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Contents

Editorial

Reviews

General articles

Case reports

Romanian Journal of Ophthalmology, Volume 64, Issue 2, April-June 2020. pp:83-84

EDITORIAL

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Intellectual Capital and the Romanian organization performance in Ophthalmology

The concept of intellectual capital was first used in the last decade of the 20th century, being officially recognized by Thomas A. Stewart in 1998.

According to Aymen Raheem Abdulaali, who wrote the paper entitled "The Impact of Intellectual Capital on Business Organization", in the Academy of Accounting and Financial Studies Journal, "intellectual capital tends to be an important resource and a key contributor to the economic success and value creation in a business". In other words, Intellectual capital is an intangible value trigger in an organization that should bring advantages to both the organization and its beneficiaries. This approach suggests that in terms of competitive advantage, Intellectual Capital represents an asset for any type of organization. However, literature on Intellectual Capital does not offer a commonly accepted perspective of the concept but rather provides a description of its dimensions and some examples that may be included under the Intellectual Capital umbrella. As such, according to Molodchik and Shakina (2013), the dimensions of the Intellectual Capital refer to Human Capital, Structural Capital and Relational Capital. The Human Capital encompasses the management capabilities of an organization and the knowledge and skills of the employees, whereas the Structural Capital involves innovative capabilities and internal or IT process systems. In addition, the Relational Capital consists of the networking capabilities of an organization with different stakeholders such as consumers, mass-media, suppliers, government and other partners. According to Gheorghe, Purcarea, Gheorghe (2018), health care organizations comprise a vast palette of formal and informal knowledge, both structured and unstructured, used by individuals and groups of individuals as well as revealed by intangible resources merged with embedded relationship capabilities, thus defining the Health Care Intellectual Capital.

Barney J, who wrote the article entitled "Firm resources and sustained competitive advantage", stated that the performance of the health care organizations and, implicitly, of the ophthalmological organization, may be explained by the different types of intellectual capital, different approaches and capacities for leveraging intellectual capital. It is a fact that Health Care Intellectual Capital cannot be totally managed to fit the aims of the ophthalmological organizations but rather improve their performance. Thus, in order to improve the performance of the Health Care Intellectual Capital, the ophthalmological organizations should focus more on training, namely on the Human Capital. Without a proper training of the Human capital, the development of the organization, the implementation of any strategy or innovation, will result into a complete failure.

Another important issue that must be taken into consideration by the managers of the ophthalmological organizations is the volume of data that is continuously growing, being reflected in the Structural Capital. If it is not managed efficiently, the outcome may be a tremendous loss for the ophthalmological organization performance, which will also significantly influence the Human capital, leading, according to Jenna M. Evans, Adalsteinn Brown and G. Ross Baker, to "instability among

leader and front-line staff, the limitations of administrative and clinical databases for supporting research and learning".

Moreover, the managers of the ophthalmological organizations have an important role of answering the demands of the stakeholders, thus, the Relational Capital helps identifying "the resource configurations that best support achieving the complex mandates of ophthalmological organizations".

In conclusion, even though it is difficult to measure, Health Care Intellectual Capital has proved to be a vital element in ensuring the survival of any ophthalmological organization, because, according to Swewart (2008), cited by Aymen Raheem Abdulaali in "The Impact of Intellectual Capital on Business Organization", in 2018, "intellectual capital refers to skills, knowledge, experience and customer relationships that offer an organization a competitive advantage over the competitors". Thus, it can be stated that intellectual capital is of core importance in offering a real value to any ophthalmological organization. In addition, ophthalmological organizations should use all their existent resources to ensure their success.

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REVIEW

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Evaluating glaucoma surgeries in the MIGS context

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Abstract

The challenges of glaucoma management are many: the disease is chronic, progressive, often asymptomatic, and very often, the quality of life and costs of treatment is unacceptable to the patient. This is true for both medical therapy and conventional glaucoma surgery. The choice of therapy, especially the transition from the former to the latter, is now being bridged by Minimally Invasive Glaucoma Surgeries (MIGS). Choosing from the several options now available in the surgical armamentarium requires a deeper understanding of the available modalities. This review aims to provide an overview of the decision-making process, keeping in mind age, type of glaucoma, life expectancy, socioeconomic status, patient expectations, and coexisting cataract.

Keywords: glaucoma, minimally invasive glaucoma surgery, MIGS, trabeculectomy, glaucoma drainage device

Introduction

Glaucoma surgeries, unlike cataract surgeries, are not one-time procedures. There is a frequent need of stringent postoperative follow-up for the management of various early and late post-operative complications and repeated procedures because of gradual decrease in the efficacy of procedure over time. Despite refinements of the surgical technique, and the introduction of newer surgical procedures, the outcomes of glaucoma surgery remain suboptimal.

In the quest for the perfect glaucoma surgery, a lot of innovations and devices have come into market. These are collectively labelled MIGS (Minimally Invasive Glaucoma Surgery) and are ab-interno glaucoma procedures often sparing the conjunctiva, and thought to be less aggressive than the standard glaucoma surgical procedures, namely, trabeculectomy and glaucoma drainage devices (GDD) (**Table 1**) [**1**].

Even though surgical success criteria have been defined by WGA (World Glaucoma Association) consensus in 2011, the criteria for success of many surgeries have been variably defined in different trials (**Table 2**). Even over the last decade, there has also been a growing understanding that the criteria for success cannot be generalized and have too many variables. These include the purpose of procedure, its efficacy as well as safety, patient age, stage of glaucoma, etc. In a present scenario, there are many surgical options for patients as well as for surgeons and there is a demand of tailored management for each patient. This review aimed to critically evaluate each of these, making the surgical decision process a little less ambiguous.

Table 1. Available MIGS devices and mechanism of action

Mechanism	Example	Outflow Pathway	FDA approval
Increase in trabecular outflow	1. iStent/ iStent inject 2. Hydrus implant	Implant is inserted through trabecular meshwork to Schlemm's canal	• Mild-moderate open angle glaucoma (OAG) in conjunction with cataract surgery
	3. Ab-interno trabeculotomy with Trabectome device or Kahook dual blade	Removes the trabecular meshwork and inner wall of Schlemm's canal	• Medically uncontrolled primary or secondary OAG with or without cataract extraction
	4. Gonioscopy assisted transluminal trabeculotomy (GATT)	Gonioscopic guided ab-interno trabeculotomy using microcatheter (iTrack) or sutures (prolene/ nylon) after performing a 1-2 mm goniotomy	
	5. Ab-interno canaloplasty using iTrack	Ab-interno viscodilatation of Schlemm's canal	• Mild-moderate POAG with or without cataract surgery
Increase in uveoscleral outflow	Cypass	Implants are inserted into suprachoroidal space after creating a localized cyclodialysis	• Cypass withdrawn from market
	Solx Gold shunt		• Not yet approved
	iStent supra		• CE approved for mild-moderate POAG with or without cataract surgery, but not yet FDA approved
Subconjunctival filtration	Xen implant,	Implant is inserted through trabecular meshwork to subconjunctival space	• Medically uncontrolled POAG, pseudoexfoliation or pigmentary glaucoma patients or refractory glaucoma after failed previous surgery with or without cataract surgery
	Innfocus		• Not yet approved
Decrease in aqueous humour production	Endolaser Cyclophotocoagulation	Ab-interno cyclophotocoagulation to ablate ciliary processes by direct visualization	• Refractory glaucoma with or without cataract surgery • In medically controlled glaucoma in combination with cataract surgery

Table 2. Criteria used for defining surgical success in evaluating glaucoma surgery

Surgery	Success criteria
Trabeculectomy	• IOP 6-21 mmHg and at least 30% IOP reduction [**2**] • IOP 5-21 mmHg and IOP decrease of ≥ 20% [**3,4**] • IOP ≥ 6 - ≤ 18 mmHg [**5**] • IOP > 5 - ≤ 18 mmHg or 20% reduction [**6,7**] • IOP 6-16 mmHg without medication (complete success), ≥ 6 - ≤ 16 mmHg with one antiglaucoma medicine or needling (Qualified success) [**8**] • IOP ≤ 15 mmHg [**9**]
Glaucoma Drainage Devices	• IOP ≤ 21 or > 20% IOP reduction, success rates at IOP levels ≤ 17, ≤ 14 mmHg also evaluated [**10,11**] • IOP ≤ 21, ≤ 16 mmHg [**12**], qualified success - up to 2 topicals • 5-21 or ≥ 25% IOP reduction [**13**] • IOP ≥ 5 - ≤ 18 mmHg [**14**]
Deep Sclerectomy	• IOP reduction > 25% [**15**] • IOP of < 18 mmHg and at least 20% IOP reduction [**16**]
MIGS	• IOP reduction ≥ 20% on the same or fewer medications in a study on Xen implant without cataract surgery [**17**] • IOP reduction and medicine reduction in a study on Trabeular bypass stents in combination with cataract surgery [**18**]

Which surgery to choose?

Glaucoma surgery is no longer considered the last-ditch effort to decrease intraocular pressure (IOP) in the end stage glaucoma, or in patients not effectively controlled by maximal medical treatment. Patients, and doctors alike, are increasingly considering surgery for patient comfort, when patients do not want to use eye drops, and choose a safer surgical option for a better quality of life. But not a single surgery fits every patient. The choice of surgery can be guided by several factors like:

a. **Desired IOP level:** Without doubt the single most important criteria to evaluate a glaucoma surgery remains its efficacy in controlling the IOP. That said, there is a need to realize that the criteria for success of IOP control ≤ 21 mmHg with or without medications (qualified or complete success respectively) might not be valid in each case. IOP level < 21 mmHg might not be good for moderate-advanced glaucoma or with Trab/ tube surgeries, whereas the same might be considered excellent for MIGS when performed in early glaucoma. Similarly, in cases of MIGS, if a patient still has to use medicines, when the surgery was performed early on in the disease to ensure freedom from eye drops, the procedure would be considered a failure.

b. **Type of glaucoma and age of the patient:**

Early and Moderate Primary Open Angle Glaucoma (POAG)

In early POAG, medical or laser treatment are usually effective options, however, some patients who are intolerant/ non-compliant to medicines or not very well controlled with medical/ laser treatment, MIGS (for example iStent, Trabectome, Hydrus, endolaser cyclophotocoagulation) are good surgical options in terms of reduction in IOP, as well as the number of glaucoma medications, especially since they are conjunctiva sparing and have lesser complications. However, some MIGS devices are ab-interno procedures but are implanted subconjunctivally like Xen implant or Innfocus, which might not be the first choice in these patients, as they involve conjunctiva and have bleb related complications similar to trabeculectomy.

