endothelial damage in patients with soft cataracts, typical anterior chamber depth, and few guttata with no other corneal abnormalities. However, if the nucleus is hard and endothelial cell count is low, then prechopping, ultrasound-sparing techniques (femtosecond laser-assisted, Akahoshi pre-chop, ultrachop,[3] etc.) should be used. Also, during quadrant removal, dispersive OVD injection should be repeated every three to five units of effective phacoemulsification time.[4,5] Zero-ultrasound techniques such as extra capsular cataract extraction or manual small incision cataract surgery should be considered in the cases with very low endothelial cell count, especially avoiding contact between the nucleus and the endothelium, as it can damage the compromised endothelium as normal phacoemulsification.

Viscodynamic extraction is another zero-ultrasound technique that can be used. It involves a sclero-corneal tunnel, small nucleus fragmentation using any method (femtosecond laser,[6] ultrachopper or Akahoshi prechopper), and subsequent fragment removal through the sclerocorneal wound. At the same time, dispersive viscoelastic is injected liberally into the anterior chamber to push the fragments out of the eye. In patients with corneal decompensation, the surgeon should consider a triple procedure with posterior lamella keratoplasty technique of choice.

Discussing the risk with the patient-

In today's litigious society, in a patient with poor endothelium, it is imperative to preoperativelydiscuss the risk of pseudophakic bullous keratopathy andsubsequent vision reduction even after successful cataract surgery to avoid any future conflicts. However, documented specular microscopy findings can easily turn the tables in the surgeon's favour even when conflicts arise.

References :

1. Laing RA, Sandstorm MM, Leibowitz HM. Clinical specular microscopy. I. Optical principles. Arch Ophthalmol1979;97:1714-9.
2. Dawson DG, Geroski DH, Edelhauser HF. Corneal endothelium:Structure and function in health and disease. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea. 3rd ed. Mosby: Elsevier Health Sciences. 2010. p. 57-70.
3. Galvis V, Tello A, Escaf LJ, Rojas V, Cortez MA. Phaco prechopping as an option in high-volume cataract services. Tech Ophthalmol2007;5:1:1-7.
4. Arshinoff SA. Dispersive-cohesive viscoelastic soft shell technique. J Cataract Refract Surg1999;25:2:167-73.
5. Tarnawska D, Wylegata E. Effectiveness of the soft-shell technique in patients with Fuchs' endothelial dystrophy. J cataract Refract Surg2007;33:1907-1912.
6. Conrad-Hengerer I, Al Juburi M, Schultz T, et al. Corneal endothelial cell loss and corneal thickness in conventional compared with femtosecond laser-assisted cataract surgery: Three-month follow-up. J Cataract Refract Surg 2013:39:1307.
7. Juan G. Gaviria, Luis Escaf, Juanita Londoño, Luz M. Melo. Surgery 101: Managing Endothelial Risk. www.reviewofophthalmology.com

Subconjunctival Injection of Bevacizumabfor Corneal Neovascularization after Penetrating Keratoplasty, A Prospective, Open Label,Non-comparitive Study

Shefali Mazumdar, MS; **S.K.Satsangi,** MS; **Sushma Chaurasia,** MS
Department Of Ophthalmology, S.N.Medical College, Agra
Correspondence e-mail : shefalimazumdar@gmail.com

Abstract :

Objectives : To evaluate the efficacy of sub conjunctival Anti-VEGF Bevacizumab in post keratoplasty corneal neo vascularization in terms of graft survival.

Study design : Prospective ,open label Non-comparitive study.

Participants : A total of 17 eyes of 17 post PK patients with more than two quadrant corneal neo vascularization were administered 3 doses of 2.5 mg/0.1ml of sub conjunctival Bevacizumab each at monthly intervals, starting from first dose been given on day of enrollment and followed up for a minimum period of 6 months.

Outcomes : Primary outcomes:

- Reduction in the number of segments involved
- Change in the number of preexisting corneal vessels crossing Graft-Host Junction.

Secondary outcomes : Effect on Graft clarity, CCT, visual acuity and side effects related to drug.

Results : From baseline visit to the last follow up visit, the mean reduction in the number of vascularised corneal segments was 47% in patients having 4 quadrant (13-16 segments) CoNV and 75% in patients having 3 quadrants(9-12 segments) CoNV. In 35% patients all corneal vessels crossing graft host junction receded. Out of 17 cases,11 patients had Graft clarity of +4 ,at the end of 6th month follow up.(p=0.0017significant) and 13 patients (76.47%) were with a central corneal thickness less than 600 micrometer (. p=0.0005 significant). Visual acuity showed no significant change. No local/ systemic adverse reaction was reported during the study period.

Conclusion : Sub conjunctival Bevacizumab was found to be effective as adjuvant in Post Penetrating Keratoplasty Corneal neo vascularization. Drug is well tolerated in most of the patients without any local or systemic side effects.

Key Words : CoNV (Corneal neo vascularization), Bevacizumab, CCT(central corneal thickness), GHJ (graft host junction)

Introduction :

Keratoplasty (corneal transplantation) is a surgical procedure in which the diseased cornea is replaced with a healthy donor cornea. Being an immunologically privileged structure, Corneal Transplantation is considered as the most common and successful form of human solid tissue transplantation.[1,2] Corneal neo vascularization is an adverse factor for the success of Penetrating Keratroplasty, with the survival rates been less than 50% even with local and systemic immunosuppression.[3]

Depending on the number of quadrants involved, Corneal Neo vascularization may be classified into low risk(1 quadrant),medium risk (2 quadrant), or high risk (more than 2 quadrant).[4]

Current treatment modalities for treating CoNV include medications, such as steroids or non-steroidal anti-inflammatory agents, laser photo coagulation, fine-needle diathermy, photo dynamic therapy or restoration of the ocular surface with the use of conjunctival, limbal, or amniotic membrane transplantation. These have demonstrated variable and largely limited clinical success.[5,6] Furthermore, none of these treatments specifically target the molecular mediators of angiogenesis.

Role of anti-vegf in corneal vascularization :

VEGF is a member of a family of proteins, which include VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor. Among these, VEGF-A isoforms have received the most attention as mediators of pathologic CoNV.[9] VEGF-A is known to increase migration and mitosis of endothelial cells, increase methane mono-oxygenase activity, and play a role in the creation of new blood vessel and vessel fenestrations. Vascular endothelial growth factor inhibitors are emerging as the new pharmacological therapy in the management of post

keratoplasty graft rejection. Bevacizumab is FDA approved for intravenous administration in the treatment of various cancers, is a full-length, humanized murine monoclonal antibody with a molecular weight of 149kD. Bevacizumab recognizes all isoforms of VEGF and recently it's off label use has also been considered as a new treatment modality for CoNV.[7,8]

Toevaluate the efficacy and safety of subconjunctival Bevacizumab on CoNV in Post Kerato plastypatients, a prospective, non randomized open label study was done in the Department of Ophthalmology, S.N. Medical College from Feb 2018 to July 2019.

Material and Methods :

A total of 17 eyes of 17 patients were enrolled for study.

Inclusion criteria :

- Patients with corneal neo vascularization post PK(more than 2 quadrants).
- The patient who signed the consent to be in the regular follow up / treatment.

Exclusion criteria :

- Patientshaving uncontrolled Glaucoma.
- Active Inflammation/infection in eye
- Poor Corneal Epithelialization
- Patient, not suitable for Bevacizumab use viz uncontrolled systemic hypertension, recent Myocardial Infarction , recent CVA , stroke and Pregnant females .

To assess vascularization :

Corneal photographs were taken with slit lamp mounted digital camera. For every patient a computerized grid was made, in which the whole of the corneal surface was divided into 16 equal segments and number of segments having vascularization were noted along with the number of vessels crossing Graft Host junction. (Figure1)

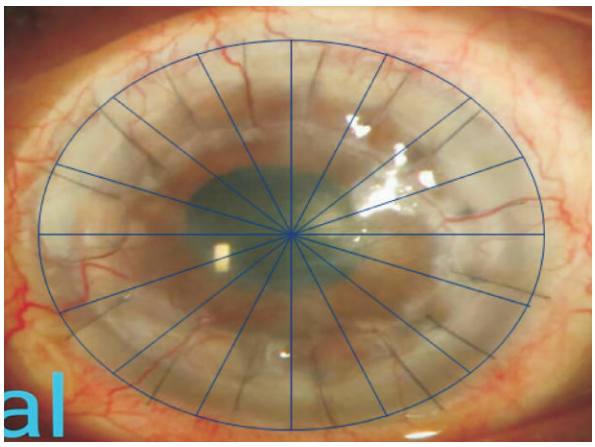


Figure 1 : Computarised grid made on Coraea

Table 1 : Base line Characterstics

Base Line Characterstics	No. of Pts. (17)
1. Age :	
0-20	01
21-40	08
41-60	03
60-80	05
2. Gender :	
Male	11
Female	06
3. Background diseaseFor which PK / Triple was done :	
Corneal scarring(Trauma/ulcer)	10
PBK (Decompensated Cornea)	04
Infective keratitis	02
Degeneration	01
4.CoNV (number of segments) at time of enrollment (post PK)	
9-12 segments	04
13-16 segments	13

After taking Informed consent, under aseptic condition, 3subconjunctivalinjections of 2.5 mg/.1 ml Bevacizumab were given to all 17patients at monthly intervals starting from day of enrollement and followed up for a period of minimum 6 months.

The Primary outcome in our study was the assessment ofthe effect of sub conjunctivalinj. (0.25 ml) of Bevacizumab on CoNV, by the following variables .

- Reduction in number of segments involved.
- Change in the number of preexisting Corneal vessels crossing Graft Host Junction.
- Appearance of any new blood vessel

The secondary outcomes were the effect of sub conjunctival Bevacizumabon Graft Clarity, CCT and Visual Acuity and side effects related to sub conjunctival Bevacizumab.

Statistical analysis :

Data was analyzed using Microsoft excel 2010. Paired student's t-test were used for hypothesis testing of grouped values of pre injection and 1, 3 and 6 month follow-up viz vessels segments , vessels crossing Graft Host junction, visual acuity, CCT and Graft clarity. A p-value <0.05 was considered statistically significant.

Results :

17 eyes of 17 patients (12 males and 7 females) were included in this study. The demographic characterstic of the study population including age, gender, eye , background disease for which keratoplasty was done and severity of CoNV(post PK) at the time of enrollment are listed in table 1

All 17 patients were followed up for a minimum period of 6 month.

From baseline visit to the last follow up visit, out of 17 patients the mean reduction in the number of vascularised corneal segments was 47% in 13 patients with 4 quadrant (13-16 segments) CoNV and 75% in rest 4 patients, with 3 quadrants(9-12 segments) CoNV, (table 2). So overall out of 17 pts 9 patients showed significant reduction in the number of segments involved (p=0.002 at 6 month significant).(Figure2)

Before injection all 17 patients were having at least some blood vessels crossing graft host junction, though in most of them, number was <10. At the end of 6 month follow up in 6 patients Graft Host Junction became free of CoNV. (p=0.002, significant)(table3) (Figure 3)

In our study we have noticed the improvement in Graft Clarity after sub conjunctival injection of Bevacizumab in significant number of patients. Before injection we had only 4 patients with grade 4 + Graft Clarity, which increased to 11 patients by the end of 6 month study period.(p=0.0017; significant).

Significant number of patients also showed improvement in CCT from baseline visit to final visit. Before injection only 5 patients had CCT <600 microns, which increased to 13 patients at the end of 6 month F/U. (p=0.0005 significant).

Visual acuity did not show any significant improvement /change from base line to final follow up visit.

No systemic or ocular side effect is noted during the entire study period.

Table 2 : Segment wise involvement of CoNV.

NUMBER OF VASCULARIZED SEGMENTS									
Timings		**13-6**	**%**	**9-12**	**%**	**5-8**	**%**	**0-4**	**%**
BEFORE INJ		13	76.47	4	23.52	0	-	0	-
F/U	**1 MONTH**	6	35.29	5	29.41	4	23-52	2	11.76
	3 MONTH	6	35.39	2	11.76	5	29.41	4	23.52
	6 MONTH	7	41.17	1	5.88	6	35.29	3	17.64

Table 3 : CoNV with respect to Graft Host Junction.

NUMBER OF VESSELS CROSSING GRAFT_HOST JUNCTION													
Timings		**>20**	**%**	**16-20**	**%**	**11-15**	**%**	**6-10**	**%**	**1-5**	**%**	**0**	**%**
BEFORE INJ		1	5.88	2	11.76	1	5.88	6	35.29	7	47.18	0	-
F/U	**1 MONTH**	1	5.88	0	-	3	17.65	5	29.41	5	29.41	4	23-52
	3 MONTH	1	5.88	0	-	1	5.88	4	23.52	5	29.41	6	35-39
	6 MONTH	1	5.88	0	-	0	-	5	29.41	5	29.41	6	35-39

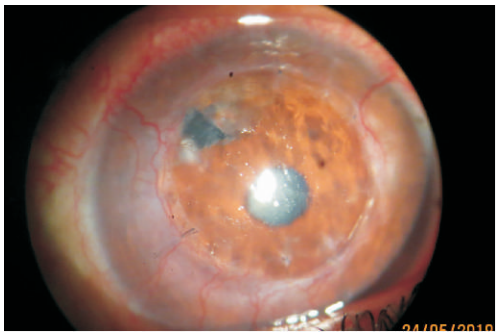


Figure 2a :Baseline pic (8month Post PK with 360 degree CoNV)

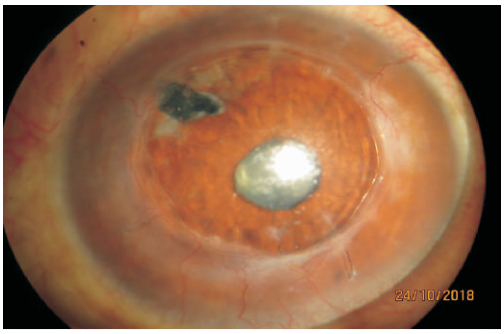


Figure 2b : 2 months after 3rd dose of sub conjunctival 0.25 mlBevacizumab (5 month F/U visit). significant decrease in the caliber and length of preexisting vessels is noted and no new blood vessel is seen .BCVA 6/24p

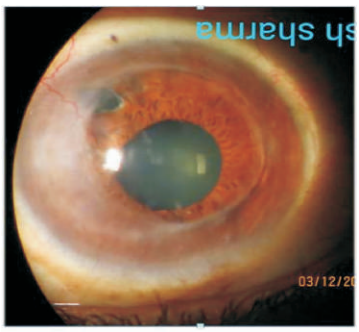


Figure 2 c : Graft clarity 4+and BCVA 6/24p maintained after 7 month of Follow up.