Trabeculectomy may also not be a good option in these cases because of the significantly higher risk of post-operative complications, increase in cataract formation, higher failure rates because of strong healing response in young [**19**]. If the trabeculectomy in this scenario results in qualified success with persistent need of medicines, it would actually be considered a failure.

In a young patient, with early glaucoma, safety of a procedure is the main priority and the procedure has to be effective on long-term without vision threatening complications. Conjunctiva sparing surgeries should be preferred so as to preserve the conjunctiva for future surgery if needed. At present, there is no ideal surgery that is safe and conjunctival sparing with long-term efficacy. This is especially relevant since the long-term outcome with MIGS is yet to be ascertained [**20**,**21**].

On the other hand, in elderly patients with limited life expectancy, MIGS can be offered with good safety profile over trabeculectomy. Non-penetrating deep sclerectomy (NPDS) is another safer option with similar success rates as of trabeculectomy, but with fewer complications [**22**,**23**].

Severe POAG

Severe cases usually require lower target IOPs and MIGS might not be a good option in these cases as many of the stents (Schlemm canal based) are unable to maintain lower levels of IOP because of downstream resistance and episcleral venous pressure [**24**]. Trabeculectomy and deep sclerectomy, or even suprachoroidal shunts, may be better surgical options in these cases.

Primary tube surgery is considered another good option in view of good success rates with fewer complications compared to trabeculectomy (Trab) with Mitomycin-C (MMC), as has been reported in Primary Tube versus Trabeculectomy (TVT) study (overall success 81% vs. 92% and complete success 14% vs. 59% respectively, in Baerveldt implant versus Trab MMC, low rate of serious vision threatening complications or reoperation for complications like hypotony maculopathy, bleb leak, hyphaema (1% vs. 7% respectively) [**11**].

Secondary glaucomas

They are a heterogenous group and the surgical results in each of these may vary as per etiology. In the absence of active inflammation, and in patients with healthy conjunctiva, Trab MMC has good success rates as in steroid induced, traumatic and post keratoplasty glaucoma (73% success rate at 22 months) [**25**], however, in neovascular glaucoma (NVG) or uveitic glaucoma, trabeculectomy has poor success rates (overall success rate 54%, 9% complete, 45% qualified in NVG) [**26**] and GDDs are more useful in these cases. MIGS are not good options in these cases although steroid induced glaucoma or pseudoexfoliative glaucoma may be managed with MIGS; currently, there is insufficient literature on their efficacy.

Angle closure disease

Angle closure glaucoma is not amenable to treatment by MIGS unless the angle is adequately open after iridotomy/ iridoplasty/ cataract extraction. These patients can be managed with cataract extraction or trabeculectomy in isolation or combined phacotrabeculectomy.

Co-existent cataract and glaucoma

In angle closure disease, cataract surgery alone helps in IOP control, however, in few cases of angle closure disease and in open angle glaucoma, combined surgery is required [**27**]. In combination with cataract surgery, MIGS have been reported to have good success rates and can be preferred in both types of glaucoma if the angle is fairly open to visualize structures, whereas phacotrabeculectomy is less often performed and less preferred because of longer surgical time, high chances of intraoperative complications and poor success rates compared to stepwise surgery [**28**].

c. Surgeon expertise: Contrary to popular opinion, MIGS procedures have a relatively steep learning curve. They require training in direct gonioscopy, clear identification of angle structures and hands on training for angle-based procedures. Similarly, the deep sclerectomy procedure, which is often considered safer compared to conventional trabeculectomy because of its non-penetrating nature, also has a steep learning curve. The procedure may be complicated by inadvertent rupture of Descemet's membrane (3.5-7% of the cases) changing the procedure to a penetrating one, similar to Trab [**29**].

d.Feasibility of procedure and contraindications: There are several conditions when MIGS cannot be used, as in cases with poor visibility of the angle because of extensive anterior synechiae, corneal opacity, and ocular surface disease. Surgery is difficult in patients with narrow palpebral apertures, cervical spine abnormalities, and in unco-operative patients who are not able to follow commands.

Many of these procedures including iStent and Hydrus are approved in conjunction with cataract surgery, which may not be appropriate in young patients or patients having very early cataract. So, in these cases, conventional trabeculectomy is still the first choice of surgery, however, it must be kept in mind that trabeculectomy surgery leads to progression of cataract [**30**]. There are several MIGS, including Trabectome, Xen implant, gonioscopy assisted transluminal trabeculotomy, which can be performed alone without cataract surgery. Thus, an informed decision has to be made in these circumstances after a discussion with the patient. Availability of devices and the additional cost of the surgery represent another major concern with regard to the feasibility of MIGS.

e. Safety of the procedure and complications: Safety is of utmost importance and risk-benefit ratio must be considered in deciding the type of procedure. The complications that are relatively more acceptable in patients with advanced disease, might not be so in patients with an early disease. Therefore, complications that may be considered acceptable can vary according to the procedures. MIGS and deep sclerectomy are considered safer options and MIGS are better in terms of sparing the conjunctiva and avoiding the use of anti-metabolites. Similarly, hypotony after DS may be acceptable as it doesn't lead to hypotony maculopathy, however, this may not be the case with trabeculectomy. Though MIGS procedures are presumed to have lesser complications, they can have unique complications of stent malpositioning or obstruction apart from the complications of immediate postoperative rise in IOP, hyphaema, hypotony, etc., which are usually transient and not vision threatening. If the same procedure results in a complication that can have a long-term impact on vision, it should not be acceptable. Because of this reason, Cypass shunt was voluntarily withdrawn from the market by Alcon in 2018, because of unacceptably high endothelial cell loss even though a significant loss occurs with trabeculectomy and GDD procedures as well [**31**]. **Table 3** summarizes the complications associated with different procedures.

Table 3. Complications following glaucoma surgery: A comparative overview

	Trab	Trab with express shunt	Baerveldt	AGV	NPDS	MIGS
Hypotony	16.8 - 39.3% [**32-34**]	10.5% [**35**]	13% [**32,36**]	2% [**36**]	4.3-9.9% [**34,37**]	13.8% with Cypass [**38**] 15.3% with Xen [**39**]
Hypotony maculopathy	5.18% [**35**]	3.17% [**35**]	1% [**32**]	Rare reports [**40,41**]	0-2.1% [**42,43**]	1.08% with Xen [**44**] 1.3% with Cypass [**45**]
Hyphaema	14.9-17.2% [**33,34**]	1.6% [**35**]	5% [**46**]	18.3% [**33**]	7.4-12.4% [**34,37**]	24.3% with Xen [**47**] 0.02% for iStent [**48,49**] 19.04% for Hydrus [**50**] 2.7% for Cypass [**45**]
Shallow anterior chamber	11.8-32.1% [**33,34**]	4.74% [**35**]	3% [**46**]	11.11% [**33**]	2.9-8.9% [**34,37**]	0-2.3% [**51**]
Choroidal detachment	3.2-15.9% [**34,52**]	10.38% [**35**]	3% [**46**]	12% [**53**]	8.6-10.2% [**34,37**]	15.3% with Xen [**39**]

Progressive cataract	29-35% [**30,34**]	12% at 2 years [**54**]	8% [**36**]	8% [**36**]	6.6-12.7% [**34,37**]	12.2% with Cypass [**55**] 11.1% with iStent [**56**]
Loss of light perception	2% [**32**]	3.2% [**57**]	26% [**36**]	12% [**36**]		No reports yet [**17**]
Bleb leak	6.7-13.6% [**33,35,44**]	16.8% [**35**]				1.93% with Xen [**44**]
Endophthalmitis	1.6% [**35**]	1.6% [**35**]	0.5-1.4% [**58,59**]	1.7% [**60**]	Rare, isolated reports of blebitis [**61**]	0.5% with Xen [**62**]
Endothelial cell loss	-3±8% to 9.6% at 1 year [**39, 63**]	-10±8% at 12 months [**39**]	Mainly with anterior chamber implantation 7.2% at 6 months 12% at 1 year [**64**] 4.54% per year [**65**]	9% at 6 months to 12% at 1 year [**66**]	4.5% at 1 year [**63**]	2.1% in one month with Xen implant in cases with dynamic corneal contact [**67**], 18.4% with Cypass at 5 years in Compass-XT study (unpublished data)
Stent malpositioning						12.2% with Xen [**47**]
Stent obstruction						4% with iStent [**68**] 2.4-5.4% with Cypass [**38,45**]
Need of needling	23-30.76% over 3 years [**44,69**]	15.9% over 30 months follow-up [**69**]				43.24% [**44**]
Need of Re-surgery	7-28% over a 5-year period [**53,70**]	5.12% during 1st year [**71**], 30.6% at 3 years [**72**]	5.4–17% over 5 years [**33,73**]	17–40% over 5-year period [**36,53**]	3.7–5.4% after 1–3 years [**74,75**]	14.1% with Xen after 12 months of surgery [**17**] 4.3% with InnFocus at 3 years [**76**] 7.4% with iStent [**39**]

f. Survival of surgery: The longevity and survival of the procedure is yet another confounding factor. For surgeries that are minimally invasive and repeatable, the longevity thought extremely desirable, is not absolutely imperative. Especially since a lot of these surgeries are conjunctiva sparing, they do not preclude more definitive surgeries at a later date. For example, iStent has been reported to decrease IOP of up to 40% at 1 year and 16.3% at 5 years with reduction in medication load in up to 85% of the cases at 1 year and 43% at 5 years [**77,78**]. Thus, if they offer a few drug free years to the patient, they must be considered successes. Survival of surgery on long-term is of less importance when choosing it for elderly patients with a limited life expectancy, where their quality of life impact and morbidity should be considered more important.

g. Ancillary procedures: Procedures like needling and goniopuncture are not considered failures of trabeculectomy and NPDS respectively, but merely ancillary procedures. Similarly, the hypertensive phase of the Ahmed

Glaucoma valve (AGV) is considered par for course, as is the two-stage surgery for Baerveldt like devices. In the case of MIGS, a second surgery may also be similarly considered an ancillary procedure since the surgery is not very invasive, except for the significant costs involved. In case of MIGS, multiple MIGS with different sites of action can be performed simultaneously or sequentially as a safer alternative to a more invasive glaucoma surgery [**79**].

h. Health economics: Cost effectiveness is yet other criteria that must be kept in mind when judging a procedure. For a glaucoma surgery, the cost factor has to be considered in terms of cost of the surgery, efficacy of the procedure in terms of the decrease in drugs use or follow-up visits and the comparison of the cost of one-time procedure with the overall cost of drugs for that period of time. For example, adding the express shunt to trabeculectomy increases its cost significantly, does not increase its longevity, and in fact, turns a surgery that can be used in both POAG and PACG into a surgery that can only be used in open angles [**7**]. Thus, its success criteria need to be significantly more stringent. Another thing to remember concerning the health economics of glaucoma is the high cost of the minimally invasive devices. Unless they result in a significant economic saving by significantly decreasing or eliminating the use of anti-glaucoma medication for a significant period of time, or decreasing postoperative follow-ups, their use cannot be justified in terms of costs. Trabecular bypass shunts have been shown to be cost effective over standard care with improvement in quality of life [**80**]. Long-term data regarding cost-effectiveness is currently inexistent. Trabeculectomy is still the cheapest surgical option amongst all glaucoma procedures and the most commonly performed procedure [**81,82**].

i. Quality of Life, QoL: The QoL impact of each of these surgeries must also be part of the success criteria. Bleb dysesthesias, multiple interventions by needlings and complicated treatment regimens postoperatively, complication rates, etc., may significantly affect the QoL of a patient following trabeculectomy. Therefore, its use in a patient with early disease may not be justified. Regarding MIGS, QoL data is not available as there are limited studies at present. A study has reported comparable Qol in patients undergoing MIGS (iStent, Trabectome) or trabeculectomy at 6 months postoperatively, however, better social functioning, color vision, and postoperative day 1 visual acuity, were seen in MIGS group, but the trabeculectomy group required lesser topical antiglaucoma medicines [**83**].

Consensus amongst glaucoma surgeons

A survey of American Glaucoma society (AGS) published in 2017 for preferred practice preferences for the type of glaucoma surgery among AGS members has also reported that Trab MMC, GDD and MIGS constituted 59±30%, 23±23% and 14±20% respectively as an initial surgery in POAG. Although the use of GDD surgery has increased and trabeculectomy has decreased from 1996 to 2016 [**81**], Trab MMC was still the most popular primary glaucoma surgery among surgeons.

MIGS are emerging devices that are expected to have improved safety, however, there is a need of more randomized controlled trials and long-term results are awaited. They definitely have a future in patients who are non-compliant or intolerant to medications and can act as a bridge between medical/ laser treatment and conventional glaucoma surgeries, having different indications compared to conventional glaucoma surgeries. A tailored approach depending on the patient profile, type of glaucoma, and life expectancy can help in the better management of glaucoma patients.

Conclusion

Glaucoma is a continuum from early to end stage, thus each surgery has a unique space with respect to success and failure criteria applicable. With the introduction of the newer surgical procedures, the algorithm for the choice glaucoma surgery has become more complex. However, this also implies that better and safer surgical procedures, which may be better suited to the needs of the individual, are now available. In addition, a combination of surgical procedures may be performed for any patient during his or her clinical lifetime in order to best preserve their quality of life.

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Conflict of interest

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REVIEW

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Retinal migraine

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Abstract

Retinal migraine is usually defined by transitory attacks of fully reversible monocular visual loss, mostly with aura. An accurate diagnostic can be completed based upon the International Classification of Headache Disorders-2 (ICHD-2) criteria. In view of this, we summarized some clinical features, treatment principles, complications, prognosis and prophylaxis.

Keywords: migraine, retinal blood vessels, eye vascular network, monocular visual loss

Introduction

Retinal migraine is an ophthalmo-pathological condition described as a transient monocular scotoma or vision loss, being accompanied or followed by a headache. The timing, the intensity and the aura (if present or preceded), may differ from person to person. Among other causes, apparently, the major one stays the ischemia or vascular spasm in, or behind the affected eye. A distinction should be noted, when a confusion between the terms "retinal migraine" and "visual migraine" arises. Visual migraine results from the cortical spreading depression and is denominated as scintillation scotoma. Retinal migraine is a rare retinal disorder. The symptoms are usually transient, but the pathophysiological mechanisms still remain not completely elucidated [**1,2**].

Pathophysiological effectors and mechanisms

Substance P, nitrous oxide, calcitonin generated peptides have been suspected as chemical effectors in the possible pathophysiological mechanisms of retinal migraine, by exercising a non-desired effect leading to the plasma extravasation, neurogenic inflammation, vasodilatation. Other neuro-ophthalmological structures involved are: periaqueductal gray (PAG), locus coeruleus (LC), dorsal Raphe nucleus (DRC), retinal vasculature, and activation of the retinal-thalamic-visual pathway [**3**].

On the contrary, photophobia in migraine may start in cone-driven retinal pathways, exerting a hypersensitive-excitation effect on light-sensitive thalamic neurons. Photophobia is aggravated by the light-intensity dependence, when the eyes of the patients are exposed to

different wavelengths of visible light. Fundoscopy (**Fig. 1**) and fluorescence angiogram expose a delayed tilling or occlusion of the central retinal artery and its branches, (**Fig. 2**) with, either normal ciliary circulation or irregular/ discontinuous choroidal defects and capillary leakage flux [**4**]. The vascular theory still remains doubtful due to the complexity of retinal vascular supply. Retina has a binary circulation: central retinal artery supplies, inner retinal layers. Those microstructures lack adrenergic innervation, maintain sensory-nerves and are auto-regulated [**5**].

Symptomatology

When aura is present: flashing, sparkling, twinkling lights (scintillations). Non-aura: blind spot, a partial loss of vision, temporary blindness, scotoma. A retinal migraine attack begins with monocular visual symptoms, afterwards when relaxation time of the blood vessels is manifested, blood flow resumes and sight returns.

Diagnostic tools and laboratory tests

They should be directed and based on the patient's medical history and physical exam. Some laboratory blood markers, such as platelet count, coagulogram, homocysteine and protein S (optional), can be precious adjuvants as diagnostic tools. Tourniquet or capillary-fragility test (Rumpel-Leede test/ Hess test) can sometimes be a good option too. Optical coherence tomography, retinal oximetry, scanning laser ophthalmoscopic angiography, Doppler studies in order to investigate fundoscopy, visual field examination during the attack are also useful options.

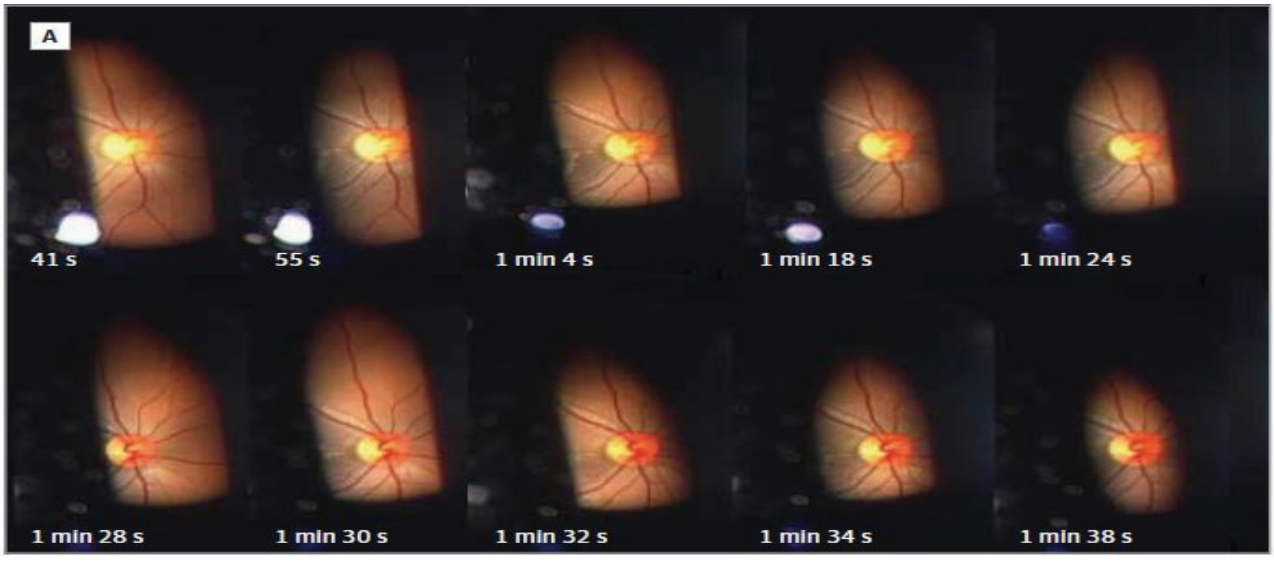

Fig. 1 Video-assisted fundoscopy recorded for 1 min. 48 sec during the migraine attack. Dynamic changes in the retinal artery and veins can be detected.
Source: *Ota I, Kuroshima K, Nagaoka T. Research Letter. Fundus video of retinal Migraine. JAMA Ophthalmology. November 2013; 131(11): 1481-1482* ***[6]***