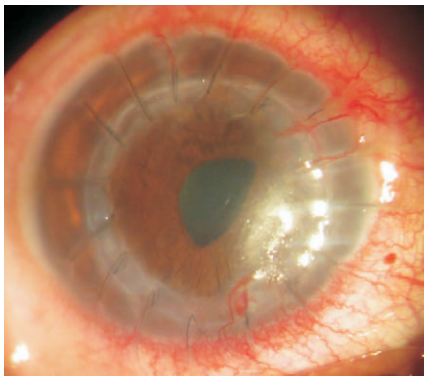


Figure 3 a : (Baseline pic before subconjunctival injection of Bevacizumab) Patient presented with signs of rejection . UCVA 6/60

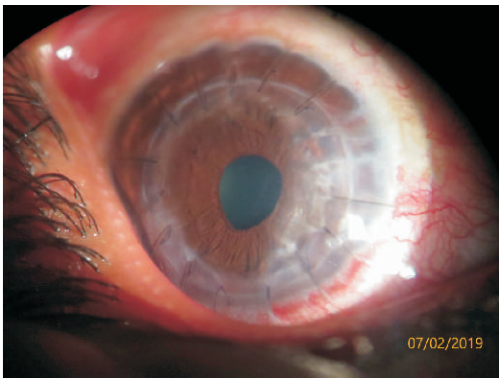


Figure 3b : 4 month post PK with 270 degree CoNV

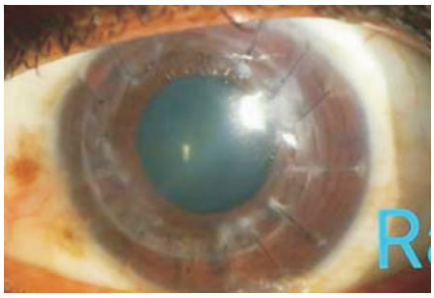


Figure 3c : After 6 month follow up

Table 4 : Graft clarity before injection and at follow up visits

GRAFT CLARITY											
		0	%	1+	%	2+	%	3+	%	4+	%
BEFORE INJ		0	0	1	5.88	2	11.76	10	58.82	4	23.53
F/U	1 MONTH	0	0	1	5.88	1	5.88	4	23.53	11	64.71
	3 MONTH	0	0	1	5.88	1	5.88	4	23.53	11	64.71
	6 MONTH	0	0	1	5.88	1	5.88	4	23.53	11	64.71

Table 5 : CCT before injection and on follow up

CENTRAL CORNEAL THICKNESS											
		401-500	%	501-600	%	601-700	%	701-800	%	>800	%
BEFORE INJ		0	-	4	23.52	6	35.29	5	35.29	2	11.76
F/U	1 MONTH	3	17.64	6	35.29	6	35.29	0	-	1	5.88
	3 MONTH	5	29.41	9	52.94	1	5.88	1	5.88	1	5.88
	6 MONTH	3	29.41	8	47.05	1	5.88	1	5.88	1	5.88

Table 6 : Visual acuity before injection and on follow up

VISUAL ACUITY (logMAR)											
		0.5-0.8	%	0.9-1.2	%	1.3-1.5	%	1.6-1.8	%	1.9-2.1	%
BEFORE INJ		3	17.64	9	52.94	4	23.52	0	-	1	5.88
F/U	1 MONTH	2	17.64	8	47.05	5	29.41	0	-	1	5.88
	3 MONTH	5	29.41	7	41.11	1	5.88	3	17.64	1	5.88
	6 MONTH	7	41.11	4	23.52	2	11.76	1	5.88	3	17.64

p=0.012 (non significant)

DISCUSSION :

Corneal neovascularization is a risk factor for graft failure and rejection after keratoplasty supported by Bachmann B ,et al.[9]

In our study we observed the efficacy of sub conjunctival AntiVEGF Bevacizumabin patient with post operative Corneal neo vascularization (more than 2 quadrants) in terms of Graft survival.

Most of the cases included in our study were young with 8 (47.05%) cases in the age group of 21-40 years. There was a male preponderance in our cases. The leading indications for Penetrating Keratoplasty in our study were corneal scarring post trauma or ulcer (59%), supported by LaxmanDasar et al[10]in 2013. They had studied the indications of penetrating keratoplasty in Southern India.

To quantify CoNV we prepared a computerized Grid, dividing cornea into 16 equal segments. The parameters we noted down were number of segments involved with CoNV, number of blood vessels crossing Graft Host junction, CCT, Graft Clarity and Visual Acquity.

At the time of enrollment, out of 17 patients,13 pts were having CoNV in all 4 quadrants (13-16). Rest 4 patients were having 3 quadrant CoNV between 9-12 segments .There is a statistically significant decrement in vessels post injection when compared to pre injection in both the groups .In our study ,the maximum effect was noted at1 month after sub-conjunctival injection of Bevacizumab supported by TSchollmayer et al (2008) who performed a retrospective case series study of nine eyes of nine patients with corneal transplant and neo vascularization. They followed up all the patients till 6 months and concluded that topical and sub conjunctivalbevacizumab is effective in regressing neo vascularization in keratoplastypatients .[11]

Lochab D, et al. in 2018[12]also evaluated the effect of sub conjunctival anti-VEGF on corneal neo vascularization post penetrating keratoplasty. In all patients who were subjected to subconjunctivalBevcizumab, the regression of neovascularization at 1 week, 4 weeks and 6 weeks were noted and there was a significant decrease in neo vascularization in central segments 1.97± 3.72 as compared to pre 5.[13] ±7.12(p=0.001) and also in peripheral segments at 6 weeks 29.90 ± 15.73 as compared to pre Bevacizumab .

The second parameter we evaluated was the number of vessels, crossing graft host junction before injection and on follow up visits. All cases at base line had at least some vessels crossing Graft Host (in most of cases number was less than 10). At last follow up ,in 6 patients (35.29%) GHJ was free of CoNV. There is also a decrease in length and caliber of vessels. Our results are similar to those of Bahar et al. who reported partial regression of corneal vessels using 2.5 mg/0.1 Bevacizumab in seven patients with CoNV(13).

In our study we found significant improvement of Graft clarity and which was maintained till the last follow up. Before injection, we had only 4 patients with grade 4 + Graft Clarity, which by the end of study period had increased to 11 patients with grade 4+ clarity. We can conclude that regression of corneal neo vascularization enhances the Graft Clarity.

We also noted significant reduction in CCT after sub conjunctival Bevacizumab injection. Only 4 patients were having normal central corneal thickness (<600 microns) prior to injection, which increased to 13 at the end of 6 month follow up.[14] No ocular or systemic complications were noted during study period. You et al[15] reported that pain at the subconjunctival injection site in nine eyes (31.0%), subconjunctival hemorrhages in eight eyes (27.6%), and ocular irritation in one eye (3.4%). There were no systemic complications, such as increased blood pressure or transient ischaemia, in their study. Krizova et al [16] also reported tiny epithelial corneal defects in three patient's post subconjunctivalBevacizumab. Erdurmus et al have reported

dry eye in one patient after subconjunctivalBevacizumab injection (2.5 mg/0.1 mL).[17]

Conclusion :

The use of sub conjunctival Bevacizumab seems to be an effective adjuvant therapy for Corneal Neo vascularisation, especially in cases which are unresponsive to conventional antiin flammatory therapy. sometimes repeated injection are required to augment or in cases of recurrence of CoNV but it is proved to be safe .Our study has small follow up period so long follow up studies are needed to confirm its definite role as key therapeutic agent in the inhibition of corneal neo vascularisation.

References:

1. David G.Cogan, Corneal neovascularization :Investigative ophthalmology and visual science April 1962,Vol 1,253-261.
2. Qazi Y, Wong G, Monson B, Stringham J, Ambati BK. Corneal transparency: genesis, maintenance and dysfunction. Brain Res Bull 2010;81(2-3):198-210.
3. MG, Stark WJ, Gottsch JD, Stulting RD, Sugar A, Fink NE, et al. Risk factors for corneal graft failure and rejection in the collaborative corneal transplantation studies. Collaborative Corneal Maguire Transplantation Studies Research Group. Ophthalmology 1994 Sep;101(9):536-47
4. Hill JC. High risk corneal grafting. Br J Ophthalmol 2002 Sep;86(9): 945
5. Ey RC, Hughes WF, Bloome MA, Tallman CB. Prevention of corneal vascularization. Am J Ophthalmol 1968;66(6):1118– 1131.
6. Ma DH, Chen JK, Kim WS, Hao YX, Wu HC, Tsai RJ, et al. Expression of matrix metalloproteinases 2 and 9 and tissue inhibitors of metalloproteinase 1 and 2 in inflammation-induced corneal neovascularization. Ophthalmic Res 2001;33(6):353-62
7. Andreoli CM, Miller JW. Anti-vascular endothelial growth factor therapy for ocular neovascular disease. CurrOpinOphthalmol 2007;18(6):502-8.
8. Keating AM, Jacobs DS. Anti-VEGF treatment of corneal neovascularization. Ocul Surf 2011;9(4):227–237.
9. Bachmann B, Taylor RS, Cursiefen C. Corneal neovascularization as a risk factor for graft failure and rejection after keratoplasty: an evidence based meta-analysis: Ophthalmology. 2010Jul;117(7):1300-5.
10. Dasar L, Pujar C, Gill K.S, Patil M, Salagar M. Indications of penetrating keratoplasty in southern India. J Clin&Diag Res. 2013 Nov;7(11); 250507.
11. Schollmayer P, Stunf S, Lavric A. Pfeifer V. Topical and subconjunctivalbevacizumab in corneal neovascularization in keratoplasty patients. ActaOphthalmologica, 2008 Sept;86(s243):0-0.
12. Lochab D, Dhasmana R, Gupta N. Effect of subconjunctivalantivascular endothelial growth factor on corneal neovascularization after penetrating keratoplasty. Sudanese J Ophthalmol 2018;10:14-7
13. Bahar I, Kaiserman I, McAllum P, Rootman D &Slomovic A (2008a): Subconjunctivalbevacizumab injection for corneal neovascularization. Cornea. 2008 Feb; 27(2): 142–147.
14. Dastjerdi MH, Al-Arfaj KM, Nallasamy N, Hamrah P, Jurkunas UV, Pineda R 2nd, Pavan-Langston D, Dana R. Topical bevacizumab in the treatment of corneal neovascularization: results of a prospective, open-label, noncomparative study. Arch Ophthalmol 2009;127(4):381–389.
15. You IC, Kang IS,LeeSH,Yoon KC. Therapeutic effect of subconjunctivalinjection of Bevacizumab in the treatment of Corneal neovascularization.ActaOphthalmol 2009;87:653-8.
16. Krizova D, Vokrojova M, Liehneova K, Studeny P. Treatment of corneal neovascularization using anti-VEGF bevacizumab. J Ophthalmol 2014 Mar; 2014:178132.
17. Erdurmus M &TotanY :Subconjunctivalbevacizumab for corneal neovascularization. Graefes Arch ClinExpOphthalmol. 2007 Oct; 245(10): 1577–1579.

Charles William Simcoe

The Simcoe Cannula was developed about 40 years ago by C. William Simcoe MD, an ophthalmologist in Oklahoma, USA. Bill Simcoe was born in Still water on June 5, 1931 and passed away in his Tulsa home on October 22, 2017.

Dr. Simcoe also developed many innovations such as Simcoe irrigation and aspiration cannula & C-loop haptics. While examining and reshaping a paper clip, he had an idea of how to invent a much safer intraocular lens design the Simcoe open C loop which has become the industry standard in modern cataract surgery. He refused to patent any of his inventions and are widely used now in cataract surgery

A native of Still water, Charles William Simcoe was a Korean War and Marine Corps veteran. He was a graduate of the University of Oklahoma medical school. Through Project Orbis, a nonprofit dedicated to preventing blindness, Simcoe travelled the globe, teaching doctors how to perform safer, less costly cataract surgeries.

Pathophysiological Changes of Retinal Inner Layers in Diabetic Macular Edema

Malvika Singh, MBBS; **Akshay Mohan,** MBBS; **Sandeep Saxena,** MS, FRCSEd, FRCS, FRCOphth, FACS, FAMS, FAICO

Department of Ophthalmology, King George's Medical University, Lucknow

Abstract :

Diabetic macular edema (DME) remains the major cause of vision loss in the highly prevalent type 2 diabetes. Retinal inner layers comprise of 4 layers, namely; ganglion cell layer -inner plexiform layer complex, inner nuclear layer and outer plexiform layer. Spectral domain optical coherence tomography (SD-OCT) is a non-invasive imaging tool for in vivo cross-sectional retinal histology. SD-OCT is an important tool in diagnosing and managing a patient with DME. Disorganization of retinal inner layers (DRIL) is defined as the failure to ascertain any of the inner retinal layers' boundaries. DRIL has been found to be a predictor of visual acuity (VA) in DME.Serial OCT scans demonstrating changes in DRIL correlate with the severity of diabetic retinopathy (DR). Many artificial intelligence softwares can read SD-OCT and identify DRIL to screen patients of DR.

Keywords : Diabetic Macular Edema, Disorganization of Retinal Inner Layers, Spectral Domain Optical Coherence Tomography

INTRODUCTION :

The 2015 International Diabetes Federation Atlas reported that DM affects 415 million people worldwide.[1] The global burden due to diabetes is mostly contributed by type 2 diabetes (80-95% of the total diabetic population).The prevalence rate of DR in the Indian subcontinent is reported from 12% to 37% in patients with type 2 DM. DR is the leading cause of vision loss in adults aged 20–74 years.[2]Diabetic macular edema (DME) is responsible for most of the visual loss experienced by patients with diabetes as it remains the major cause of vision loss in the highly prevalent type 2 diabetes.[3]

RETINAL INNER LAYERS :

Spectral domain optical coherence tomography (SD-OCT) is a non-invasive reliable imaging tool for in vivo cross-sectional retinal histology.

Retinal inner layers comprise of 4 layers, namely; ganglion cell layer -inner plexiform layer (GCL-IPL) complex, inner nuclear layer (INL) and outer plexiform layer (OPL). These are visualized on SD-OCT.

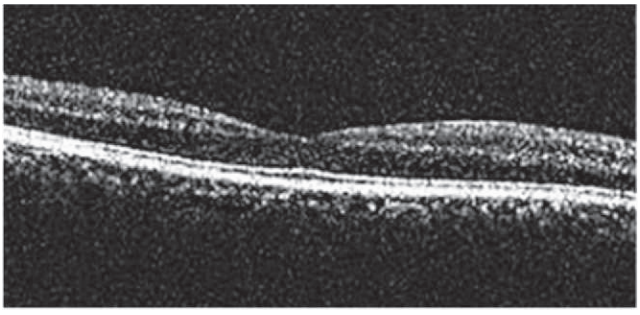


Figure 1 : SD-OCT image showing intact inner retinal layers

Increased severity of DR has been found to be associated with disorganization of retinal inner layers(DRIL). DRIL has been found to be a predictor of visual acuity (VA) in center-involved DME.[4] DRIL was defined as the failure to ascertain any of the inner retinal layers boundaries.[4-6] DRIL was graded as Grade 0: absence of DRIL, and Grade 1: presence of DRIL .

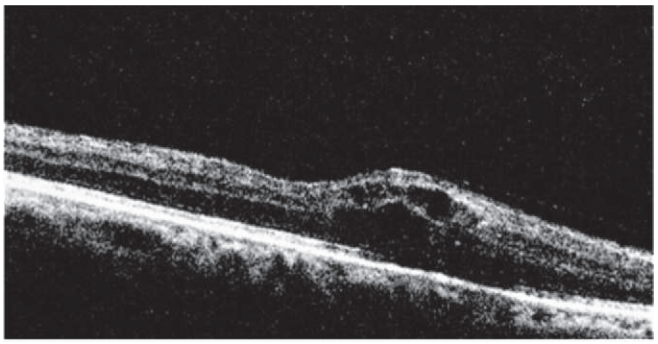


Figure 2 : SD-OCT showing DRIL with disruption of ELM and EZ.