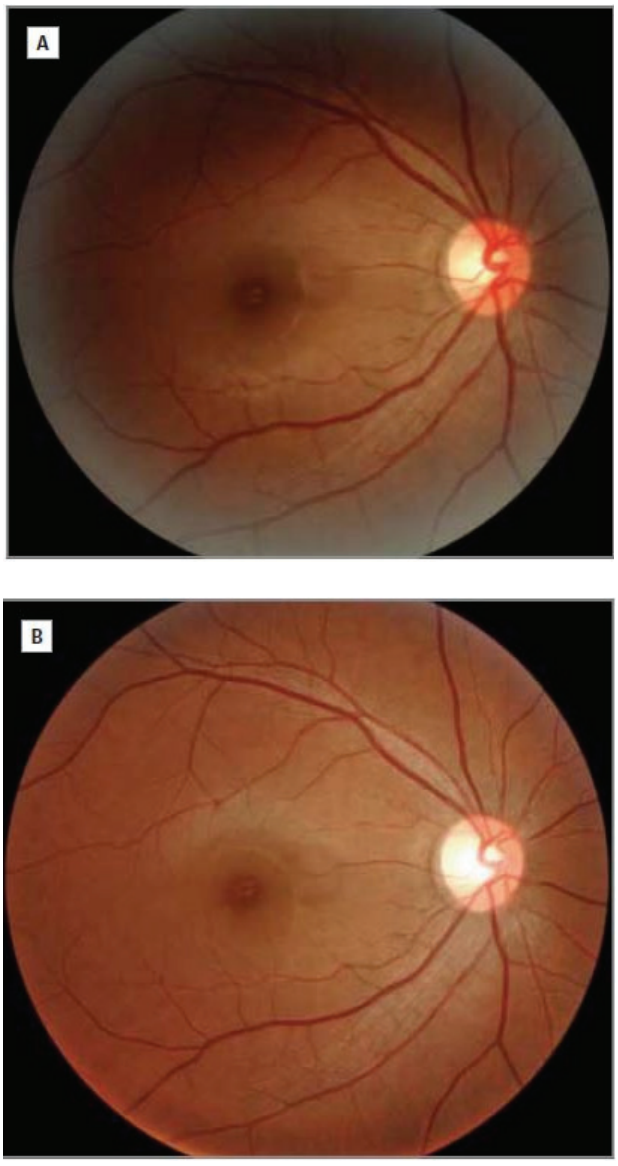

Fig. 2 Fundoscopy of the eye, immediately after the attack onset (A), and at one-month distance after the attack (B).
Source: *Ota I, Kuroshima K, Nagaoka T. Research Letter. Fundus video of retinal Migraine. JAMA Ophthalmology. November 2013; 131(11): 1481-1482 [**6**]*

Reported complications

- reversible and irreversible central retinal artery occlusion
- retinal infarction
- branch retinal artery occlusion
- retinal hemorrhages and disc edema
- ischemic optic neuropathy
- choroidal ischemia
- dilatation of retinal veins
- vitreous hemorrhage
- retinal pigmentary changes
- stroke

Treatment

Analgesics and nonsteroidal anti-inflammatory drugs, caffeine, treatment with triptans, ergotamine compounds, may be a favorable option. Triptans and ergotamines, both exert an effect by stimulating the serotonergic receptors in the cerebral and cardiac vasculature. They should be instituted as therapy within 24h of each other [**7**].

Prevention

It is well documented that visual disturbances caused by retinal migraine attack disappear without treatment within one hour or less. People performing activities that require clear vision, when a retinal migraine occurs, need to stop the activity and relax until the vision returns to normal, preferably in a dark or a semi obscure good freshly aerated room. If driving, they should park on the side of the road and wait for the vision disturbances to pass completely. They should also avoid common migraine triggers and stress, and they should get a regulated sleep and a healthy nutrition.

Conclusions

Retinal migraine is a challenge and sometimes a pitfall before being diagnosed. Aura, is the most essential characteristic, but most cases labeled as “retinal migraine”, are not migraines. Sometimes, a vasculo-allergic migraine can be underdiagnosed or overdiagnosed as a retinal migraine. On the other hand, monocular visual phenomena typically originate in the retina, choroid and optical nerve. It is believed that retinal vasospasm initiates transient monocular visual loss, being the most plausible explanation. Optic nerve infarction and retinal infarction can occur due to the retinal vascular changes and the particularities during the migraine attack. Taking into account that vasospasm is the most common

cause of the symptoms and the use of aspirin has its own risk and has been reported not very effective, the adequate use of verapamil and nifedipine, should constitute a good treatment option. No drug trial has been reported in retinal migraine, this being the reason why the treatment should be prescribed and orientated according to each patient's needs. An inter-disciplinary consult of a neurologist and an ophthalmologist is a wise prerequisite.

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REVIEW

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Photoprotection role of melanin in the human retinal pigment epithelium. Imaging techniques for retinal melanin

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Abstract

The human eye is made up of multiple layers of pigmented tissues that have in componence melanin. In the eye, one can separate melanosomes from various embryonic origins. The pigment-producing cells in the stroma of the iris, ciliary body and the choroid (uveal melanocytes) are neural crest derivatives. On the other hand, ciliary, iris and retinal pigment epithelial cells are developed from the neural ectoderm. One universally accepted role of melanin is to react as neutral-density filter in scattering light. Melanin acts as a free radical stabilizer and has the ability to absorb near-infrared, visible light and UV radiation.

This paper reviews the current knowledge on ocular melanin, including ocular melanogenesis, roles of melanin in retinal metabolic processes and some imaging techniques that identify melanin in the retina.

Keywords: eumelanin, pheomelanin, retinal pigment epithelium, antioxidant properties, imaging techniques

Introduction

The morphology of the human eyeball can be fractionated into three basic tunics: the fibrous tunic, also known as tunica fibrosa oculi (cornea and sclera), the vascular tunic or the "uvea" (iris, ciliary body and choroid) and the nervous tunic (retina) [**1,2**]. Melanin is normally present in the uveal coat and retinal pigment epithelium (RPE). Melanocytes in the ciliary body and iris are identified in the stroma. Choroidal melanocytes are located in choroidal stroma and suprachoroidal space. The choroidal melanocytes function has not yet been fully elucidated [**3-6**]. Melanin is also present in the pigment epithelium cells [**1**]. The melanin pigment is synthetized in a specialized cluster of cells also known as melanocytes. Melanin is produced through an intricate chemical way (**Fig. 1**). Its synthesis precursor is an aromatic amino acid: α-tyrosine [**7**].

Melanin and ocular melanogenesis

The retinal pigment epithelium is naturally intensely pigmented. Melanin in the retinal pigment epithelium is mostly eumelanin. There are two types of eumelanin, which are brown and black, synthetized from levodopa or tyrosine. The melanin amount in the RPE reduces importantly in aged eyes. Consequently, melanin biosynthesis is null or tiny in adult human RPE cells. The turnover of retinal melanosomes is not fully elucidated [**8-11**]. In the uveal layer, the features of melanin pigment differ with the iris color. Uveal melanocytes consist both of eumelanin and pheomelanin, but pheomelanin is frequently present more than eumelanin [**12-14**]. Pheomelanin is a xanthous pigment that is synthetized when glutathione or cysteine is included in the oxidation phase of levodopa [**7**].

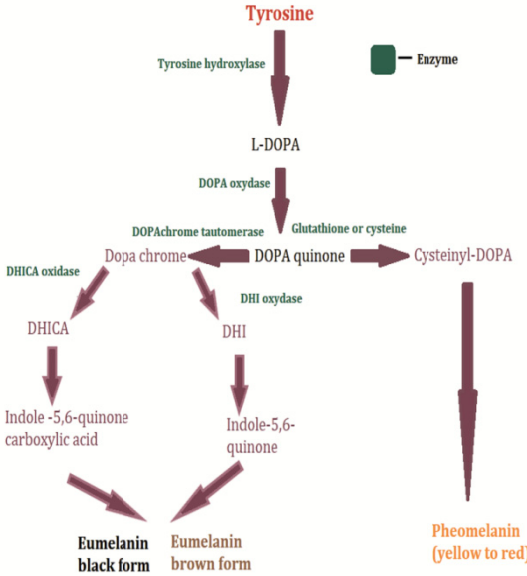

Fig. 1 Melanin synthesis pathway

Retinal pigment epithelium

The retinal pigment epithelium (RPE) is a layer of cuboidal epithelial cells placed between choriocapillaris and the outer segment of the photoreceptor cells. The human eye consists of approximately 4-6 million RPE cells per eye. The RPE cells are polarized cells. They have microvilli on their apical portions that engage with the outer segment of photoreceptor cells. The basal area (which is adjacent to Bruch's membrane) has many infoldings. In essence, the RPE contributes to the blood-retina barrier. Besides the organelles found in other cells, the RPE has melanin granules and phagosomes [**1,2**]. The cytoplasm of the RPE cells is rich in pigment granules (melanosomes). These organelles evolve in situ during the genesis of the optic cup and firstly develop as nonmelanized premelanosomes. Their development differs strongly from that of the pigment granules in uveal melanocytes [**2**]. Melanin in the retinal pigment epithelium is a mixed polymer synthesized from α-tyrosine [**15**]. Melanin pigment has intrinsic, indole semiquinone-like radicals in its componence [**16,17**]. Extrinsic indole semiquinone-like radicals are generated under visible and ultraviolet irradiation [**18**]. Retinal melanin has an important photoprotective function by neutralizing reactive oxygen species (ROS) and reducing free radicals damage [**19,20**]. Also, the RPE is abundant in peroxisomes, suggesting that it is effective in detoxifying a lot of free radicals. Pigment granules are plentiful in the cytoplasm of pigment epithelium cells, principally in the apical portion. During growth, stimulation of the tyrosinase promoter triggers the initiation of melanogenesis in this cell and evidences the attribution of the neuroectoderm to pass into RPE. However, most melanogenesis process befalls before birth. Melanin synthesis process in the retinal pigment epithelium occurs throughout life at a slow rate. *With advancing age*, the melanin granules interfere with lysosomes. Thus, the posterior pole of an elderly human is less pigmented. Melanin is a free-radical stabilizer. One major capacity of melanin is to behave as a neutral-density filter for scattered light [**2**]. On the other hand, retinal pigment epithelium contains lipofuscin – yellow-brown pigment granules composed of lipid debris of lysosomal digestion. In comparison with melanin, lipofuscin in the RPE enhances after birth and continues to increase with age. Light damage mediated through photosensitized oxidations has been considered to result in lipid peroxides. This suggests that there could possibly be a liaison between melanin

concentration and lipofuscin enhancement in the RPE [**21-23**].

Major roles of the retinal pigment epithelium

- Phagocytosis of photoreceptor outer-segment discs,
- Transport of nutrients and ions to photoreceptors,
- Visual pigment regeneration,
- Decreasing light scatter,
- Blood-retinal barrier,
- Synthesis and maintenance of interphotoreceptor matrix,
- Synthesis and secretion of growth factors,
- Immune modulation [**2**].

Imaging retinal melanin: current technologies

Ocular imaging has numerous benefits, both to make better patient carefulness and to realize scientific research. Quantifying melanin in the eyeball ensures data regarding to the global health status of the RPE and of adjacent anatomical parts. The published literature recommends a series of techniques that are used to identify ocular melanin: optical coherence tomography (OCT), near-infrared autofluorescence imaging technique (NIR-AF), photoacoustic imaging, fundus photography and fundus reflectometry.

Optical coherence tomography (OCT)

Optical coherence tomography is a three-dimensional imaging practice that is successfully used in ophthalmology for imaging the human eye. OCT is built on low-coherence interferometry utilizing near-infrared light. OCT subtypes such as polarization-sensitive OCT (PS-OCT) and photothermal OCT (PT-OCT) have been invented to recognize melanin using its polarization and absorption qualities. PS-OCT emerges to be a useful completion of OCT. Depolarization in the retinal pigment epithelium was utilized as a tissue particular contrast. The allotment of the depolarization of the RPE was based to be correspondent with the dispersion of the melanin pigment [**24**]. On the other hand, photothermal OCT identifies optical absorbers in tissues better than OCT. Photothermal OCT is based on the heat-producing properties of antibody-conjugated gold nanoparticles to realize molecular contrast. PT-OCT has the benefit of the photothermal impact, where photons absorbed by the melanin pigment are emanated as heat [**25**]. Swept-source OCT (SS-OCT) is a more recent technique that confers important benefits for analyzing ocular tissues. Backscattered light is the functional principle of SS-OCT. This is compared to a reference beam that, when overlapped, makes an interference pattern. SS-OCT has a better penetrance for retinal melanin and choroid in contrast to other OCT imaging techniques [**26**].

Photoacoustic imaging technique

This imaging technique uses ultrasounds to underline optical absorbers. Photoacoustic imaging applies a pulsed-laser and an ultrasonic transducer. The light emitted by pulsed laser is absorbed by retinal melanin pigment. The photoacoustic imaging signal severity is correlated with melanin absorption, which makes it possible to differentiate the signal from retinal pigment epithelium and the choroid [27].

Fundus photography

Fundus photography makes a bidimensional image of the retina. This imaging practice can show changes in pigmentation. However, images are only qualitative and it is not possible to differentiate retinal and choroidal melanin [**28**]. To obtain quantitative information, fundus reflectometry was used.

Fundus reflectometry

The method of fundus reflectometry is practiced with a retinal densitometer. Retinal densitometer includes a light emitter and several filters that can modify the light's wavelength, which comes into the eye and an analyzer (photomultiplier) for the light exiting the eyeball. This imaging technique ensures quantitative details about melanin pigment distribution in the posterior pole [**29**].

Near-infrared autofluorescence imaging (NIR-AF)

Scanning laser ophthalmoscopy (SLO) is an alternative method of visualizing the posterior pole. It uses the mechanism of confocal laser scanning microscopy for screening examinations

of cornea and retina. SLO has activated near-infrared autofluorescence imaging mode of the posterior pole (NIR-AF). SLO obtains bidimensional pictures of the eye fundus. A pinhole can gather light from a different layer of the eye fundus. Two endogenous fluorochromes are imaged: lipofuscin and melanin. However, it is tough to evaluate melanin spread using NIR-AF. This technique is not enough to differentiate retinal melanin from choroidal melanin [**30**].

Protective effects of ocular melanin

Melanin is an effective absorbent of infrared light, visible light and ultraviolet radiation [**31**]. The melanin pigment can annihilate over 99.9% of the absorbed UV radiation [**11**]. In the anterior pole of the eyeball, the melanocytes block visible and infrared light and ultraviolet radiation. In the posterior pole (RPE), melanosomes decrease the photo oxidative stress and act like a shield against the scattered light [**32**]. Melanin is a free-radical stabilizer and can dismiss numerous toxins [**2**].

Conclusions

Melanin pigment is normally found in the uveal coat and RPE, and acts as a defender of the photoreceptor cells to keep the retinal health. Melanin granules in the retinal pigment epithelium (RPE) have many important functions, which have not yet been completely elucidated. Melanin protects the cells from oxidative stress injury. This pigment is proficient to stabilize free radicals and decreases cytotoxic lipid peroxidation. Thus, melanin decreases light toxicity and protects against cytotoxic impacts caused by inflammatory processes. Melanin has the ability to absorb infrared light, visible light and ultraviolet radiation.

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Conflict of interests

The authors declare no conflict of interest.

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REVIEW

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Metastatic endophthalmitis - Has the trend of causative organism changed in the modern antibiotic era - A Systematic Review

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Abstract

Endogenous endophthalmitis, EE, a less common form of endophthalmitis, occurs when the microorganisms spread to the eye through the bloodstream, from a septic focus elsewhere in the body, that breaches into the integrity of the eyeball itself. The etiopathogenesis of endogenous endophthalmitis has changed over the past two decades, the aim of this review being to study the changing trends in causative organism in the era of modern antibiotics.

Keywords: metastatic, endophthalmitis, inflammation, infiltration

Introduction

Endophthalmitis is the inflammation of inner coats of the eyeball that progressively involves the vitreous cavity. It is a serious vision threatening complication. For this reason, prompt etiological diagnosis and treatment are imperative in cases of endophthalmitis. Therefore, it is extremely important for the clinician to pick up the early signs and symptoms of the disease, so that the treatment can be initiated immediately, improving final patient outcomes.

Endophthalmitis may be classified as exogenous (post-traumatic or postoperative) or endogenous (metastatic). Exogeneous endophthalmitis occurs when the outer wall of the eye sustains a break due to surgical intervention or trauma or severe infection in cornea or contiguous structures that breach the integrity of globe.

Endogenous endophthalmitis, EE, is less common and occurs when the microorganisms spread to the eye through the bloodstream, from a septic focus elsewhere in the body. This means that endogenous endophthalmitis is a result of the spread of a blood borne infection, with the primary infective focus being elsewhere, rather than any breaches in the integrity of the eyeball itself. With the advent of effective antimicrobial drugs, endogenous endophthalmitis has become very rare [**1,2**]. It usually affects immunocompromised, debilitated and hospitalized patients since they are more susceptible to infections, and instrumentations and intravenous access means they have a higher risk of septicemia and metastatic foci of blood borne infections. Such patients often have signs of sepsis or metastatic infection elsewhere in the

body. Though, in today's scenario, with the advent of modern antibiotic regimens, the occurrence of once common causes of septicemia like Salmonella, Staphylococcus aureus, Escherichia coli, etc. is decreasing; other organisms like coagulase negative Staphylococci, Candida species and non-fermenting gram negative bacilli are causing more and more blood stream infections in immunocompromised, chronically ill and hospitalized patients [**3-5**].

This review aims to ascertain if there has been a change in the pattern of ocular manifestations and causative organisms of metastatic endophthalmitis, in the current era of modern antibiotics.

Methods

The database search was conducted from January to June 2018. The search engines used included PubMed, Medline, OVID and Google Scholar. The following medical subject heading (MeSH) terms were searched separately and then cross matched: bacterial endogenous or metastatic endophthalmitis, endophthalmitis other than postoperative, while limiting the search to English and human studies.

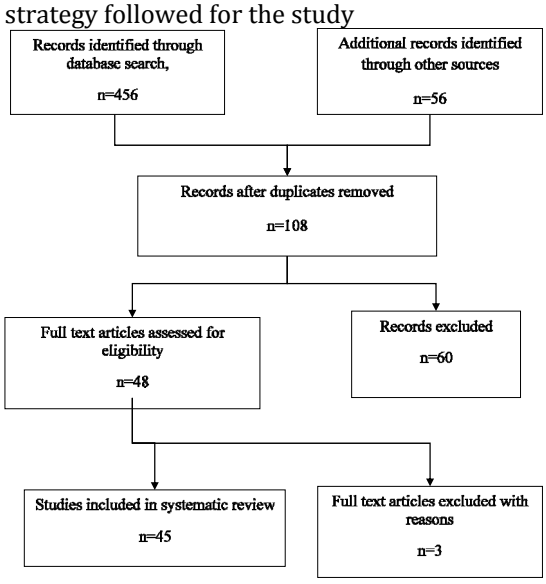
From the initial MeSH searches, original articles and review articles that were published after January 2000 were analyzed. An in-depth assessment of articles was carried out; citations, and cross references from relevant key articles were used to identify additional publications.

The inclusion criteria for the studies were:

- setting: country, inpatients/ outpatients/ both,
- underlying infection: site, organism, susceptibility pattern,
- participants: age and number of participants, outcomes.

The studies with ill-defined visual acuity and not following WHO standard guidelines/ methodology were excluded. Secondary publications reviewing different causes of endogenous or metastatic endophthalmitis were also included. Thus, a total of 37 articles were found to be suitable for inclusion in this review (**Chart 1**).

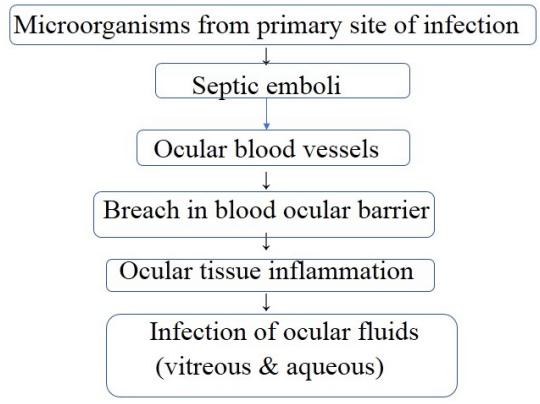
Chart 1. Flowchart depicting summary of review strategy followed for the study



Results and discussion

As described earlier, EE is a rare entity nowadays because of effective antimicrobial agents and better diagnostic techniques leading to effective treatment of primary site of infection. The etiopathogenesis of endogenous endophthalmitis is briefly described in **Chart 2**.

Chart 2 Pathogenesis of endogenous endophthalmitis



EE patients with no obvious primary site of infection should undergo a thorough detailed examination of abdomen, heart, lungs, teeth, limbs, abdomen, that includes investigations like abdominal USG, echocardiography, abdominal/ chest CT, blood/ urine/ sputum cultures.

We analyzed 45 case series and case reports of endogenous endophthalmitis between

2000 and 2018, so as to identify the most common primary sites of infection, most common pathogens and their effective antimicrobial treatment.

Liver abscess

In 2000, Cahil M et al. reported a case of EE associated with liver abscess treated with intravenous Ciprofloxacin and hydrocortisone, topical antibiotic, steroid and mydriatics, PPV+ retinopexy, patient's visual outcome was PL in R/ E and 6/ 12 in L/ E [**6**]. In 2000, Ang LPK et al. reported a case of EE associated with liver abscess, treated with intravitreal, topical, subconjunctival cefazoline and gentamycin and intravenous ceftriaxone and gentamycin but could not regain any vision [**7**].