S. No.	RETINAL LAYER	BLOOD SUPPLY
1.	Ganglion cell layer	Central retinal artery
2.	Inner plexiform layer	Central retinal artery
3.	Inner nuclear layer	Central retinal artery
4.	Outer plexiform layer	Central retinal artery, ophthalmic artery via choriocapillaris

PATHOPHYSIOLOGICAL CHANGES TAKING PLACE IN RETINAL VESSELS IN DME :

In DME, basement membrane thickening, pericyte loss,[7,8]increased expression of ICAM-1[9], oxidative and nitrosative stress[10], rheological changes[11]and decreased capillary perfusion lead to capillary endothelium damage. This results in fluid leakageout of the capillaries resulting in DME, capillary closure and decreased capillary blood flow. These changes lead to decreased blood flow to retina with consequential retina lischemia and increased vascular endothelial growth factor (VEGF) release[12]. Retinal oximetry studies have shown that increase in retinal venous oxygen saturation is associated with increasing levels of DR. Several studies also found increased retinal arterial oxygen saturation in patients with DR.[13]

Retinal blood flow in adjacent capillaries increases due to retinal is chemia thereby increasing shear stress in the vesselwall. Increased viscosity and capillary closure also contribute to increasing shear stress on the vessel wall.[14] Tooke hypothesized that increased glycation and thickening of the basement membrane results in "locking" of the vessel.[15] This tends to increases hear stress as the vessel diameter is unable to change, leading to mechanical injury to the vascular endothelium.

Capillary pressure is increased in diabetes mellitus due to the presence of dilated vasculature; the systemic blood pressure is more easily transmitted to the micro circulation.

Vessel wall of larger vessels of the retinal circulation suffer more circumferential stress damage. This occurs as the circumferential stress that is responsible for mechanical damage to the endothelium of the vessel wall is direct lyproportional to the perfusion pressure and radius and inversely proportional to the thickness of the vessel wall.[16] As a result, the vessel has a tendency to dilate. As stated by Laplace law, vesselwall tension resisting distension pressure is inversely proportional to the radius of the vessel. Vessel has a tendency towards dilatation as the vessel wall tension required to counteract distending pressure is not achieved in a dilated vessel, resulting in subsequent hyperperfusion.

Blood flow to adjacent retinal capillaries is increased due to retinal is chemia, resulting in increase in vessel wall shear stress.[14] Resistive index has been characterised as a marker of vascular resistance which increases with increasing resistance, with vascular compliance taken into account.[17]

DISRUPTION OF RETINAL INNER LAYERS IN DME :

Role of SD-OCT :

DRIL has been highlighted as a predictive biomarker for VA in DME. This biomarker may be useful not only as a predictor of VA but also for stratification of eyes with regard to a high likelihood of future VA improvement or decline.[6]

DRIL as visualized on SD-OCT represents an anatomic interruption in the visual transmission pathway. Disruption has been hypothesized to result when bipolar axons snap after their elasticity limit has been exceeded due to edema.[6,18]

Our recent study found that presence of DRIL correlated with severity of DR. A significant positive correlation was found between DRIL and central subfoveal thickness (CST) and cube average thickness (CAT) and ellipsoid zone disruption on SD-OCT. [5]

Role of doppler ultrasonography :

CRA supplies the retinal inner layers.[19]Our other colour doppler study also highlighted an increase in RI of CRA in DME. This was found to correlate significantly with an increase in CST and CAT.[20]Hence it can be concluded that increased RI of CRA also plays a significant role in pathogenesis of DRIL.

Another microvascular complication of diabetes is diabetic nephropathy. Resistive index of intrarenal artery has been used to detect renal dysfunction in patients of diabetic nephropathy. Shirin et al concluded that resistive index has value in identifying diabetic patients who are developing nephropathy and can be used as an additional diagnostic tool as RI of renal artery well correlates with serum creatinine and albuminuria which are the biochemical parameters to diagnose diabetic nephropathy.[21]

Role of serum VEGF :

In our earlier study, we have found that significantly elevated levels of serum VEGF come into play even before the evidence of DR. Increase in VEGF has been found to correlate with increase in CST and CAT. Estimation of serum VEGF is a useful laboratory test for predicting the onset of DR.[22]

Role of Artificial Intelligence :

Artificial intelligence systems are being developed to screen patients of diabetic retinopathy, read OCTs and identify lesions in retinal layers. The current AI screening systems for DR have been developed using two-dimensional images and lack stereoscopic qualities. Additionally, the medicolegal aspects and the regulatory approvals vary in different countries and settings. However, it can be an effective way to screen patients of diabetic retinopathy in a physicians' or endocrinologists' OPD.[23]

TAKE HOME MESSAGE :

1. SD-OCT is an important tool in diagnosing and managing a patient with DME. Serial OCT scans demonstrating improvement or decline in DRIL correlates with the severity of diabetic retinopathy.

2. Serum VEGF levels serve as a simple and reliable biomolecular biomarker for severity of DR.
3. Administration of intra-vitreal anti-VEGF causes reduction in DME and may show improvement in DRIL.
4. Doppler ultrasonography of CRA can be an additional easy modality of screening patients with DR.
5. Artificial intelligence is an upcoming tool for the screening of patients for DRIL in DME

References:

1. International Diabetes Federation. IDF Diabetes Atlas, 7th edition. Brussels, Belgium: International Diabetes Federation; 2015.
2. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376(9735):124–36.
3. Tong L, Vernon SA, Kiel W, Sung V, Orr GM. Association of macular involvement with proliferative retinopathy in type 2 diabetes. Diabet Med. 2001;18:388–94.
4. Maheshwary AS, Oster SF, Yuson RM, et al. The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in diabetic macular edema. Am J Ophthalmol2010;150:63-7.
5. Nadri G, Saxena S, Stefanickova J, et al. Disorganization of retinal inner layers correlates with ellipsoid zone disruption and retinal nerve fiber layer thinning in diabetic retinopathy. J Diab and Compl2019;33:550-3.
6. Sun JK, Lin MM, Lammer J, et al. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol2014;132:1309–16.
7. Kuwabara T, Cogan DG. Retinal vascular patterns VI: mural cells of the retinal capillaries. Arch Ophthalmol. 1963;69:492–502.
8. Takahashi K, Brooks RA, Kanse SM, Ghatei MA, Kohner EM. Endothelin I is produced by cultured bovine retinal endothelial cells and endothelin receptors are present on associated pericytes. Diabetes. 1989;38:1200–1202.
9. Jain A, Saxena S, Khanna VK, Shukla RK, Meyer CH. Status of serum VEGF and ICAM-1 and its association with external limiting membrane and inner segment-outer segment junction disruption in type 2 diabetes mellitus. Mol Vis. 2013;19:1760–1768.
10. Sharma S, Saxena S, Srivastav K, Shukla R, Mishra N, Meyer CH, Kruzliak P, Khanna VK. Nitric oxide levels in diabetic retinopathy and its association with disruption of photoreceptor IS-OS junction and topographic alterations in retinal pigment epithelium. Clin Exp Ophthalmol. 2015;43:429–436.
11. DE McMillan.The effect of diabetes on blood flow properties. Diabetes. 1983;32(suppl 2):56–63.
12. Crawford TN, Alfaro DV, Kerrison JB, Jablon EP. Diabetic retinopathy and angiogenesis. Curr Diabetes Rev. 2009;5:8–13.
13. Rilvén S, Torp TL, Grauslund J. Retinal oximetry in patients with ischaemic retinal diseases. Acta Ophthalmol. 2017;95:119–127.
14. Fry DL. Certain histological and chemical responses of the vascular interface to acutely induced mechanical stress in the aorta of the dog. Circ Res. 1968;159(24):93–108.
15. Tooke JE. Microvascular haemodynamics in diabetes mellitus. Clin Sci. 1986;70:119–125.
16. Burton AC. Relation of structure to function of the tissues of the walls of blood vessels. Physiol Rev. 1954;34:619–642.
17. Bude RO, Rubin JM. Relationship between the resistive index and vascular compliance and resistance. Radiology. 1999;211:411–7.
18. Pelosini L, Hull CC, Boyce JF, McHugh D, Stanford MR, Marshall J. Optical coherence tomography may be used to predict visual acuity in patients with macular edema. Invest Ophthalmol Vis Sci. 2011;52(5):2741-2748.
19. Blodi FC. Eugene Wolff's anatomy of the eye and orbit. Arch Ophthalmol. 1977;95:1284.
20. Khatri M, Saxena S, Kumar M, et al. Resistive index of central retinal artery is a bioimaging biomarker for severity of diabetic retinopathy. Int J Retina Vitreous. 2019;5:38.
21. Shirin M, Sharif MM, Gurung A, Datta A. Resistive Index of Intrarenal Artery in Evaluation of Diabetic Nephropathy. Bangladesh Med Res Counc Bull. 2015;41(3):125-130.
22. Ahuja, S., Saxena, S., Akduman, L. et al. Serum vascular endothelial growth factor is a biomolecular biomarker of severity of diabetic retinopathy. Int J Retin Vitr5, 29 (2019).
23. Ting DSW, Pasquale LR, Peng L, et al Artificial intelligence and deep learning in ophthalmology British Journal of Ophthalmology2019;103:167-175.

Role of Intralesional Bleomycin in Periocular Capillary Hemangioma

Shalini Mohan, MS, DNB, MNAMS; **Namrata Patel,** MS; **Anshika Gupta,** MBBS; **Sneha Agrawal,** MBBS; **Vineeta Gupta,** MS*
Department of Ophthalmology, GSVM Medical College, Kanpur, UP, India, *Department of Ophthalmology, AIIMS, Rishikesh, UK;
Correspondence email : namrata.patel375@gmail.com

Abstract :

Background : Capillary hemangioma is one of the most common benign orbital tumor of childhood that appears in early childhood. Primary conjunctival capillary hemangioma resolves in majority of cases spontaneously. However, some periocular and conjuctival hemangioma may not regress and require treatment to prevent serious complication and/or to restore cosmesis. There are many therapeutic options available but these tumors do not always respond well to conventional treatment.

Aim : To treat periocular / conjunctival capillary hemangioma by Intralesional bleomycin, a cytotoxic agent.

Results : The Bleomycin (0.5mg/Kg) diluted in normal saline was used in two cases of periocular and conjunctival capillary hemangioma. Comeplete resolution occurred in one case after two injections while other is regressing after two injections. No significant side effects were noted.

Conclusion : Intralesional bleomycin turned up to an useful treatment modality for periocular capillary hemengioma refractory to other conventional treatment and reduces the need of surgical intervention.

Key words : Periocular, Bleomycin, Capillary hemangioma, Intralesional

Introduction :

Periocular capillary hemangioma is are one of the most common benign vascular tumor of childhood.[1] Histologically, they are characterized by proliferating endothelial cells. They can present within a few weeks after birth or in early childhood. Usually followed by rapid proliferating phase tumor starts regressing but clinical course can be variable.[2] These cases are more common among females.[3] Acceptable indications for intervention may include rapidly enlarging lesions, obstruction of the visual axis, significant induced astigmatism, and cosmetic concerns. There are several treatment option available.

Here we are presenting two cases of periocular hemangioma exemplifying the successful use of in tralesional bleomycin injection (IBI) without surgical excision. Bleomycin is an antineoplastic agent, now being used as a sclerotherapeutic agent in such vascular tumors.[4]

Case Reports :

A written and informed consent was taken from the parents of both patients.

Case 1 :

A 13-year-old female with complaints of a purpule-colored mass in the right upper lid since childhood reported to our institution. No history of other systemic illness found. On ocular examination, best-corrected visual acuity was 20/20 in both eyes for distance. on slit lamp examination anterior- and posterior-segment were within normal limits in both the eyes. On external examination, a violacious red-colored upper lid mass was present. Widest diameter was around 1.5 cm .

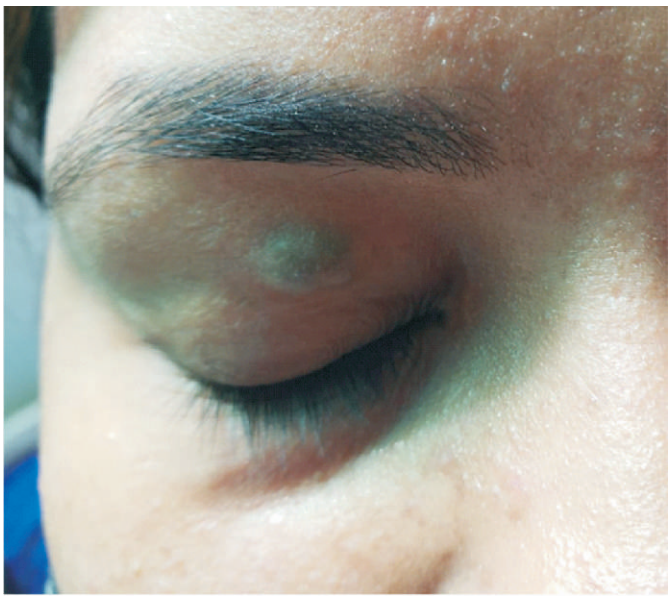


Figure 1a : Upper lid hemangioma

Ocular motility was full in all gazes. Based on clinical findings, the diagnosis of an upper lid capillary hemangioma was made.

Ocular motility was full in all gazes. Based on clinical findings, the diagnosis of an upper lid capillary hemangioma was made.

Patient was managed conservatively for which intralesional bleomycin (dose of 0.5 mg/kg diluted in volume with normal saline along with lignocaine) was injected taking all aseptic precautions. Two injections were given over a period of 2

months and response was assessed resulting into near total regression .

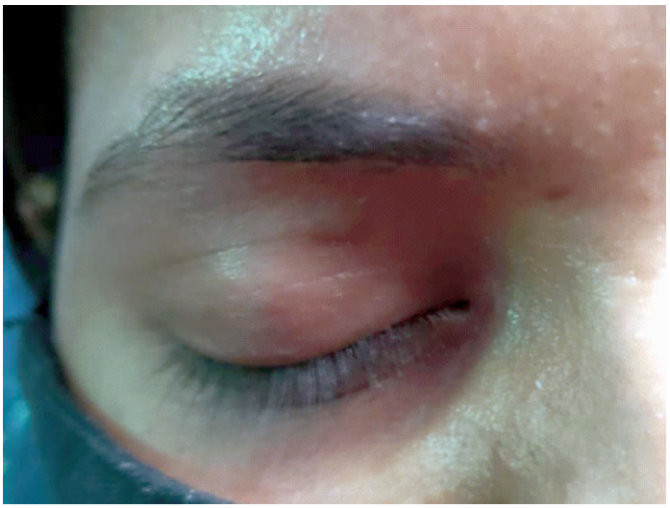


Figure 1b : Regression of hemangioma post Injection Bleomycin

Case 2 :

A 17-year-old female with complaints of a red-colour mass in the right eye since childhood came to us. Complete ocular examination was done. Best-corrected visual acuity was 20/20 in both eyes for distance. Anterior- and posterior-segment were normal in both the eyes On external examination, a red-colored subconjunctival mass involving both bulbar and palpebral part was present in right eye extending from limbus to fornices, involving quadrants from 1'o clock to 8'o clock .