In 2003, Tang et al. reported a case of EE associated with suppurative liver disease, the patient was treated with intravenous cefotaxime and intravitreal vancomycin along with amikacin. The outcome of this patient was not encouraging, with a complete loss of vision and the eye ended up in phthisis [**8**].

In 2007, Yang et al. reported 22 patients of EE associated with liver abscess, 15 patients were diabetic, biliary stones being present in 2 patients. They were treated with systemic 3rd generation cephalosporins and aminoglycosides. 11 patients had to be eviscerated as the intraocular inflammation could not be controlled, 8 patients gained vision of PL, 3 patients gained vision of 6/ 60-1/ 60 [**9**].

Another case of EE with liver abscess, reported by Wong et al. in 2007, was treated with intravenous cefuroxime and intravitreal vancomycin and amikacin. The patient gained a vision of 6/ 12 [**10**].

In 2011, Ishii et al. reported an EE case associated with liver abscess and *Klebsiella pneumoniae* septicemia. The patient was treated timely with pars plana vitrectomy (PPV)+ Lensectomy+ Silicon fitted intraocular lens (SFIOL) and regained vision of 6/ 6 [**11**].

In 2011, Dehghani et al. reported a case of EE associated with liver abscess, treated with intravitreal ceftazidime and vancomycin & PPV & systemic ciprofloxacin. The patient recovered vision of light perception only [**12**].

In 2015, Tsai et al. reported a diabetic patient with liver abscess subsequently developing EE and subdural abscess because of septicemia. The patient was treated with intravenous antibiotics, pars plana vitrectomy, as well as intravitreal ceftazidime and amikacin. The patient recovered vision of 6/ 6 [**13**].

Another bilateral EE case was reported by Moore et al. in 2015 and associated liver abscess treated with systemic and intravitreal antibiotics, oral, topical and intravitreal steroids and ultimately PPV, pt. gained good vision of 6/ 12 in R/ E and 6/ 24 in L/ E by this intensive treatment regimen [**14**].

Recently, in 2018, Kim et al. reported a case of EE associated with liver abscess, which was treated with intravenous cefotaxime, metronidazole and amikacin along with pars plana vitrectomy, but could not recover any vision (no light perception) [**15**].

In 2018, Wu MY et al. reported a case of B/ L EE associated with liver abscess, UTI, pneumonia, which was treated with intravenous ceftriaxone. The patient regained vision of 6/ 60 B/ E [**16**].

In all these case reports, laboratory reports revealed that the patients had *Klebsiella pneumoniae* septicemia. Therefore, current evidence, though anecdotal, revealed that *Klebsiella* septicemia is the most important cause of EE in liver abscess patients and can be treated effectively with intravenous 3rd generation cephalosporins. If severe intraocular infection is present, then intravitreal antibiotics and pars plana vitrectomy should also be considered at the earliest in order to preserve vision (**Table1,2**). In 2003, Yoon et al. concluded that *Klebsiella pneumoniae* EE incidence is increasing and if managed aggressively with early PPV and intravitreal injections, could lead to better visual outcomes as compared to conservative treatment that can increase chances of evisceration and enucleation. Early PPV decreases the bacterial and inflammatory load and enhances the antibiotics penetration [**17**].

Table 1. Summary of different studies with age, gender and eye affected

Sr. No.	Author, Journal, Year of study	Age	Sex	Eye affected
1.	Dogra et al., IJO 2019 [**2**]	35	M	B/ L
2.	Kim et al., CMH 2018 [**15**]	55	F	R/ E
3.	Rubin et al., CAN J Ophthalmol 2018 [**31**]	68	M	L/ E
4.	Wu et al., Reports 2018 [**16**]	64	M	B/ L
5.	Xu H et al., BMC Ophthalmol 2018 [**34**]	61	M	R/ E
6.	Mali et al., JAMA Ophthalmol 2015 [**39**]	50	F	L/ E
7.	Tsai et al., BMC Ophthalmology 2015 [**13**]	56	M	L/ E
8.	Moore et al., MJA 2015 [**14**]	51	M	B/ L
9.	Tan et al., Eye 2014 [**44**]	78	F	R/ E
10.	Sahu et al., Int Ophthalmol 2013 [**36**]	22-30	F	3 L/ E 1 R/ E
11.	Malathi et al., case reports in Ophthalmol. Med 2012 [**32**]	18	M	R/ E
12.	Carcasi et al., Nefrologia 2012 [**26**]	51 78	M F	L/ E L/ E
13.	Dehgani et al., Case Report Ophthalmol 2011 [**12**]	79	M	L/ E
14.	Rahman et al., Int. Ophthalmol 2011 [**35**]	26	F	R/ E
15.	Wu et al., CAN J Ophthalmol 2011 [**33**]			
16.	Whist et al., Ophthalmology & Eye diseases 2011 [**41**]	45	F	R/ E
17.	Chheda et al., ARCH Ophthalmol 2011 [**38**]	54	M	L/ E
18.	Ishii et al., Int Ophthalmol 2011 [**11**]	80	F	L/ E
19.	Itoh et al., Case report Ophthalmol 2010 [**24**]	56.5	M	1 R/ E 1 L/ E
20.	Ang et al., Eye 2010 [**42**]	55	F	B/ L
21.	Hayasaka K et al., Int Ophthalmol 2008 [**27**]	76	M	R/ E
22.	Yodprom et al., Ocular immunology and inflammation 2007 [**30**]	54	M	L/ E
23.	Yang et al., Ophthalmology 2007 [**9**]	33-78	17 M, 5F	B/ L in 5
24.	Wong et al., HKMJ 2007 [**10**]	49	M	R/ E
25.	Saleem et al., NDT 2007 [**25**]	75	M	L/ E
26.	Dua S et al., Am J Transplant 2006 [**22**]	28	F	B/ E L>R
27.	Motley et al., Retina 2005 [**23**]	25	M	L/ E
28.	Chan et al., Am. J. Ophthalmol 2005 [**21**]	69	F	B/ L sequential
29.	Subramanian et al., ARCH Ophthalmol 2003 [**37**]	48	F	R/ E
30.	Tang et al., The Lancet 2003 [**8**]	60	M	L/ E
31.	Arcieri et al., BJID 2001 [**3**]	49	M	B/ L
32.	Betriu et al., JCM 2001 [**29**]	62	M	L/ E
33.	Menon et al., Eye 2000 [**43**]	57	M	R/ E
34.	Reedy et al., Intensive care med 2000 [**28**]	71	F	L/ E
35.	Cahil et al., Br J Ophthalmol 2000 [**6**]	40	M	B/ E
36.	Arroyo, ANN Ophthalmol 2000 [**40**]	57	M	B/ L
37.	Ang et al., Eye 2000 [**7**]	37-85	2M,2F	2L/ E 1R/ E 1B/ L

Table 2. Summary of endogenous endophthalmitis case reports

Sr. No.	Author, Journal, year of study	No. of cases	Underlying infection	Organism causing EE	Drug sensitivity	Final visual outcome
1.	Dogra, IJO 2019 [**2**]	1	Pancreatic pseudocyst	Klebsiella pneumoniae	intravitreal vancomycin + ceftazidime + colistin Intravenous colistin Topical steroids and cycloplegics	OD 6/ 6 OS 6/ 9
2.	Kim et al., CMH 2018 [**15**]	1	Liver abscess	Klebsiella pneumoniae	Intravenous cefotaxime, metronidazole and amikacin Vitrectomy	NOPL
3.	Rubin et al., CAN J Ophthalmol 2018 [**31**]	1	Infected gall bladder in a diabetic CKD pt.	Klebsiella pneumoniae	intravitreal vancomycin + dexamethasone + amikacin PPV Intravenous ceftriaxone and oral moxifloxacin	PL+
4.	Wu et al., Reports 2018 [**16**]	1	Liver abscess, pneumonia, UTI in a diabetic pt.	Klebsiella pneumoniae	Intravenous ceftriaxone	6/ 60 OU

5.	Xu et al., BMC [**34**] Ophthalmol 2018	1	Endoscopy in peptic ulcer pt.	Klebsiella pneumoniae	intravitreal ceftazidime PPV Retinotomy and abscess aspiration	HM
6.	Mali et al., JAMA Ophthalmol 2015 [**39**]	1	Dental cleaning	Streptococcus intermedius	intravitreal vancomycin + Clindamycin systemic antibiotics	20/ 25
7.	Tsai et al., BMC Ophthalmology 2015 [**13**]	1	DM, Liver abscess, subdural abscess	Klebsiella pneumoniae	PPV + intravitreal ceftazidime n amikacin	6/ 6
8.	Moore et al., MJA 2015 [**14**]	1	Liver	Klebsiella pneumoniae	Systemic ceftriaxone, oral and topical steroids, intravitreal vancomycin + ceftazidime + dexamethasone, PPV	6/ 12 OD 6/ 24 OS
9.	Tan et al., Eye 2014 [**44**]	1	Phlebitis	Serratia marcescens	Intravenous ceftriaxone + vancomycin then switched to Meropenem, Daptomycin, Doxycycline Topical antibiotics and antiglaucoma Evisceration	NOPL
10.	Sahu et al., Int Ophthalmol 2013 [**36**]	4	Pregnancy, abortion	Bacillus mycoides (1) Klebsiella pneumoniae (1) None (2)	1. Systemic, topical, intravitreal ceftazidime, vancomycin and dexamethasone 2. oral and topical ofloxacin 3. PPV 4. Oral itraconazole	CF to NOPL
11.	Malathi et al., case reports in Ophthalmol. Med. 2012 [**32**]	1	Diarrhoea for 10 days	Salmonella typhi. + fungus	Systemic antibiotics, intravitreal Amphotericin B+ Vanco + ceftazidime	
12.	Carcasi et al., Nefrologia 2012 [**26**]	2	Tunneled haemodialysis catheter	Staph. aureus	Systemic Vancomycin and gentamycin, vitrectomy and intravitreal vancomycin and ceftazidime	NOPL
13.	Dehgani et al., Case Report Ophthalmol 2011 [**12**]	1	Liver abscess	Klebsiella pneumoniae	intravitreal vancomycin + ceftazidime PPV systemic Ciprofloxacin	PL+
14.	Rahman et al., Int. Ophthalmol 2011 [**35**]	1	PROM	Sphingomonas paucimobilis	intravitreal vancomycin + amikacin Oral Moxifloxacin and steroids	6/ 9
15.	Wu et al., CAN J Ophthalmol 2011 [**33**]	1	Colonoscopy	E. coli	intravitreal vancomycin + amikacin + ceftazidime PPV & lensectomy Intravenous vancomycin + Metronidazole + ciprofloxacin	NOPL
16.	Whist et al., Ophthalmology & Eye diseases 2011 [**41**]	1	Systemically well	Staph epidermidis	intravitreal vancomycin + amikacin + foscarnet PPV and lensectomy Intravenous vancomycin	HM
17.	Chheda et al., ARCH Ophthalmol 2011 [**38**]	1	Brain abscess after tooth extraction	S. constellatus	intravitreal vancomycin + Clindamycin + ceftazidime Intravenous ceftriaxone + Metronidazole	6/ 60
18.	Ishii et al., Int Ophthalmol 2011 [**11**]	1	Liver abscess	Klebsiella pneumoniae	PPV + Lensectomy + SFIOL	6/ 6
19.	Itoh et al., Case report Ophthalmol 2010 [**24**]	2	1. After heart surgery-endocarditis, gingivitis, brain abscess 2. Acute pyelitis and prostatic abscess	1. Streptococcus anginosus 2. Staphylococcus sp	1. PPV + systemic imipenem 2. intravitreal ceftazidime + vancomycin + systemic imipenem	1. 6/ 7.5 2. 6/ 4.8
20.	Ang et al., Eye 2010 [**42**]	1	Systemically well	P. acne	Intravenous crystalline penicillin, topical moxifloxacin, prednisolone Oral steroids	6/ 9 B/ L
21.	Hayasaka et al., Int Ophthalmol 2008 [**27**]	1	Liver cancer, pulm. T.B., Spondylitis	Streptococcus bovis	PPV + SOI Intravenous Meropenem	6/ 60