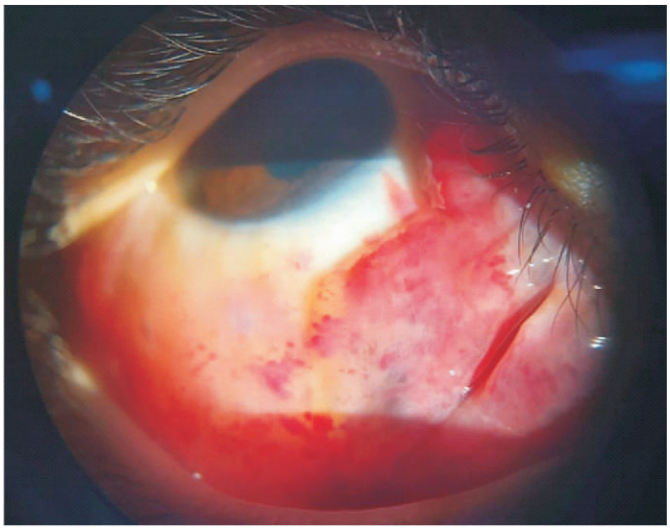


Figure 2a : Periocular capillary hemangioma

It was associated with mild upper eyelid ptosis and fullness below the lower lid. Ocular motility was full in all gazes. Magnetic resonance imaging was done. It showed the lesion involving anterior part of the orbit. Based on clinical and imaging findings, the diagnosis of peiocular capillary hemangioma involving conjuctiva was confirmed.

Intralesional bleomycin injection was given at multiple locations under local anesthesia and dose of 0.5 mg/kg was used. Total of 2 injections were given at 1 month interval .The hemangioma is regressing and no adverse effect related to the treatment was noted .

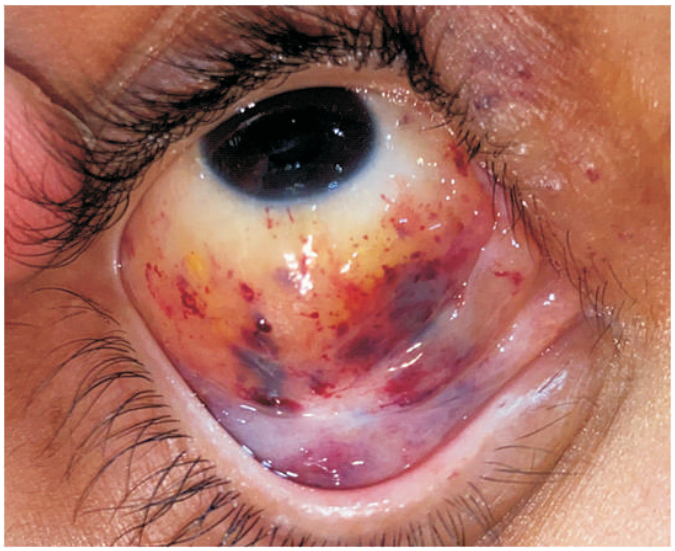


Figure 2b : Regressing hemangioma post Injection Bleomycin

Discussion :

The prevalence of periocular capillary hemangioma ranges from 1% to 3%.[1] Capillary hemangiomas are capillary unit structure of endothelial cells surrounded by pericytes.[5] These tumors can present as small isolated lesions, or large masses that can cause visual impairment. Many capillary hemangiomas can be diagnosed on examination, but occasionally identification may require the imaging and biopsy. Spontaneous involution occurs in majority of cases. However some periocular and orbital capillary hemangiomas require treatment to prevent serious complications, to lessen the surgical burden and to obtain cosmesis .When treatment is necessary, there are a number of therapeutic options available.

Bleomycin was used in both the cases as patients were not responding to conventional corticosteroid therapy, beta blockers and surgical excision was not possible due to the extent of the lesion. Bleomycin is a chemotherapeutic agent derived from Streptomyces verticillus, a soil fungi. The mechanism of action of Bleomycin is to induced apoptosis in rapidly growing cells via oxidative damage and has a sclerosing effect on the vascular endothelium. Due to its sclerosing effect on the endothelium of the abnormal vasculature intralesional bleomycin is useful in the management of vascular neoplasm.[6,7] Bleomycin injections have also been used for the treatment of basal cell carcinoma and Kaposi sarcoma.[4]

The common adverse reaction after intralesional bleomycin are erythema, pain, swelling , bleeding, hypopigmentation and flu-

like symptoms .The adverse effect of intralesional bleomycin therefore compares favorably with that of conventional modalities of treatment.

Conclusion :

Intralesional bleomycin is useful in the treatment of periocular and superficial orbital hemangioma when conventional modalities have not been successful. Surgical excision of entire mass is not possible and the patient is also concerned about cosmesis. This could be an important step forward in the treatment of disease that can prove very difficult to manage.

References:

1. Haik BG, Karcioglu ZA, Gordon RA, Pechous BP. Capillary hemangioma (infantile periocular hemangioma) Surv Ophthalmol. 1994; 38(5):399–426. [PubMed] [Google Scholar]
2. Tambe K, Munshi V, Dewsberry C, et al. Relationship of infantile periocular hemangioma depth to growth and regression pattern. J AAPOS. 2009; 13:567–570.
3. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. N Engl J Med. 1999; 341:173–181. [PubMed] [Google Scholar]
4. Meyer D, Gooding C. Intralesional bleomycin as an adjunct therapeutic modality in eyelid and extraocular malignancies and tumors. Middle East Afr J Ophthalmol. 2015; 22:410–4. [PMCID: PMC4660524] [PubMed: 26692709]
5. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. N Engl J Med. 1999; 341:173–181. [PubMed] [Google Scholar]
6. Pienaar C, Graham R, Geldenhuys S, Hudson DA. Intralesional bleomycin for the treatment of hemangiomas. Plast Reconstr Surg 2006;117:221-6.
7. Muir T, Kirsten M, Fourie P, Dippenaar N, Ionescu GO. Intralesional bleomycin injection (IBI) treatment for haemangiomas and congenital vascular malformations. Pediatr Surg Int 2004; 19:766-73.

Popular class of diabetes medications may be protective against glaucoma

A popular class of diabetes medications called GLP-1R agonists (Trulicity and Rybelsus) may also protect against glaucoma in diabetic patients, according to a new study led by researchers in the Scheie Eye Institute at the University of Pennsylvania's Perelman School of Medicine. The findings were published in the British Journal of Ophthalmology.

The researchers looked at retrospective data of 1,961 diabetic patients who were new users of this class of drugs and matched them to 4,371 unexposed control subjects. After 150 days on average, 10 patients in the medicated group were newly diagnosed with glaucoma (0.5 percent) compared to 58 patients (1.3 percent) in the control group. The findings suggest that GLP-1 receptor agonists may decrease a diabetic patient's risk of developing glaucoma by half.

The findings are supported by a Penn Medicine study from 2020, which found that GLP-1R agonists reduced neuroinflammation and prevented retinal ganglion cell death in mice. This class of drugs has also shown similarly protective effects against Alzheimer's and Parkinson's diseases in animal models, and clinical trials are underway to test the medications against neurodegenerative diseases in humans.

Source :

University of Pennsylvania

Journal reference :

Sterling, J., et al. (2021) Glucagon-like peptide 1 receptor agonist use is associated with reduced risk for glaucoma. British Journal of Ophthalmology. doi.org/10.1136/bjophthalmol-2021-319232.

Emerging role of Rho-Kinase Inhibitors – Review

Alka Gupta, MS; **Anu Malik,** MS
Department of Ophthalmology, G.S.Medical College, Hapur
Correspondence e-mail : dralkag@gmail.com

Abstract :

This review article targets to provide information regarding the role of ROCK and its inhibitors in glaucoma, corneal diseases, and retinal pathologies. Rho-associated protein kinase (ROCK) is a well-characterized effector of Rho GTPase, a small GTP-binding protein. The Rho/ROCK signaling pathways contribute to a wide range of fundamental cellular events, such as cell adhesion, motility, proliferation, differentiation, and apoptosis. We found strong evidence demonstrating that inhibition of Rho kinase considerably decreases IOP, increases healing of the corneal endothelium, and decreases progression of diabetic retinopathy. The main side effect of ROCK inhibitors is conjunctival hyperemia that is often present in more than half of the patients in certain formulations. Other properties such as neuro protection (enhancing optic nerve blood flow and promoting axonal regeneration), anti-fibrotic activity, and endothelial cell proliferation may enhance the visual prognosis and surgical results in glaucoma.

The aim is to provide authoritative and cutting-edge reviews of topical state-of-the-art basic research that is expected to have broad clinical impact in the next few years.

Keywords : Glaucoma; Intraocular Pressure; Aqueous humor; Trabecular Meshwork, ROCK; Rho Kinase Inhibitors.

Introduction

The Rho kinase (ROCK) signaling pathway is involved in several cellular events that include cell proliferation and cytoskeleton modulation leading to cell adhesion. The ROCK pathway in the human eye has been hypothesized to play important roles in corneal endothelial cell physiology and pathologic states. In addition, ROCK signaling has been identified as an important regulator of trabecular meshwork (TM) outflow, which is altered in glaucomatous eyes. These roles in corneal and glaucomatous disease states have led to the growing interest in the development of drugs selectively targeting this pathway (ROCK inhibitors).

A search for Rho kinase inhibitors led to the discovery of several molecules of therapeutic interest, leaving us today with new ocular hypotensive agents approved for clinical use: ripasudil in Japan and netarsudil in the United States. These represent members of the first new class of clinically useful ocular hypotensive agents since the US Food and Drug Administration approval of latanoprost in 1996. The development of Rho kinase inhibitors as a class of medications to lower IOP in patients with glaucoma and ocular hypertension represents a triumph in translational research.

Few studies began a focus on the role of cell mechanics in the aqueous humor outflow pathways and the role of Rho kinase in this process.They were able to show that cytoskeletally-active agents such as latrunculin (that depolymerizes f-actin) and H7 (a protein kinase inhibitor that affects rho kinase) significantly decreased aqueous humor outflow resistance.[1-4]

Rho kinase inhibitors are effective alone or when combined with other known ocular hypotensive medications. They also offer the possibility of neuroprotective activity, a favorable impact on ocular blood flow, and even an antifibrotic effect that may prove useful in conventional glaucoma surgery. Local adverse effects, however, including conjunctival hyperemia, subconjunctival hemorrhages, and cornea verticillata, are common.

Development of Rho kinase inhibitors targeted to the cells of the outflow pathway and the retina may allow these agents to have even greater clinical impact. The aim of this review is to discuss the idea underlying the development of Rho kinase inhibitors as a therapy to lower IOP and to summarize the results of the clinical studies reported to date. The neuroprotective and vasoactive properties of Rho kinase inhibitors, as well as the antifibrotic properties, of these agents are reviewed in the context of their possible role in the medical and surgical treatment of glaucoma. The use of Rho Kinase (ROCK) inhibitors as therapeutic agents in ophthalmology has been a topic of discussion for several years, particularly in the realm of glaucoma, Fuchs' endothelial dystrophy, and diabetic retinopathy.

Rho kinase Signaling Pathway :

Rho kinase is a downstream effector of the RhoA protein, a

small GTPase. GTPases alternate between two conformations: a Guanosine Triphosphate (GTP)-bound active conformation and a Guanosine Diphosphate (GDP)-bound inactive conformation.

This GTPase activation regulation is controlled by Guanine nucleotide Exchange Factors (GEFs), GTPase Activating Proteins (GAPs), and Guanine nucleotide Dissociation Inhibitors (GDIs) .[5, 6, 7] After activation of RhoA, the coiledtail serine/threonine kinase, the downstream effector Rho kinase, becomes active. The Rho kinase has two isoforms, ROCK1 (ROKβ) and ROCK 2 (ROKα). Although both isoforms share similar effects, they also fulfill some isoform-specific roles. Rho kinase phosphorylates various intracellular substrates, including the two seen in Figure 1,

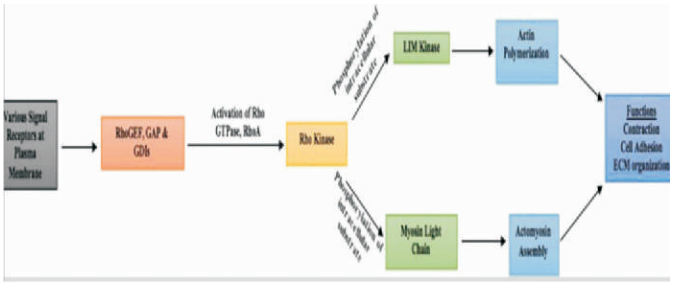


Figure 1 : RhoGEF: Rho Guanine nucleotide Exchange Factor; GAP: GTPase Activating Proteins; GDI: Guanine nucleotide Disassociation Inhibitor; RhoA: Ras Homolog Gene Family Member A; ECM: Extracellular Matrix; GTPase: Guanosine triphosphatase

the myosin light chain, and the LIM kinase.[6]

These substrates then interact to control actomyosin contractility, membrane permeability, cellular adhesion, cell stiffening, cell morphological changes, extracellular matrix organization, as well as DNA synthesis .[5, 8]

The Rho/ROCK signaling pathways contribute to a wide range of fundamental cellular events, such as cell adhesion, motility, proliferation, differentiation, and apoptosis. The role of ROCK in the control of a wide spectrum of biological events has made it a subject of intensive investigation as an important therapeutic target in a wide range of diseases, including vascular disease, cancer, neuronal degenerative disease, asthma, and glaucoma.

Drugs : Ripasudil 0.4% (available in India) , Netarsudil 0.02% (Available in India) , SNJ-1656 and AR-12286 (under trial) and fixed-dose combination (FDC) of netarsudil with latanoprost.

Ripasudil :

Ripasudil, also known as K-115 from various clinical trials, is an ophthalmic solution used as a treatment of glaucoma. It has the chemical formula of C15H18FN3O2S and has the International Union of Pure and Applied Chemistry (IUPAC),name being 4-fluoro-5-(((2S)-2-methyl-1,4-diazepan-1-yl)sulfonyl) isoquinoline .[9]

This new drug was shown to lower IOP within two hours of instillation of the drop solution, and was proven to do so consistently over a period of a full year .[9, 10] The most commonly seen adverse effect of Ripasudil is conjunctival hyperemia. This is a dose-dependent side effect and is seen in the majority of patients treated with Ripasudil. Conjunctival hemorrhage was also seen in treated patients, however, this side effect showed no dose dependency.[11]

Ripasudil (K-115): Ripasudil hydrochloride hydrate, (0.4% or Ripasudil) a fluorinated analog of Fasudil, is a small molecule ROCK inhibitor developed and introduced by Kowa Company, Ltd (Naka-ku, Nagoya, Japan) for treatment of glaucoma and OHT in 2014.[12]

Phase 1 and Phase 2 clinical trials as well as a 24-hour time-course study established Ripasudil 0.4% BID as a clinically useful concentration and dosing frequency for the treatment of glaucoma and OHT.

A phase II clinical trial was conducted during year 2013, in Japan, that determined the optimal dosage of ripasudil, K-115. A group of individuals with open angle glaucoma were assigned to four different groups: a placebo, 0.1% ripasudil, 0.2% ripasudil, and 0.4% ripasudil. The results of this study showed that over an eight-week period, there was a decrease in baseline IOP in all groups using ripasudil. It also showed that as concentration of dosage increased, IOP decreased. After comparing the results of the trial, researchers concluded that the optimal dosage, based on dose-response alone, was the 0.4% dose, which had a reduction in baseline IOP of -4.5 mm Hg, two hours after the last instillation of the drop. However, this study also showed that there may be a direct correlation between increased dosage and increased cases of conjunctival hyperemia. The reported cases of conjunctival hyperemia were 13.0%, 43.4%, 57.4%, and 65.3% in the placebo, 0.1% ripasudil, 0.2% ripasudil, and 0.4% ripasudil groups, respectively [10]. In Japan, a ripasudil drop solution was approved at a 0.4% concentration, as a twice daily treatment, to be used to treat glaucoma .[12]

In 2014, ripasudil, a ROCK inhibitor, gained approval in Japan to be specifically used for treatment of ocular hypertension and glaucoma . As recently as December 18th, 2017, Rhopressa, a Rho kinase inhibiting drug consisting of Netarsudil, gained Food and Drug Administration (FDA) approval; the first of its kind to do so in the United States of America .[13] Netarsudil (AR-13324) is not only a ROCK inhibitor but also norepinephrine

transporter inhibitor leading to additional benefits in glaucoma.

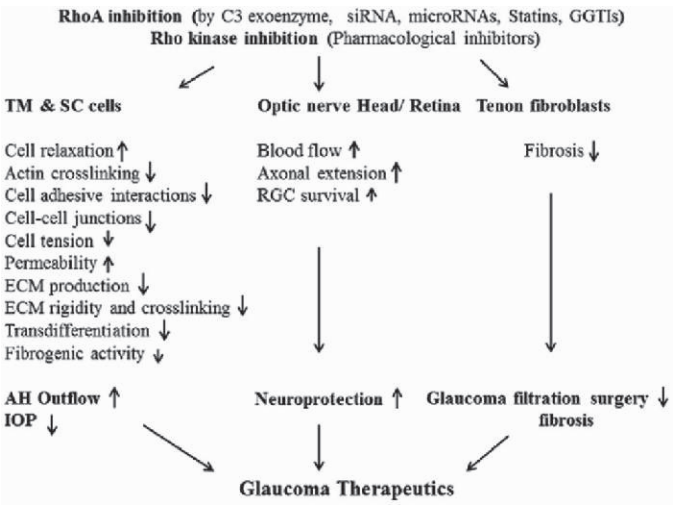
A non-comparative, year-long, open-label study reported IOP reduction of 2.6–3.7 mmHg from baseline with POAG or OHT patients after monotherapy.[14]

Side effects of Ripasudil included dose-dependent conjunctival hyperemia and non-dose dependent conjunctival hemorrhage. Nonocular side effects were rare and generally not severe: constipation (0.6%), headache (0.1%), dizziness (0.1%), nausea (0.1%), and others.

The Rho Kinase Elevated IOP Treatment trials 1 and 2 (ROCKET-1 and ROCKET-2), two phase three clinical trials, investigated safety and effectiveness relating to netarsudil and timolol in a sample of patients with elevated IOP. In a double-masked, randomized non-inferiority clinical trial, Netarsudil once a day (q.d.), produced significant lowering from baseline IOP, which was non-inferior to timolol (ROCKET-1). Netarsudil twice a day (b.i.d.) showed non-inferiority to timolol as well (ROCKET-2) .[15] In the United States, a netarsudil drop was approved in a 0.02% concentration, as a one drop q.d. treatment to lower IOP for treatment of glaucoma .[16]

Application of Rho Kinase Inhibitors in Ophthalmology Glaucoma :

Glaucoma is classified as a progressive form of optic neuropathy. The most predominant risk factor with either type is elevated IOP. In open angle glaucoma, it is proposed that this elevation in IOP is due to the clogging of AH drainage canal, through the Trabecular Meshwork (TM).[17] Although the physiological mechanism for this impairment is not entirely known, it is proposed that the best therapeutic remedy for open angle glaucoma is lowering the IOP by enhancing the outflow of AH, as shown in



Rho kinase inhibitors have been tested and proven to alter cell shape in the trabecular meshwork, allowing for enhanced AH outflow and the lowering of IOP .[18, 19]

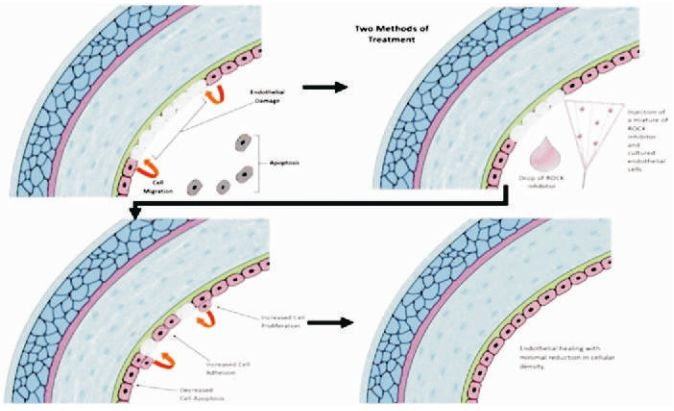
Mechanism :

Rho kinase inhibitors help lower IOP by increasing AH outflow, reducing AH production, and decreasing episcleral venous pressure (EVP).[20] This is done in two different ways, which involves Rho kinase pathway inhibition and, as with Netarsudil, norepinephrine transport inhibition.

Many ROCK-inhibiting drugs chemically include a norepinephrine transport inhibitor. This norepinephrine transport inhibitor helps reduce AH production and decreases EVP, which according to the modified Goldman equation, have a direct relationship with IOP.[21, 22] Norepinephrine transport inhibition lowers AH production by vasoconstriction, reducing blood flow to ciliary processes. A study showed that AH production may be reduced by 20% to 23% by the norepinephrine transport inhibitor .[22] This inhibitor affects the EVP via vasoconstriction, similar to the way brimonidine, a well-known vasoconstrictor, has been shown to lower EVP in animals .[23] The reduction in EVP accounts for more than a third of the reduction in IOP, as shown in a study using Dutch Belted rabbits .[24]

Mechanism of Action of ROCK Inhibitor in Corneal Endothelium Healing :

Due to the wide range of cellular responses controlled by Rho kinase signaling pathway, it is hypothesized that ROCK inhibitors could play a part in both increasing cell adhesion and proliferation in the corneal endothelium .[25] This would allow for the preservation of corneal endothelial cells and the slowing of apoptosis. For this reason, the use of Rho kinase inhibitors may also help with acute corneal endothelial damage, that can potentially occur in cataract surgery.[26] Successful clinical trials have been performed to show the positive effects of Rho kinase inhibitors on the corneal endothelium. [26, 27]



Role in vitreoretinal pathologies :

ROCK signalling pathway in the pathogenesis of DMO has increased interest in this field. Activation of the Rho kinase pathway also has a direct correlation with microvascular endothelial damage via inactivation of the nitric oxide synthase. Inhibition of nitric oxide levels prevents vasodilation and allows for apoptosis, which increases the leukocyte-induced damage. Leukocyte stasis plays a role in the microvascular complications in DR.[28] ROCK pathway has been reported to regulate certain adhesion molecules in vascular endothelial cells.[29]

ROCK inhibitors can be beneficial for patients with symptoms of DR, by reducing the adhesion of leukocytes and increasing nitric oxide levels. They also prevent RGC apoptosis.[30] ROCK inhibitors might represent a new treatment strategy in early stages of DR which usually is only observed with no ophthalmic therapeutic intervention. Intravitreal implants to deliver these ROCK inhibitors are also being studied. In the later stages of DR, retinal neovascularization and epiretinal fibrovascular membranes are formed, the contraction of which can cause tractional retinal detachment. ROCK inhibition has effectively prevented contraction of these membranes in animal model.[31] ROCK inhibitors have also been studied as therapeutic agents for diabetic macular edema [32] and retinal ischemia.

Adverse Effects of ROCK Inhibitors :

Although ROCK inhibitors showed a promising safety profile, they have both local and systemic adverse events. ROCK inhibitors induce conjunctival hyperemia and sub conjunctival hemorrhage due to their vasodilatory effect. The latter may increase the clearance of concomitantly administered topical drugs thereby reducing their intended ocular effects.[33] Other local effects include: blepharitis, ocular irritation, increased lacrimation, and blurred vision. On the systemic level, they may cause blood pressure reduction and an associated increase in heart rate.[34] Strategies allowing reduced systemic exposure as a soft drug approach have been applied to develop ROCK inhibitors for localized applications.[35] In addition, systemic ROCK inhibition was found to induce a reversible reduction in lymphocyte counts in few individuals.[36]

Conclusion:

ROCK inhibitors appear to be a promising new drug with a special mechanism of action. They can be considered as second line of treatment or as adjuvants. Along with the IOP lowering action, it increases ocular blood flow and prevents RGC death. ROCK inhibitor can consequently possibly be considered as first line of remedy in NTG. It is valuable in patients in whom IOP is not under control with maximum medical therapy, which is a common scenario in developing countries like ours.

Ripasudil may be taken into consideration as the initial drug while restarting antiglaucoma medications in post-trabeculectomy patients due to its antifibroblastic activity. ROCK inhibitors have shown promising results in secondary glaucomas as well. Its additional uses such as corneal endothelial protection and role in DR and macular edema are helpful in patients with glaucoma with these diseases. Conjunctival hyperemia being reported in a signficant number of patients might limit its use. Reassuring the patient prior to starting the drug regarding this possible side effect might go a long way in improving compliance. Additional clinical trials investigating the reviewed treatment options of Rho kinase inhibitors are necessary to further validate previous findings on the topic. Nonetheless, it is clear that Rho kinase inhibitors have the potential to be another potent therapeutic option for several chronic diseases in ophthalmology.

References :

1. Tian B, Kaufman P, Volberg T, et al. H-7 disrupts the actin cytoskeleton and increases outflow facility. Arch Ophthalmol. 1998;116:633–43.
2. Peterson JA, Tian B, Bershadsky AD, et al. Latrunculin-A increases outflow facility in the monkey. Invest Ophthalmol Vis Sci. 1999;40(5):931–41.
3. Peterson JA, Tian B, Geiger B, Kaufman PL. Effect of Latrunculin-B on Outflow Facility in Monkeys. Experimental Eye Research. 2000;70(3):307–13.
4. Tian B, Geiger B, Epstein DL, Kaufman PL. Cytoskeletal involvement in the regulation of aqueous humor outflow. Invest Ophthalmol Vis Sci. 2000;41(3):619–23.
5. Rao VP, Epstein DL. Rho GTPase/Rho kinase inhibition as a novel target for the treatment of glaucoma. BioDrugs. 2007;21(3):167-77.
6. Rao PV, Pattabiraman PP, Kopczynski C. Role of the Rho GTPase/Rho kinase signaling pathway in pathogenesis and treatment of glaucoma: Bench to bedside research. Exp Eye Res. 2017;158:23-32.
7. Burridge K, Wennerberg K. Rho and Rac take center stage. Cell. 2004;116(2):167-79.
8. Hall A. Rho GTPases and the actin cytoskeleton. Science. 1998;279(5350):509-14.
9. PubChem OCD. Compound Summary for CID 9863672, Ripasudil USA: National Center for Biotechnology Information; 2018 [updated 2018; cited 2018]. 10. Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Araie M, et al. Phase 2 randomized clinical study of a Rho kinase inhibitor, K-115, in primary open-angle glaucoma and ocular hypertension. Am J Ophthalmol. 2013;156(4):731-6.
11. Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Fukushima A, et al. One-year clinical evaluation of 0.4% ripasudil (K-115) in patients with open-angle glaucoma and ocular hypertension. Acta Ophthalmol. 2016;94(1):e26-34
12. Garnock-Johns KP. Ripasudil first global approval. Drugs. 2014;74(18):2211–2215.
13. Sturdivant JM, Royalty SM, Lin CW, Moore LA, Yingling JD, Laethem CL, et al. Discovery of the ROCK inhibitor netarsudil for the treatment of open-angle glaucoma. Bioorg Med Chem Lett.

2016;26(10):2475–80.
14. Kaneko Y, Ohta M, Inoue T, et al. Effect of K-115 (ripasudil), a novel rock inhibitor, on trabecular meshwork and Schlemm's canal and endothelial cells. Sci Rep. 2016;6:19640.
15. Serle JB, Katz LJ, McLaurin E, Heah T, Ramirez-Davis N, Usner DW, et al. Two Phase 3 Clinical Trials Comparing the Safety and Efficacy of Netarsudil to Timolol in Patients With Elevated Intraocular Pressure: Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2) Am J Ophthalmol. 2018;186:116–27.
16. Hoy SM. Netarsudil Ophthalmic Solution 002%: First Global Approval. Drugs. 2018;78(3):389–96.
17. Alvarado J, Murphy C, Polansky J, Juster R. Age-related changes in trabecular meshwork cellularity. Invest Ophthalmol Vis Sci. 1981;21(5):714–27.
18. Kameda T, Inoue T, Inatani M, Fujimoto T, Honjo M, Kasaoka N, et al. The effect of Rho-associated protein kinase inhibitor on monkey Schlemm's canal endothelial cells. Invest Ophthalmol Vis Sci. 2012;53(6):3092–103.
19. Isobe T, Mizuno K, Kaneko Y, Ohta M, Koide T, Tanabe S. Effects of K-115, a rho-kinase inhibitor, on aqueous humor dynamics in rabbits. Curr Eye Res. 2014;39(8):813–22.
20 Toris CB, McLaughlin MA, Dworak DP, Fan S, Havens S, Zhan GL, et al. Effects of Rho Kinase Inhibitors on Intraocular Pressure and Aqueous Humor Dynamics in Nonhuman Primates and Rabbits. J Ocul Pharmacol Ther. 2016;32(6):355–64.
21. Kazemi A, McLaren JW, Kopczynski CC, Heah TG, Novack GD, Sit AJ. The Effects of Netarsudil Ophthalmic Solution on Aqueous Humor Dynamics in a Randomized Study in Humans. J Ocul Pharmacol Ther. 2018;34(5):380–6.
22. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 004% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. J Glaucoma. 2015;24(1):51–4. d
23. Reitsamer HA, Posey M, Kiel JW. Effects of a topical alpha2 adrenergic agonist on ciliary blood flow and aqueous production in rabbits. Exp Eye Res. 2006;82(3):405–15.
24. Kiel JW, Kopczynski CC. Effect of AR-13324 on episcleral venous pressure in Dutch belted rabbits. J Ocul Pharmacol Ther. 2015;31(3):146–51.
25. Okumura N, Okazaki Y, Inoue R, Kakutani K, Nakano S, Kinoshita S, et al. Effect of the Rho-Associated Kinase Inhibitor Eye Drop (Ripasudil) on Corneal Endothelial Wound Healing. Invest Ophthalmol Vis Sci. 2016;57(3):1284–92.
26. Okumura N, Kinoshita S, Koizumi N. Application of Rho Kinase Inhibitors for the Treatment of Corneal Endothelial Diseases. J Ophthalmol. 2017;2017:2646904.
27. Nakagawa H, Koizumi N, Okumura N, Suganami H, Kinoshita S. Morphological Changes of Human Corneal Endothelial Cells after Rho-Associated Kinase Inhibitor Eye Drop (Ripasudil) Administration: A Prospective Open-Label Clinical Study. PLoS One. 2015;10(9):e0136802
28 Noda K, Nakao S, Ishida S, Ishibashi T. Leukocyte adhesion molecules in diabetic retinopathy. J Ophthalmol 2012;2012:279037.
29. Anwar KN, Fazal F, Malik AB, Rahman A. RhoA/Rho-associated kinase pathway selectively regulates thrombin-induced intercellular adhesion molecule-1 expression in endothelial cells via activation of I kappa B kinase beta and phosphorylation of RelA/p65. J Immunol 2004;173:6965-72.
30. Arita R, Hata Y, Nakao S, Kita T, Miura M, Kawahara S, et al. Rho kinase inhibition by fasudil ameliorates diabetes-induced microvascular damage. Diabetes 2009;58:215-26.
31. Kita T, Hata Y, Arita R, Kawahara S, Miura M, Nakao S, et al. Role of TGF-beta in proliferative vitreoretinal diseases and ROCK as a therapeutic target. Proc Natl Acad Sci U S A 2008;105:17504-9.
32. Ahmadieh H, Nourinia R, Hafezi-Moghadam A. Intravitreal fasudil combined with bevacizumab for persistent diabetic macular edema: A novel treatment. JAMA Ophthalmol 2013;131:923-4.
33. Arnold JJ, Hansen MS, Gorman GS, et al. The effect of rho-associated kinase inhibition on the ocular penetration of timolol maleate. Invest Ophthalmol Vis Sci. 2013;54(2):1118–1126.
34. Lohn M, Plettenburg O, Kannt A, et al. End-organ protection in hypertension by the novel and selective rho-kinase inhibitor, SAR407899. World J Cardiol. 2015;7:31–42.
35. Bolanda S, Deferta O, Alenet J, et al. 3-[2-(aminomethyl)-5-[(pyridin-4-yl)carbamoyl]phenyl] benzoates as soft ROCK inhibitors. Bioorg Med Chem Lett. 2013;23(23):6442–6446.
36. Shaw D, Hollingworth G, Soldermann N, et al. Novel ROCK inhibitors for the treatment of pulmonary arterial hypertension. Bioorg Med Chem Lett. 2014;24:4812–4817.