22.	Yodprom et al., Ocular immunology and inflammation 2007 [**30**]	1	HIV	Salmonella choleraesuis	Intravitreal vancomycin + ceftazidime Intravenous ceftriaxone	NOPL
23.	Yang et al., Ophthalmology 2007 [**9**]	22	Liver abscess, DM in 15 patients, biliary stones in 2	Klebsiella pneumoniae	Systemic antibiotics, 3rd generation cephalosporins and aminoglycosides	NOPL in 11 (evisceration) PL in 8 6/ 60-1/ 60 in 3
24.	Wong et al., HKMJ 2007 [**10**]	1	liver abscess	Klebsiella pneumoniae	Intravenous cefuroxime + intravitreal vancomycin + amikacin	6/ 12
25.	Saleem et al., NDT 2007 [**25**]	1	Dialysis catheter exit site infection related septicemia	Staph. aureus	Intravenous Flucloxacillin + intravitreal vancomycin and amikacin	6/ 12
26.	Dua et al., Am J Transplant 2006 [**22**]	1	B/ L lung transplantation for end stage bronchiectasis secondary to CF	Pseudomonas aeruginosa	Intravitreal cefta + vanco + amphotericin B Systemic vancomycin, piperacillin, tazobactam, colistin PPV L/ E	HM
27.	Motley et al., Retina 2005 [**23**]	1	Cystic fibrosis	Pseudomonas aeruginosa	Systemic ceftazidime + tobramycin + ciprofloxacin, intravitreal and subconj. Antibiotics, enucleation	NOPL
28.	Chan et al., Am. J. Ophthalmol 2005 [**21**]	1	Bronchiectasis	Pseudomonas aeruginosa	Systemic and intravitreal ceftazidime, PPV	20/ 40
29.	Subramanian et al., ARCH Ophthalmol 2003 [**37**]	1	Dental cleaning	α-hemolytic streptococci	intravitreal vancomycin + amikacin PPV	CF at 1 m
30.	Tang et al., The Lancet 2003 [**8**]	1	Suppurative liver ds, DM	Klebsiella pneumoniae	Cefotaxime Intravitreal vancomycin + amikacin	NOPL
31.	Arcieri et al., BJID 2001 [**3**]	1	Infective endocarditis	Gram positive coccobacillus group B Streptococcus	Fluoroquinolones	PL OS NOPL OD
32.	Betriu et al., JCM 2001 [**29**]	1	CA. Larynx, Laryngectomy done, on radiation therapy and steroids	Listeria monocytogenes	Oral ciprofloxacin plus topical fort. Vancomycin and intravitreal vancomycin	HM
33.	Menon et al., Eye 2000 [**43**]	1	Not found	Pseudomonas aeruginosa	Systemic cefotaxime and steroids, intravitreal vancomycin + amikacin	NOPL
34.	Reedy et al., Intensive care med 2000 [**28**]	1	Cholangiocarcinoma complicated by ascending cholangitis	Pseudomonas aeruginosa	Topical Cefazoline + tobramycin Intravitreal vancomycin + tobramycin Oral ciprofloxacin	NOPL
35.	Cahil et al., Br J Ophthalmol 2000 [**6**]	1	Liver abscess	Klebsiella pneumoniae	Intravenous Ciprofloxacin 400mg twice daily and hydrocortisone 100 mg three times Topical antibiotic, steroid and mydriatic PPV + retinopexy	PL in R/ E 6/ 12 in L/ E
36.	Arroyo, Ann Ophthalmol 2000 [**40**]	1	Prostate abscess	Staph. aureus	intravitreal vancomycin + ceftazidime + amikacin PPV topical and systemic antibiotics	OD 6/ 6 OS PL +
37.	Ang et al., Eye 2000 [**7**]	4	Pneumonia in 2 pt Liver abscess and UTI in 1 pt each	Klebsiella pneumoniae	Intravitreal, S/ C, Topical cefazoline and gentamycin Intravenous ceftriaxone + gentamycin	NOPL in 3 pts 6/ 6 in 1 patient

In 2014, Sridhar et al. reported that endogenous *Klebsiella* pneumoniae endophthalmitis (EKPE) is associated with poorer visual outcomes and higher rates of evisceration and enucleation as compared to exogenous *Klebsiella pneumoniae* endophthalmitis [**18**].

In 2016, Odouard et al. reported that time since presentation from the onset of symptoms is crucial, as late presentation can increase chances of evisceration and enucleation. In addition, this early PPV and intravitreal antibiotic and corticosteroid injections can lead to a better visual outcome [**19**].

In 2017, Shields et al. reported that EKPE is associated with poor visual outcomes, 58% of the eyes in their series had a final visual outcome of LP or NLP. EKPE is commonly seen in patients of Asian ethnicity with liver abscess. Early detection and aggressive treatment can lead to better visual outcome [**20**].

Pulmonary diseases

In 2000, Ang et al. reported 2 cases of EE associated with pneumonia and *Klebsiella pneumoniae* septicemia, treated with intravitreal, topical, subconjunctival cefazoline and gentamycin and intravenous ceftriaxone and gentamycin [**7**]. One patient could not regain any vision and one patient gained vision of 6/ 6 B/ E. The difference in visual outcome was explained by the time lapse in presentation from the onset of symptoms. The patient with NOPL visual outcome presented later than the patient who gained vision of 6/ 6 (**Table 1,2**).

In 2005, Chan et al. reported a case of EE associated with bronchiectasis. The patient was treated with systemic and intravitreal ceftazidime and PPV. The patient attained good vision of 20/ 40 [**21**].

In 2006, Dua et al. reported a case of EE in a patient with B/ L lung transplantation for end stage bronchiectasis secondary to CF. The patient was treated with Intravitreal cefta + vanco + amphotericin B and systemic vancomycin, piperacillin, tazobactam, colistin and PPV, but could gain vision of HM only [**22**].

In 2015, Motley et al. reported a case of EE and choroidal abscess associated with cystic fibrosis. The patient was treated with intravenous ceftazidime, ciprofloxacin and tobramycin, intravitreal and subconjunctival injections of same antibiotics, retinectomy and abscess excision, but the intraocular infection could not be controlled and ultimately the patient required enucleation [**23**].

In all these three pulmonary diseases associated cases of EE, the causative organism was *Pseudomonas aeruginosa*.

Infective endocarditis

In 2001, Arcieri et al. reported a patient who developed bilateral EE following *group B Streptococcus* septicemia along with infective endocarditis. The patient was treated with intravenous fluoroquinolones, but could only recover perception of light in one eye, while the other eye could not perceive light [**3**].

In 2010, Itoh et al reported a case of EE in a patient after heart surgery. After surgery, the patient developed septicemia, endocarditis, gingivitis and brain abscess. *Streptococcus anginosus* was the causative agent. The patient was treated with PPV and systemic imipenem. The patient achieved good vision of 6/ 7.5 [**24**].

While the evidence is limited, *gram positive streptococci* septicemia in infective endocarditis patients is the most commonly reported cause of EE. This infection may be amenable to treatment with intravenous penicillin and fluoroquinolones. However, visual results reported so far are not encouraging with most patients requiring surgical interventions like enucleation or pars plana vitrectomy (**Table 1,2**).

Tunnelled haemodialysis catheters

In 2007, Saleem et al. reported a case of EE associated with a dialysis catheter exit site infection and *Staphylococcus aureus* blood stream infection (BSI). This patient was treated with intravenous flucloxacillin and intravitreal vancomycin and amikacin, and recovered a vision of 6/ 12 [**25**].

In 2012, Carcasi et al. also reported a similar case of EE associated with dialysis catheter exit site infection and *Staphylococcus aureus* blood stream infection. The patient was treated with intravenous vancomycin and gentamycin along with intravitreal vancomycin and ceftazidime. Despite pars plana vitrectomy, the patient could not recover any vision (No PL) [**26**].

Thus, *Staphylococcus aureus* has been the most common bacterium reported causing EE in patients having dialysis catheter associated BSI. These patients may be treated with i.v. vancomycin and third generation cephalosporins and intravitreal antibiotics. Fulminant intraocular infection has a relatively poor prognosis and the patient may not recover useful vision even after pars plana vitrectomy (**Table 1,2**).

Immunosuppression

In 2000, Hayasaka et al. reported a case of EE in a liver cancer and pulmonary T.B. patient suffering from *Streptococcus bovis* bacteremia. The patient received treatment with vitrectomy and SOI and intravenous meropenem, but could only gain vision of 6/ 60 [**27**].