Visual Functions and Spectacle Usage in Elderly Patients Sustaining A Simple Fall

Rajat M Srivastava, MS; **Siddharth Agrawal,** MS; **Ashish Kumar** MBBS; **Vishal Katiyar,** MS; **Sanjiv K Gupta,** MS

Department of Ophthalmology, King George's Medical University, Lucknow, India.

Correspondence : **Siddharth Agrawal,** Additional Professor, Ophthalmology, King George's Medical University, Lucknow, India

e-mail : agrawalsiddharth@rediffmail.com

Abstract :

Aim : The aim was to study visual functions and spectacle usage in elderly patients sustaining a simple fall. Objectives were to study (i) the compromise in binocular visual acuity, contrast sensitivity, binocular visual fields and stereopsis (ii) the frequency of use and type of spectacles (iii) association of visual functions and spectacle use with simple fall

Methods : This was a prospective cross-sectional observational study of a one-year study duration (July 2018-July 2019). Consecutive patients above 60 years of age presenting to Ophthalmology OPD for refraction were recruited. History of experiencing a simple fall in the previous six months, duration since their last ophthalmology consultation and details regarding spectacle used was taken. Binocular visual acuity, contrast sensitivity, distance stereopsis, and Esterman binocular field were assessed. These factors were then analysed to study any association with history of simple fall.

Result : Out of 399 patients enrolled in the study, 229 (57.4%) were females and 170 (42.6%) males. The mean age of the patient was 65±3 years (61-78 years. 274 (68.4%) patients presented with visual acuity of less than 6/18. 128 (32.1%) patients were not using any glasses and 221 (55.4%) patients had not taken ophthalmology consultation in the previous two years. History of simple fall was given by 110 (27.6) patients. Patients with reduced distance stereopsis (p=0.00 CI 1.389-3.408), depressed binocular visual fields (p=0.01 CI 1.116-2.736), more than two years since last ophthalmology consultation (p=00 CI 1.83-4.81) and without glasses (p=0.00 CI 1.508-3.757) were more likely to have experienced simple fall in previous six months.

Conclusion : More than 50% of the elderly in the present study suffered from visual impairment, reduced stereopsis and depressed binocular visual fields and approximately one-third of them sustained falls in the previous six months. Elderly patients without spectacle correction, impaired contrast sensitivity, and depressed binocular fields were more likely to experience a simple fall.

Introduction :

It is well documented that poor vision is an important risk factor in falls caused by postural instability and that impaired vision is highly prevalent and commonly unreported in the elderly population, particularly women.[1,2,3,4] Reduced contrast sensitivity, stereopsis, use of multifocal glasses and visual field loss are other important risk factors contributing to falls.[5,6,7,8] Falls and associated fractures are an important cause of morbidity and mortality in the elderly. A study highlighted the association of potentially treatable visual impairment and fractures in elderly population. The authors also concluded that a lack of provision of ophthalmic services may be cause of fracture associated with fall in elderly.[9]

According to population estimates, India is home to more than 100 million elderly (above 60 years) and this figure is expected to treble by 2050.[10] With numerous studies pointing to association between impaired visual functions and falls among elderly, there is a paucity of such studies in elderly Indian population. Furthermore, with pressing shortage of ophthalmic care, unrecognised visual impairment is not uncommon in India.[11] The present study thus aims to study visual functions and assess the presence of visual impairment and spectacle use among elderly sustaining simple fall in the previous six months.

Methodology :

Consecutive patients presenting to Ophthalmology out- patient department (OPD) for refraction were screened. Patients above 60 years of age were identified and enrolled in the study after taking their informed consent. All the participants were enquired if they had experienced any 'simple fall' in the previous six months. A simple fall was defined as any fall due to tripping, slipping, colliding against an obstacle or stepping on an uneven surface. Any fall from height, following road traffic accidents, fights or brawls and under the influence of alcohol was excluded. All the study participants were also enquired about the time since their last ophthalmic consultation. Previous medical records were screened to ascertain the time since last ophthalmic consultation. Binocular visual acuity (VA) and contrast sensitivity assessment was done using Snellen and Pelli-Robson's charts respectively. Visual acuity assessment using spectacles was done for patients who had spectacles at presentation and the type of spectacle in use was also recorded. Distance stereopsis was measured using Randot Test. Esterman binocular visual field (EBVF) testing using Humphrey Visual Field Analyser was also done for all patients.

Visual impairment was defined as presenting binocular VA <6/18, Contrast Sensitivity was considered abnormal if below 1.5 and Visual field impairment was defined as a loss of 20 or more points on BVF.[5,9,12] Distance stereopsis less than 100 seconds of arcs was considered abnormal .[12]

Statistics and sample size calculation :

A sample size of 323 patients was calculated considering average fall prevalence of 30% using Cochran's formula N=Z2P(1-P)/e2 (Z=1.96,P=0.3,e=0.05). Descriptive analysis of numerical data was done in range and mean with standard deviation. Number of subjects with visual impairment, reduced contrast sensitivity and stereopsis, and compromised BVF was expressed in percentages. Comparison of visual functions and demographic characteristics between patients with and without fall was done using independent t-test and Chi-square test was applied to study their association with fall. A 'p' value of <0.05 was considered to be statistically significant. Statistical analysis was done using Statistical Package for Social Sciences software version .[21]

Results :

In the study population of 399 patients above the age of 60 years, there was a female preponderance (57%). The mean age of patients was 65.27 ± 3 years (61-78 years). More than 55% of patients in our study had not visited any Ophthalmologist/Optometrist in previous two years and about one third of the patients were not found to be using any glasses at presentation .

Table 1 : Clinico-epidemiological profile of the patients

1.	Age
	a. 65.27±3 years (Mean±SD)
	b. 61- 78 years (Range)
2.	Gender
	a. Male: 170 (42.6%)
	b. Female: 229 (57.4%)
3.	Last Ophthalmic Consultation
	a. ⩾ 2 years: 221 (55.4%)
	b. < 2 years: 178 (44.6%)
4.	Using Glasses at Presentation
	a. Yes: 271 (67.9%)
	b. No: 128 (32.1%)
5.	Type of Glasses
	a. Muti/Bifocal: 162 (59.8%)
	b. Unifocal: 109 (40.2%)
6.	History of Fall
	a. Yes: 110 (27.6%)
	b. No: 289 (72.4%)

Among those who were using spectacles, almost 60% of patients were found to be using multifocal/bifocal glasses. Majority of the patients in our study were found to be visually impaired with 69% of patients presenting with binocular vision <6/18 on Snellen's chart.

110 (27.6%) patients gave history of experiencing at least one instance of simple fall in last six months of presenting to us. Mean age of the patients with fall history was 66±4 years. Most of the patients were females. Almost 65% of patients in our study suffered from visual impairment. Among other visual functions, almost 62% patients had impaired EBVF, 30% had abnormal contrast sensitivity and 50% had abnormal distance stereopsis (Table 2).

Table 2 : Clinico-epidemiological profile of the patients

1.	Binocular Visual Acuity
	a. ⩽6/18 : 274 (68.7%)
	b. >6/18: 125 (31.3%)
2.	Contrast Sensitivity
	a. ⩽1.5: 132 (33.1%)
	b. >1.5: 267 (66.9%)
3.	Stereopsis
	a. <100 seconds of arc: 146 (36.6%)
	b. ⩾100 seconds of arc: 253 (63.4%)
4.	Esterman Binocular Visual Field
	a. <20 points depression: 192 (48.1%)
	b. ⩾20 points depression: 207 (51.9%)

Majority (68%) of patients with history of fall were using multifocal/bifocal glasses. We also found significantly better binocular visual acuity (p=0.009) and contrast sensitivity (p=0.034) among those using multifocal/bifocal glasses compared to monofocal glasses.

There was no significant association between gender (p=0.51, C.I 0.552-1.348) and age (P=0.65, C.I 0.746-1.426) with history of fall in our study. The patients who did not seek any ophthalmic consultation in the previous two years were 2.9 times more likely to sustain fall (p=0.000, C.I 1.83-4.81). Visual function analysis did not reveal any statistically increased risk of fall with impaired visual acuity (p=0.27, C.I 0.484-1.228) and contrast sensitivity (p=0.41, C.I 0.512-1.322). However, patients with reduced distance stereopsis and abnormal EBVF were 2.17 times (p=0.001, C.I 1.389-3.408) and 1.74 times (p=0.014, C.I 1.116-2.736) more likely to have experienced fall respectively .

Table 3 : Factors associated with history of simple fall among elderly (Statistically significant figures in bold)

Factor	Risk Estimate for simple fall	P-value (<0.05)	Confidence Interval (95%)
Gender	0.8	0.51	0.552-1.348
Impaired Visual Acuity	0.7	0.27	0.484-1.228
Impaired contrast Sensitivity	0.8	0.41	0.512-1.322
Reduced Distance Stereopsis	2.2	0.00	1.389-3.408
Abnormal Esterman Binocular Visual Field	1.7	0.01	1.116-2.736
Time since last Ophthalmology Consultation (> 2 years)	2.9	0.00	1.83-4.81
Use of Glasses	2.4	0.00	1.508-3.757
Type of Glasses	1.5	0.15	0.844-2.859

Though there was no significant relation between the type of glasses and fall (p=0.155 CI 0.844-2.859), those not using glasses were 2.4 times more likely to fall compared to those using glasses (p=0.00 CI 1.508-3.757).

Discussion :

Studies from the developed world have reported an association of poor vision and female gender with fractures in elderly following fall.[4,9] However, about 30% to 50% of falls result in minor injuries only.[9] Unlike past studies, we have analysed visual functions in all patients sustaining fall and thereby have tried to eliminate any bias created by recruiting only patients with fractures. We found 26.7% of our study participants with female preponderance to give history of fall in previous six months. This is similar to the reported prevalence range of falls across various regions of India . Unlike previous study, we did not find any association between gender and fall. This could probably be because we have considered all patients sustaining falls and not only fracture, given the fact that females are more prone to fractures .

Visual impairment is a common occurrence in elderly and a higher fall prevalence ratio among those with reduced distant visual acuity has been reported in past studies.[15] Alike a past study, in this study too binocular visual acuity was measured with glasses among those who had them at presentation and without glasses among those who did not.[9] This is believed to emulate the true visual status routinely experienced by the participants. Futher more, measuring best corrected vision may undermine the actual prevalence of visual impairment. Community based studies from India have reported 25% to 36% prevalence of visual impairment among elderly [16,17] In contrast to this, we have found 69% of the participants in our study to be suffering from visual impairment. Since the study participants were recruited from an Ophthalmology OPD, over estimation of visual impairment among participants is plausible. More than 65% of the participants with fall in our study presented with impaired binocular distant visual acuity . In spite of higher occurrence of visual impairment among fall patients, our study did not find any significant association between visual impairment and fall. This lack of significance could be explained by relatively high occurrence of visual impairment in the overall study population. Furthermore, studies have pointed to contrast sensitivity, depth perception and visual field loss besides visual acuity to be associated with falls among elderly.[5,24] Similarly, this study also points to a significant association between reduced distance stereopsis and depressed binocular visual fields with increased risk of fall. These results not only implicate impaired visual functions other than visual acuity for fall among elderly but also a regular need for their assessment.

Interestingly, 67% of the patients in our study were wearing spectacles, which is higher than the spectacle prevalence rate of 29% among elderly reported from south India.[20] This higher prevalence could again be due to bias created by selecting patients from Ophthalmology OPD. Our study found that those patients who were not using any glasses at presentation were twice more likely to have experienced fall. This reiterates the need to address uncorrected refractive error among elderly as a preventive measure against fall. Majority of the patients wearing glasses in our study were using multifocal glasses, a trend similar to the reported trend of spectacle use in India.[25] Unlike the previous studies, we did not find any significant increased risk of fall with multifocal compared to monofocal glasses in our study.[8] Detailed analysis revealed that among those with history of fall, both visual acuity and contrast sensitivity was better in patients using multi focal glasses. Perhaps image jump occurring due to changes in spectacle position while walking may be a factor for causing falls. Having said this, more than 55% of the participant had not consulted any eye care services in the previous two years. In a past study, more than 70% patients with hip fracture following fall had not seen an Ophthalmologist or an Optometrist in the preceding 3 years.[9] We found that those who had not consulted any Ophthalmologist in the last two years were 2.9 times more at risk of fall compared to those who took consultation. This suggested that perhaps majority had not got their refraction done over last two years and continued to use old glasses. Thus wearing inappropriate glasses can also enhance the risk of falls in elderly.[24]

Based on these observation we propose regular examination of distance stereopsis, contrast sensitivity and binocular visual fields in addition to visual acuity assessment of elderly patients especially in an Ophthalmology setup. Since uncorrected refractive error is high among elderly, prescribing appropriate glasses would reduce the incidence of falls among them. We also propose the use of only distance correction while walking, especially in elderly to avoid falls.

We noticed a few shortcomings in our study. Since this was a tertiary care based institutional study, the results of the study

may not be applicable on general population. Though the study was able to identify the visual risk factors among elderly with falls, a case control study design would have better elucidated the association of risk factors with fall. An analysis of coexisting ocular morbidities could have also explained the causes of visual impairment, this was not the objective of the present study. Furthermore, the occurrence of falls reported in the present study was subject to patient's recall and thus may not be totally reliable.

Conclusions :

Over 50% of elderly in the present study suffered from visual impairment, reduced stereopsis and depressed binocular visual fields and approximately one third of them sustained fall in previous six months. There was significant association between impaired stereopsis and binocular visual field with fall. Spectacle usage was seen in 67% of the elderly and majority of them used multifocal glasses. Though there was no association of fall history and type of glasses used, those who did not use any glasses were twice more likely to have experienced simple fall.

References:

1. Anand V, Buckley J, Scally A. The effect of refractive blur on postural stability. Ophthalmic Physiol Opt 2002;22(6):528–34.
2. Dargent-Molina P, Hays M, Breart G. Sensory impairments and physical disability in aged women living at home. Intern J Epidemiol1996; 25: 621–9.
3. Klein BE, Moss SE, Klein R, Lee KE, CruickshanksKJ.Associations of visual function with physical outcomes and limitations 5 years later in an older population: the Beaver Dam eye study. Ophthalmology. 2003 ;110(4):644-50.
4. Oner M, OnerA, Güney A, Halici M, Arda H, Bilal O. Evaluation of visual functions in elderly patients with femoral neck fracture. EklemHastalikCerrahisi. 2009;20(3):143-86.
5. Coleman AL, Cummings SR, Ensrud KE, Yu F, Gutierrez P, Stone KL, Cauley JA, Pedula KL, Hochberg MC, Mangione CM. Visual field loss and risk of fractures in older women.J Am Geriatr Soc. 2009 ;57(10):1825-32.
6. Abdelhafiz AH, Austin CA. Visual factors should be assessed in older people presenting with falls or hip fracture. Age Ageing. 2003 ;32(1):26-30.
7. D M Squirrell, J Kenny, N Mawer, M Gupta, J West, Z I Currie, I M Pepper and C A Austin. Screening for visual impairment in elderly patients with hip fracture: validating a simple bedside test. Eye (2005) 19, 55–59.
8. Lord SR, Dayhew J, Howland A. Multifocal glasses impair edge contrast sensitivity and depth perception and increase the risk of falls in older people. J Am GeriatrSoc 2002; 50: 1760–6.
9. Cox A et al. Visual impairment in elderly patients with hip fracture: causes and associations. Eye 2005;19:652–656.
10. United Nations Population Fund 2017. 'Caring for Our Elders: Early Responses' - India Ageing Report – 2017. UNFPA, New Delhi, India
11. Sheeladevi S, Seelam B, Nukella PB, Borah RR, Ali R, Keay L. Prevalence of refractive errors, uncorrected refractive error, and presbyopia in adults in India: A systematic review. Indian J Ophthalmol. 2019;67(5):583–592.
12. Wang J, Hatt SR, O'Connor AR, et al. Final version of the Distance RandotStereotest: normative data, reliability, and validity. J AAPOS. 2010;14(2):142–146.
13. Joseph A, Kumar D, Bagavandas M. A Review of Epidemiology of Fall among Elderly in India. Indian J Community Med. 2019;44(2):166–168.
14. Tsuda T. Epidemiology of fragility fractures and fall prevention in the elderly: a systematic review of the literature. CurrOrthopPract. 2017;28(6):580–585.
15. Ivers RQ, Cumming RG, Mitchell P, Attebo K. Visual impairment and falls in older adults: the Blue Mountains Eye Study. J Am Geriatr Soc. 1998;46:58-64.
16. Vignesh D, Gupta N, Kalaivani M, Goswami AK, Nongkynrih B, Gupta SK. Prevalence of visual impairment and its association with vision-related quality of life among elderly persons in a resettlement colony of Delhi. J Family Med Prim Care. 2019 ;4:1432-1439
17. R D, Kasthuri A. Visual and hearing impairment among rural elderly of south India: a community-based study. GeriatrGerontol Int. 2012; 12:116-22

LIKE – A NEW TECHNIQUE

Dr Krueger and others are beginning clinical investigation of a technique popularised by Dr Theo Seiler, called LIKE (lenticular implantation keratoplasty). This involves shaping donor corneal tissue with Bowman's layer using a lenticule cavity unit, which defines the precise shape profile and power. The implanted lenticule power is targeted to be greater, and placed under the large LASIK flap of moderate-to-high hyperopia eyes, making it possible to later lift the flap for a myopic or customised ablation enhancement. In the first 12 eyes treated for up to +8.5D in Europe and India, five have so far received a laser ablation one-to-three months after implantation, and one required a replacement implant.

Of the first nine, no eye lost more than one line and three gained two lines at six months. Four had slight, temporary lenticular haze, less than typically seen with LASIK, Dr Krueger said. LIKE-shaped lenticules are also being shaped for treating keratoconus by placing the lenticule in a corneal stromal pocket.

"High hyperopia, presbyopia and keratoconus are just a few of the errors that will implement this technology in the future. Refractive eye-banking will be the emerging, new market and partnership that brings this technology to our field,"

Dr Krueger concluded.

To Study the Efficacy of Intravitreal Injection Ranibizumab on Cystoid Macular Edema in the Retinal Vein Occlusion

Anzar Ahmed, M.B.B.S; **Ram Kumar Jaiswal,** M.B.B.S, M.S;
Ajit Pandey, M.B.B.S, M.S; **Avinash Gupta,** M.B.B.S
Department of Ophthalmology, BRD Medical College ,Gorakhpur • Correspondence E-mail address - ahmedanzar066@gmail.com

Abstract :

Aim and objective : To study the efficacy of intravitreal injection ranibizumab on cystoid macular edema in the retinal vein occlusion (RVO).

Method and material : in our study 22 eyes of 22 patients with cystoid macular oedema due to retinal vein occlusion were given intravitreal injection ranibizumab 0.50 mg in 0.05ml and followed up in the post op period to see the effect. An observational study has been conducted for it.

Results : The mean age group was 56.36±8.11.Total 22 patients with 17 males (77.27%) and 5 females (22.73%) were taken with no drop out.The mean average change in BCVA improved substantially from 6/60 to 6/18 and with mean central retinal thickness decrease from 546µm to 315µm . 22 patients with retinal vein occlusion were included in our study. 6 patients had CRVO while rest 16 patients had BRVO.

Conclusion : Intravitreal Ranibizumab is safe and is effective in improving BCVA in cystoid macular edema due to retinal vein occlusion.

Key words : Ranibizumab, Cystoid macular edema, Central retinal thickness

Introduction:

Retinal vein occlusion is the second most common retinal vascular disorder after diabetic retinopathy.[1] Amongst retinal vein occlusion branch retinal vein occlusion(BRVO) is most common cause. Macular edema occurring in about 60% of cases is the most frequent cause of visual loss in patients with BRVO.[2] BRVO can lead to fluid leakage which occurs in response to increased intravascular pressure behind the occlusion. In BRVO retinal is chemia induces the secretion of inflammatory mediators like vascular endothelial growth factor (VEGF) which is the major cause of breakdown of the blood-retinal barrier, endothelial dysfunction and increased vascular permeability.[3] Based on the localization, branch RVO (BRVO) is defined as occlusion of a branch of the retinal vein system and central RVO (CRVO) is defined as occlusion located in the central retinal vein.[4,5] RVO is a significant cause of vision loss with overall incidence of 0.21% among patients above 40 years of age.[6] It is estimated that approximately 16 million people develop RVO worldwide out of which BRVO comprises 80% of cases. [8]

RVO causes severe loss of vision due to macular edema, retinal neovascularization and retinal detachment.[9] Arterial stiffness is main pathogenesis for the development of BRVO. It can cause venous compression in the common adventitial sheath. [4,7] The main risk factors of BRVO are aging, cardiovascular diseases, smoking and hypertension.[10]

Several treatment modalities for treatment of macular edema secondary to BRVO which are currently available are laser photocoagulation, intravitreal dexamethasone implants and anti-VEGF agents such as ranibizumab, bevacizumab, and aflibercept.[11] Recently anti-VEGF agents are being used more frequently in macular edema in BRVO treatment. VEGF and the aqueous concentration of inflammatory factors are found significantly increased in eyes with macular edema secondary to BRVO.[12] Anti-VEGF agents can achieve anatomical resolution of macular edema, stabilization and improvement of the best-corrected visual acuity (BCVA) in BRVO patients.[13,14] Ranibizumab is the first VEGF inhibitor to be approved by USFDA for use in BRVO.[15] A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion (CRUISE) trials have demonstrated the benefits of ranibizumab on visual acuity and central macular thickness (CMT) both branched retinal vein occlusion and central retinal vein occlusion.[15,16]

Aim and objective :

To study the efficacy of intravitreal injection ranibizumab on cystoid macular edema in the retinal vein occlusion (RVO).

Method and material :

We conducted an observational study in which we observed 22 eyes of 22 patients with cystoid macular edema due to retinal

vein occlusion were given intravitreal injection ranibizumab 0.50 mg in 0.05ml and followed up in the post op period to see the effect. This is study was done in B.R.D medical college, Gorakhpur.

Inclusion Criteria :

- Age >20
- Macular oedema secondary to BRVO and CRVO
- BCVA between 6/60 -6/18

Exclusion Criteria :

- Participant not willing to give informed consent
- Any ocular infection in either eye present at time of study.
- Previous episode of RVO.
- History of corticosteroid in traocular or periocular within 3 Month.
- Any ocular disease that compromise visual acuity or require medical or surgical intervention in the study eye during study period.
- Glaucoma with in traocular pressure (IOP) ≥30 mmHg on medication at the screening or within 6 months before the baseline visit.
- Neo vascularization of the iris or neo vascular glaucoma in either eye at time of study.
- Past episode of RVO in the study eye.
- Previous treatment with any anti-angiogenic drug in either eye within 3 months before the baseline visit.
- Any systemic anti-VEGF drug taken within 6 months before the baseline visit.
- History of stroke.
- Uncontrolled blood pressure ⩾170/110mmHg

Examination :

- Informed consent was taken from all patients taken for the study and following preoperative evaluation
- Visual acuity assessment
- Intra-ocular pressure
- Slit lamp examination for anterior Segment
- Fundus examination-Direct and Indirect ophthalmoscopic
- Optical coherence tomography

Technique of injecting intravitreal Ranibizumab :

The test eye was topically anesthetized and povidone iodine (10%) disinfection was done on lids and lashes. Using sterile speculum eyelids were retracted and three times Povidone iodine (5%) drops were instilled on the ocular surface. Additional topical anesthesia was achieved via 4% lidocaine. Then Ranibizumab (0.05 ml in 0.50mg) in an insulin syringe with a 30-gauge needle was injected through the pars plana into the vitreous cavity through the sclera 3 to 4 mm posterior to the limbus at infero-temporal quadrant. After injecting Ranibizumab light perception was assessed and in traocular pressure(IOP) was taken. Then patient was asked to put topical antibiotics to the injected eye 4 times a day for 3 days. Post injection follow-up was done on day 1 , day 7, day 15 and on day 30.

OBESERVATIONS :

Table 1: Number of patients distributed into the type of RVO:

Disease	Male	Female	Total	%
CRVO	4	2	6	27.27
BRVO	1	6	16	72.73

Table 2 : Change in BCVA in BRVO patients with respect to number of patients following 1 month of 1st, 2nd Intravitreal ranibizumab injection

BCVA	1st IVR	2nd IVR
1 line(6/60)	1	2
2 line(6/36)	2	1
3 line(6/24)	10	11
4 line(6/18)	3	2
5 line(6/12)	-	-
Total no. of patients	16	16

Table 3 : Change in central macular thickness(µm) 1 month after 1st and 2nd intravitreal ranibizumab injection.

INTRAVITREAL RANIBIZUMAB INJECTION	CMT PRIOR TO IVR (µm)	CMT POST -IVR (µm)	DIFFERENCE IN CMT POST - IVR (µm)
PRE-INJECTION	546.32 ± 41.50	-	-
1ST IVR	546.32 ± 41.50	373.45 ± 87.01	173.77 ± 72.90
2ND IVR	373.45 ± 87.01	315.45 ± 74.36	58.09 ± 40.96

Results :

22 patients with retinal vein occlusion were included in our study. 6 patients had CRVO while rest 16 patients had BRVO.

The mean age group being 56.36 ± 8.11.

Observations in relation to cmt :

It was observed that the mean central macular thickness in pre-injection patients was 546.32 ± 41.50 µm.

After 1 month of post-injection of 1st intravitreal Ranibizumab the mean central macular thickness was found to be 373 ± 87.01 µm, a mean difference of 173.77 ± 72.90 µm.

2nd intravitreal ranibizumab injection had CMT of 373 ± 87.01 µm resulted in mean reduction of CMT 315 ± 74.36 µm, with a mean difference of 58.09 ± 40.96 µm.

Discussion :

This study was done to confirm the effect of Ranibizumab 0.50 mg in patients with macular edema secondary to BRVO and CRVO.

Ranibizumab treatment was associated with rapid gain of BCVA within the first month after treatment was started.

It was associated with a rapid decrease of central macular thickness of 173µm in first intravitreal injection of Ranibizumab..

IOP was stable post injection.

No injection related complications were seen.

None of patients developed systemic or ocular side effects.

Conclusion :

In observational study, an intravitreal Ranibizumab injection 0.50 mg in 0.05 ml for cystoid macular edema due to retinal vein occlusion was found safe and well tolerated with improvement in visual acuity and reduction in central macular thickness on OCT.

Gain in visual acuity and decrease in central macular thickness was statistically significant after intravitreal Ranibizumab 0.50mg in 0.05ml.

References:

1. Yamaguchi Y, Otani T, Kishi S. Serous macular detachment in branch retinal vein occlusion. Retina. 2006;26(9):1029–1033.
2. Sekiryu T, Iida T, Sakai E, et al. Fundus autofluorescence and optical coherence tomography findings in branch retinal vein occlusion. J Ophthalmol. 2012;2012:1–8.
3. Channa R, Smith M, Campochiaro PA. Treatment of macular edema due to retinal vein occlusions. Clin Ophthalmol. 2011;5:705–713.
4. Kolar P. Definition and classification of retinal vein occlusion. Int J Ophthalm Res. 2016;2:124–9.
5. Song WT, Xia XB. Ranibizumab for macular edema secondary to retinal vein occlusion: a meta-analysis of dose effects and comparison with no anti-VEGF treatment. BMC Ophthalmol. 2015;15.
6. David R, Zangwill L, Badarna M, Yassur Y. Epidemiology of Retinal Vein Occlusion and Its Association with Glaucoma and Increased Intraocular Pressure. Ophthalmologica. 1988;197(2):69–74.
7. Rehak J, Rehak M. Branch Retinal Vein Occlusion: Pathogenesis, Visual Prognosis, and Treatment Modalities. Curr Eye Res. 2008;33(2):111–31.
8. Minami Y, Nagaoka T, Ishibazawa A, Yoshida A. Correlation between short- and long-term effects of intravitreal ranibizumab therapy on ji17. BMC Ophthalmol. 2017;17(1):90.
9. Aghdam KA, Reznicek L, Sanjarim MS, Framme C, Bajor A, Klingenstein A, et al. Peripheral retinal non perfusion and treatment response in branch retinal vein occlusion. Int J Ophthalmol. 2016;9(6):858–62.
10. Rezar S, Eibenberger K, Bühl W, Georgopoulos M, Erfurth US, Sacu S, et al. Anti-VEGF treatment in branch retinal vein occlusion: a real- world experience over 4 years. Acta Ophthalmol. 2015;93(8):719–25.
11. Glanville J, Patterson J, Mccool R, Ferreira A, Gairy K, Pearce I. Effi¬cacy and safety of widely used treatments for macular oedema secondary to retinal vein occlusion: a systematic review. BMC Ophthalmol. 2014;14(14):7.
12. Noma H, Funatsu H, Mimura T, Tatsugawa M, Shimada K, Eguchi S. Vitreous inflammatory factors and serous macular detachment in branch retinal vein occlusion. Retina. 2012;32(1):86–91.
13. Noma H, Funatsu H, Mimura T, Shimada K. Comparison of the effi¬cacy of intravitreal triamcinolone acetonide for cystoid macular edema with versus without serous retinal detachment in branch retinal vein occlusion: influence on macular sensitivity and morphology. BMC Ophthalmol. 2012;12(1):1–10.
14. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology. 2011;118(8):1594–1602.
15. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macu¬lar edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117(6):1124–1133.
16. Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117(6): 1102-1112.

Successful Outcome of Autologous Simple Limbal Epithelial Transplant (Slet) in Unilateral Paediatric Limbal Stem Cell Deficiency

Akanksha Sinha, MBBS, MS

Cornea Specialist, Shankara Hospital, Mandhana, Kanpur

Introduction:

Corneal epithelium is a thin transparent layer of cornea which needs to be replenished by the limbal stem cells throughout the life and any loss of function of this non-keratinised layer leads to severe opacification resulting in reduced vision or blindness .[1] Such loss of limbal stem cells can be primary, when there is no microenvironment to help limbal stem cells thrive, like in aniridia or sclerocornea or it can be secondary to traumatic destruction of limbal stem cells by chemical or thermal injury or secondary to Steven Johnson Syndrome and ocular cicatricial pemphigoid or following multiple ocular surgeries.The triad of signs seen in patients with limbal stem cell deficiencies (LSCD) are progressive vascularization, conjunctivalization, and scarring of the corneal surface.[2]

Management options depend on whether LSCD is partial or total and whether it is involving one or both eyes. Variety of techniques have been described which include Conjunctival limbal autograft (CLAU), Cultivated limbal stem cell transplant (CLET) to the most recent and preferred revolutionary technique Simple Limbal Epithelial Transplant (SLET) described by Sangwan et al in 2012 which involves directtransplantation of small donor limbal tissue on amniotic membrane after pannus excision for ocular surface reconstruction .[2-3]

Case vignette :

A 5yr old girl child presented to us with whitish lesion along with poor vision in her left eye following an unknown injury to her left eye at the age of 10 months. On examination child's left eye was found to have total LSCD with 1 quadrant symblepharon (Fig.1a, 1b)

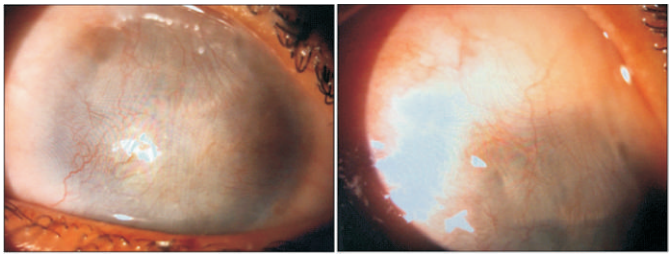


Figure 1 a : *Figure 1 b :*

Total LSCD with1 quadrant symblepharon

esotropia and amblyopia.

Her right eye was within normal limits. In view of normal B-scan and child being able to perceive projection of light rays accurately along with wet ocular surface SLET with symblepharon release and conjunctival auto graft was done. She is able to fix though unsteadily with the left eye now and is planned for lens aspiration and squint surgery subsequently along with amblyopia therapy.

Surgical technique :

Procedure was done under general anaesthesia in view of paediatric age group. Pre operative brimonidine eye drops were used twice 10 minutes prior to surgery with an aim to achieve a relatively bloodless field during surgery. Donor limbal biopsy and conjunctival auto graft was harvested from the healthy right eye. 4mm was measured with a caliper and marking of superior conjunctiva was done behind the limbus taking care not to damage limbal stem cells. A bleb was created to lift a conjunctival flap and fine dissection using a no.15 blade was done until the clear cornea was reached. Conjunctival auto graft part was excised off using a Wescott scissors and carefully placed on teflon block to be later used in the area of symblepharon. 1 clock hour donor limbal biopsy was also excised and placed on teflon block and both conjunctival graft and limbal biopsy were kept wet using balanced salt solution (BSS). The donor site was closed after repositing the conjunctival flap using fibrin glue (Tissel kit, Baxter). Recipient

eye preparation was done by complete symblepharone release and careful and gentle dissection of conjunctival pannus using a combination of blunt and sharp dissection starting from periphery. Gentle cautery was used to achieve haemostasis. Conjunctival auto graft was placed in the area of symblepharon using fibrin glue following which human amniotic membrane was placed over the recipient bed with basement membrane side facing up and secured using fibrin glue. Tucking of amniotic membrane under conjunctival edge all along the four quadrants using a blunt spatula was done ensuring it to besmooth with no folds. Limbal tissue was cut into 8 pieces and placed over the mid periphery of the cornea in a concentric pattern ensuring epithelial side of the limbal tissue was facing up. Fibrin glue was used to secure the tissue and following it a bandage contact lens was applied. Postoperatively topical prednisolone acetate 1% and moxifloxacin 0.5% was started 6 times and 4times respectively for the first week. Topical steroids were tapered weekly. Bandage contact lens was removed after 1st month and complete epithelialisation of ocular surface was noted .

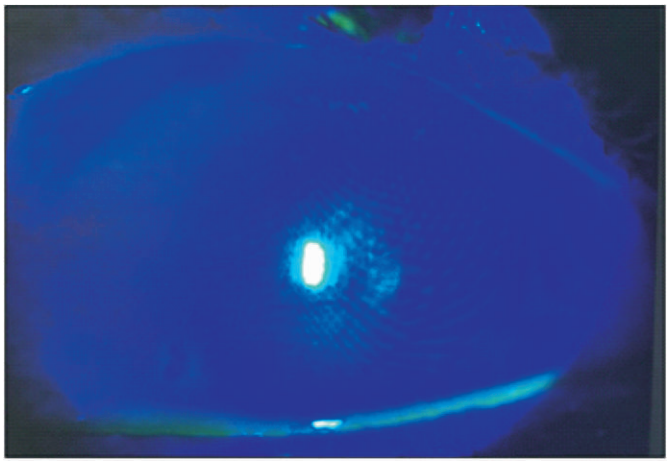


Figure 2 : Complete epithelialisation

Exuberant stromal bed

vascularity decreased with significant clearing of cornea over a period of 3 months with visible iris and lens details.

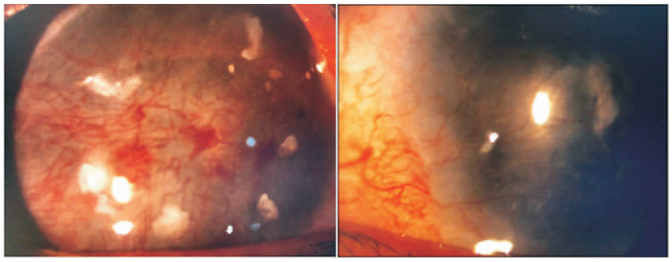


Figure 3 a : Exuberant stromal vascularity with corneal haze at 1 week decreasing at 1 month

Figure 3 b : and 3 months

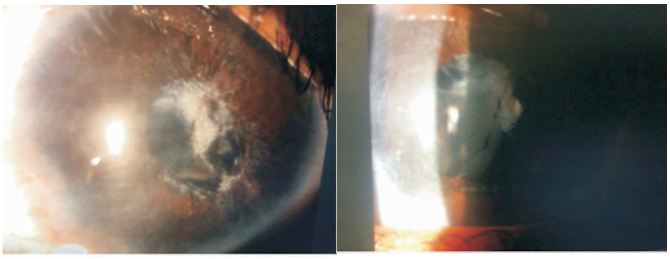


Figure 3 c : with visible iris and lens details

Figure 3 d :

No recurrence of symblepharon or LSCD was noted

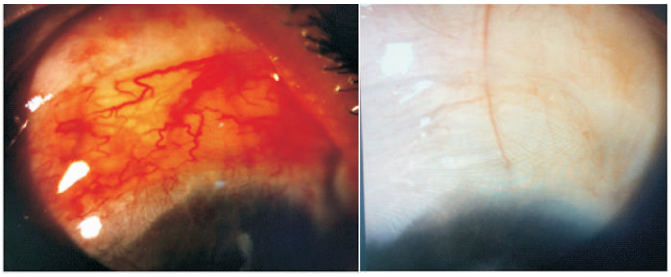


Figure 4 a :

Figure 4 b :

Conjunctival autograft well secured in the area of symblepharon with no recurrence of symblepharon at the last follow up of 6 months

Donor site was healthy. She was able to fix with her left eye, though unsteadily and is planned for lens aspiration and amblyopia therapy and subsequent squint surgery.

Discussion :

The most common indication of autologous SLET is unilateral LSCD secondary to ocular burns.

SLET is contraindicated in dry ocular surface with disorganised anterior segment and uncorrected adnexal pathologies.[1] SLET has an advantage of being a single stage procedure. It utilises a small amount of donor tissue and does not require a stem cell laboratory. SLET works by multidirectional growth of epithelial cells from each explant until a uniform confluent epithelial sheet is formed and amniotic membrane acts as a scaffold for this growth.[3] This multidirectional growth with complete epithelialisation in 2 weeks was beautifully demonstrated on serial imaging and fluorescein staining by Mittal et al and on high definition spectral domain OCT by Chaudhuri et al.[4,5] SLET being only epithelial regenerative procedure does not have an effect on stromal opacification which needs to be addressed with corneal transplant. In addition, any associated symblepharon needs to be addressed separately by conjunctival autograft to prevent it's recurrence.

The long term outcomes of SLET have been very encouraging

with achievement of a stable epithelised corneal surface in 78% of cases .[6,7]

Conclusion :

Following an accurate diagnosis of LSCD and stabilisation of ocular surface, epithelial regeneration to restore corneal epithelium by limbal stem cell transplantation is the ultimate solution. Autologous SLET has successful and encouraging outcome in patients, including paediatric age group, with unilateral LSCD with wet ocular surface.

References:

1. Shanbhag, Swapna S1; Patel, Chaitali N1; Goyal, Ritin1; Donthineni, Pragnya R1; Singh, Vivek2; Basu, Sayan1,2, Simple limbal epithelial transplantation (SLET), Indian Journal of Ophthalmology: August 2019 - Volume 67 - Issue 8 - p 1265-1277 doi: 10.4103/ijo.IJO_117_19
2. Fernandes M, Sangwan VS, Rao SK,S Basti, Sridhar MS, Bansal AK, Dua HS. Limbal stem cell transplantation Current ophthalmology ,2004 (52) :1;5-22
3. Sangwan VS, Basu S, MacNeil S, Balasubramanian D. Simple limbal epithelial transplantation (SLET): A novel surgical technique for the treatment of unilateral limbal stem cell deficiency Br J Ophthalmol. 2012;96:931–4
4. Mittal V, Jain R, Mittal R. Ocular surface epithelialization pattern after simple limbal epithelial transplantation: An in vivo observational study Cornea. 2015;34:1227–32
5. Ray Chaudhuri B, Bhaduri A, Sengupta M. The ocular surface after simple limbal epithelial transplant (SLET): A high-resolution OCT study of the early postoperative period.Indian J Ophthalmol.2019;67(8):1348-1350.
6. Basu S, Sureka SP, Shanbhag SS, Kethiri AR, Singh V, Sangwan VS. Simple limbal epithelial transplantation: Long-term clinical outcomes in 125 cases of unilateral chronic ocular surface burns Ophthalmology. 2016;123:1000–10
7. Vazirani J, Ali MH, Sharma N, Gupta N, Mittal V, Atallah M, et al Autologous simple limbal epithelial transplantation for unilateral limbal stem cell deficiency: Multicentre results Br J Ophthalmol. 2016;100:1416–20

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Secretary General
Dr. Mohita Sharma
C-53C, NTPC Township,
C Block, Sector-33, Noida-201301 Uttar Pradesh
E-mail: drmohita@tirupatieye.org
Website: www.upsosonline.com

Treasurer
Dr. Lalit Kumar
C/231, Sector-48
Noida-201301
E-mail: drlalitkumarjec@yahoo.com

LIFE TIME ACHIEVEMENT AWARDEE

BRIEF BIO DATA

NAME : **DR S K SHARMA** (SATISH KUMAR SHARMA)

EDUCATION : MBBS Maulana Azad Medical College, New Delhi 1966
MD (Eye) RP Centre, AIIMS, New Delhi 1972

EXPERIENCE : Registrar , Clinical Tutor, RP Centre for 3 Yrs
Faculty and Head Eye Dptt, University of Dar Es Salaam, tanzania
Faculty and Head Eye Deptt, University of Maiduguri, Nigeria
Faculty and Unit Head, Eye Deptt., Al Fateh University, Tripoli, Libya
In Clinical Practice at Gorakhpur Since 1990

SERVED AS : Founder Member Gorakhpur Ophthalmic Association (GOA)
Ex Scientific Secretary, President GOA
Presently Patron Gorakhpur Ophthalmic Association
Field of Special Interest Strabismus and Amblyopia

NAME : **Dr Harish Gupta,** Funder and Managing Director Manav Multi Specialty Hospital (Unit of Shubaham Hospital and Research Center Pvt Ltd), Ghaziabad (U.P.)

EDUCATION : M.B.B.S. 1973 King Georges Medical College Lucknow.
M.S.Ophthalmology King Georges Medical College Lucknow 1977.
Chief Resident Jan. 1978 to Feb 1979 KGMC Lucknow

EXPERIENCE : In Private Practice since 1979 as Cataract, Glaucoma, Squint and Oculopalstic more than 70 thousand surgery performed

SERVED AS :
1. Member executive committee
2. Organizing Secretary National CME (Latest trend in ophthalmology) at Ghaziabad 2004.
3. Organizing Secretary 42 nd UPSOS Conference at Ghaziabad 2005
4. President UPSOS 2008, first Mid Term conference of UPSOS held at Ayodhya in 2008
5. Organizing Chairman National CME (recent Advances in Ophthalmology Surgical Techniques) 2010 at Ghaziabad.

Ghaziabad Ophthalmological Society.

1. Founder Member Ghaziabad Ophthalmological Society.
2. President GOS. 2007 to 2008. Organized Live surgery work shop at Ghaziabad.

NAME : **Dr. Anand Sharma**

EDUCATION : MBBS (KGMC) 1974, MS (OPHTHALMOLOGY), KGMC,1978

EXPERIENCE : **Chief Resident** KGMC 1979-80
Appointed Lecturer GSVM MEDICAL, COLLEGE, KANPUR
Training in Phaco-surgery in Alabama Medical Centre, USA 1996

SERVED AS : **Joint Organizing Secretary** AIOC2004,**Chairman Organizing Committee** UPCON2010
President : UPSOS, **Editor :** Proceedings UPSOS
Member : Executive committee UPSOS
President, Secretary/Sc. Secretary Indian Medical Association, Varanasi
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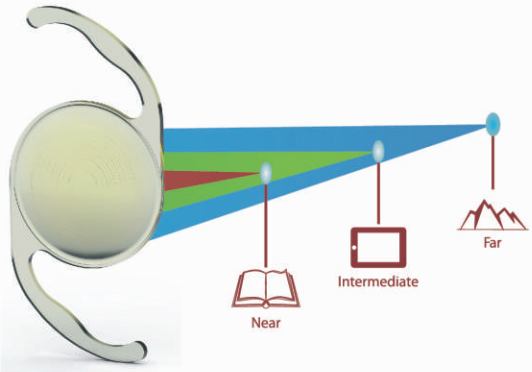

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