In the same year, Reedy et al. reported a case of EE associated with Cholangiocarcinoma and *Pseudomonas aeruginosa* septicemia. The patient was treated with topical Cefazoline + tobramycin, Intravitreal vancomycin + tobramycin and oral ciprofloxacin, but the patient's visual outcome was NO PL [**28**].

In 2001, Betriu et al. reported a case of *Listeria monocytogenes* EE in a patient with cancer of the larynx, who was undergoing radiotherapy and was on steroids. The patient was administered oral ciprofloxacin and intravitreal vancomycin, but the vision recovery was only hand movements close to face [**29**].

In 2007, Yodoprom et al. reported a case of *Salmonella choleraesuis* EE in a HIV infected individual. The patient was treated with intravitreal vancomycin, ceftazidime and intravenous ceftriaxone. But the patient's visual outcome was NO PL [**30**].

In 2018, Rubin et al. reported a case of Klebsiella pneumoniae EE associated with infected gall bladder in a diabetic CKD patient. The patient was treated with intravitreal vancomycin, dexamethasone, ceftazidime and intravenous ceftriaxone, oral Moxifloxacin and PPV. But the patient could only gain vision of PL [**31**].

Diarrhoeal disease

In 2012, Malathi et al. reported a case of EE in a patient having diarrhea for 10 days. Blood culture of the patient yielded Salmonella typhi and fungus, the patient being treated with systemic antibiotics and intravitreal Amphotericin B, vancomycin and ceftazidime, but the eye could not be salvaged and ultimately required evisceration [**32**] (**Table 1,2**).

Invasive diagnostic procedures

In 2011, Wu et al. reported a case of EE associated with post colonoscopy bacteremia with *E. coli*. The patient was treated with intravitreal vancomycin and ceftazidime, and intravenous vancomycin, metronidazole and ciprofloxacin and PPV. But the patient's visual outcome was NO PL [**33**].

In 2018, Xu et al. reported a case of *Klebsiella pneumoniae* EE after endoscopy for peptic ulcer in a diabetic heavy drinker with history of recent significant weight loss. The patient was treated with intravitreal ceftazidime, PPV, retinotomy and retinal abscess drainage. But the patient's visual outcome was only HM [**34**].

Pregnancy

In 2011, Rahman et al. reported a case of *Sphingomonas paucimobilis* EE in a post-partum lady with PROM. The patient was treated with intravitreal vancomycin and amikacin, oral moxifloxacin and steroids. The patient gained vision of 6/ 9 [**35**] (**Table 1,2**).

In 2013, Sahu et al. reported 4 cases of EE associated with pregnancy and abortion. In 1 patient the causative organism was *Bacillus mycoides*, in another patient *Klebsiella pneumoniae,* and in 2 patients no organism was identified. The patients were treated with systemic, topical, intravitreal ceftazidime, vancomycin and dexamethasone, oral and topical ofloxacin, PPV and oral itraconazole but in all the 4 patients the visual outcome was very poor (NOPL to CF) [**36**].

Dental procedures

In 2003, Subramanian et al. reported a case of *α hemolytic streptococci* EE after dental cleaning. The patient was treated with intravitreal vancomycin and amikacin and PPV, but the patient could not gain vision of counting finger at only 1 m [**37**].

In 2011, Chheda et al. reported a case of EE after tooth extraction. *Streptococcus constellatus* bacteremia caused brain abscess and EE in this patient. The patient was treated with intravitreal

vancomycin, ceftazidime, clindamycin and intravenous ceftriaxone, metronidazole but the patient could gain vision of 6/ 60 [**38**].

Another case of EE after dental cleaning was reported by Mali JO et al. in 2015, [**39**] the patients investigations revealed *Streptococcus intermedius* as the causative agent. The patient was treated with intravitreal vancomycin and clindamycin and systemic antibiotics. The patient regained vision of 20/ 25 (**Table 1,2)**

Pancreatic pseudocyst

In 2019, Dogra M et al. reported a case of *Klebsiella pneumoniae* B/ L EE, in a patient with pancreatic pseudocyst. The patient was treated with intravitreal vancomycin, ceftazidime, topical steroids and cycloplegics, intravenous and intravitreal colistin. The patient gained good vision of 6/ 6 in R/ E and 6/ 9 in L/ E [**2**] (**Table 1,2**).

Prostate abscess

In 2000, Arroyo reported a case of EE associated with *Staphylococcus sp* septicemia and prostate abscess. The patient was treated with intravitreal vancomycin + ceftazidime + amikacin, PPV, topical and systemic antibiotics. The patient gained vision of 6/ 6 OD, PL+ OS [**40**].

In 2010, Itoh et al reported a similar case treated with intravitreal ceftazidime + vancomycin and systemic imipenem. The patient's visual outcome was 6/ 4.8 [**24**].

Systemically well patient

In 2011, Whist et al. reported a case of staph epidermidis EE in a systemically well patient. The patient was treated with intravitreal foscarnet + vancomycin + amikacin, intravenous vancomycin, PPV and lensectomy. The patient regained vision of HM [**41**] (**Table 1,2**).

In 2010, Ang et al. reported a case of *Propionibacterium acne* B/ L EE in a systemically well patient. The patient was treated with topical moxifloxacin + prednisolone and intravenous crystalline penicillin and oral steroids. The patient gained good vision of 6/ 9 in B/ E [**42**]. Another case of EE reported by Menon et al. in 2000 [**43**] associated with *P. aeruginosa* septicemia, in which the patient was treated with systemic cefotaxime and steroids and intravitreal injections of vancomycin and amikacin, but the patient could not recover any vision. So, it is obvious that *P. aeruginosa* septicemia associated EE generally has a poor visual prognosis despite intensive medical and surgical treatment.

Phlebitis

In 2014, Tan et al. reported a case of *Serratia marcescens* EE in a patient with phlebitis after intravenous cannulation. The patient was treated with intravenous ceftazidime + vancomycin, topical antibiotic and antiglaucoma drugs. The patient was then switched to meropenem, then to daptomycin and doxycycline but the ocular inflammation could not be controlled, ultimately the patient requiring evisceration [**44**] (**Table 1,2**).

Conclusion

While the evidence for the associations of endogenous endophthalmitis is extremely limited, it is obvious that the most common site of primary infection for EE is the liver (liver abscess). Other primary foci include lungs (pneumonia, CF, bronchiectasis), heart (infective endocarditis), tunneled hemodialysis catheter exit site infection, and meningitis [**45-48**].

Even though endogenous endophthalmitis is a rare entity nowadays, especially because of the availability of effective antimicrobial agents, it must be kept in mind in immunocompromised patients. Diabetics, cancer patients on immunosuppression, patients on steroids, hospitalized patients with intravenous access, and patients with renal diseases on dialysis are especially vulnerable to metastatic endophthalmitis. Systemic antibiotic treatment and systemic antifungal treatment (the latter, in case of fungal EE and fungal septicemia) is usually sufficient to control the EE along with the primary site of infection. Choice of antibiotic depends upon culture and sensitivity reports of blood, urine, CSF, and local wound swabs [**49-52**].

In cases with fulminant intraocular inflammation and infection, aqueous and vitreous aspirates culture and sensitivity may guide the choice of intravitreal antibiotics. If the infection is not controlled even with this, then pars plana vitrectomy should be considered at

the earliest in order to decrease the infectious agent and toxin load. Even after this, if the infection is not controlled then enucleation or rarely, evisceration, may be performed [**53-58**].

Conflict of Interest

There is no conflict of interest between authors.

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GENERAL ARTICLE

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Odontogenic orbital inflammation

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Abstract

Objective: This study aimed to determine the most frequent clinical aspects in patients with odontogenic orbital inflammation, the computed tomography (CT) aspect, and the most appropriate treatment.

Material and Methods: This is a retrospective case-series study conducted on 3 patients with ages between 16 and 55 years old, in the Ophthalmology and Oro-Maxillo-Facial Clinics of "Sf. Spiridon" Emergency Hospital, Iaşi, Romania. The following investigations were performed in all selected cases: visual acuity (VA), ocular motility examination, anterior segment examination at slit-lamp, fundus examination, intraoral clinical examination, sinus and orbital involvement on CT scan, pathogens involved.

Results: All three patients presented swelling of the genic and periorbital regions, conjunctival chemosis, hyperemia of the conjunctiva, proptosis, pain, decreased vision and extraocular movement restriction. The CT examination identified orbital and periorbital cellulitis and ethmoidal expanded maxillary sinusitis or pansinusitis. Dental extraction, transalveolar drainage and orbital decompression were performed in all three cases. The evolution was favorable with remission of proptosis, edema of the genic and periorbital regions and conjunctival chemosis. Visual acuity remained poor in one case due to total optic nerve atrophy.

Conclusions: Our study had a small number of patients, but the data was pertinent to ophthalmologists and maxillofacial surgeons who need to be aware of typical clinical features and the most common etiologies. Late treatment of dental infections can lead to severe ocular manifestations such as orbital cellulitis. Odontogenic orbital inflammation management involves a long-term and multidisciplinary approach.

Keywords: orbital cellulitis, odontogenic, orbital decompression

Abbreviations: CT = computed tomography, VA = visual acuity, CBCT = cone beam computed tomography, TED = thyroid eye disease, MRI = magnetic resonance imaging, OOC = odontogenic orbital cellulitis, RAPD = relative afferent pupillary defect

Introduction

The most frequent causes of orbital inflammation are the following: thyroid eye disease (TED), Wegener granulomatosis, sarcoidosis, histiocytic disorders, and xanthogranuloma. Orbital inflammation produces acute damage by leakage of proinflammatory cytokines, cells and intravascular fluid, into the extracellular space [**1**].

Orbital cellulitis represents one of the pathologies that can cause tension in the orbit. Orbital cellulitis can be caused by sinusitis, eyelid inflammation, dacryocystitis or hematogenous spread of infection [**2**]. Orbital inflammation is secondary to a variety of microorganisms such as *Mycobacterium tuberculosis, Candida albicans, Aspergillus*. Moreover, orbital involvement can be associated with neoplastic disorders such as *Human Herpes Virus 8* in Kaposi Sarcoma, *Epstein-Barr virus* in Hodgkin Lymphoma and *Human Papillomavirus 16 and 18* in squamous cell carcinoma [**3**]. Most cases of orbital cellulitis have a favorable prognosis, signs and symptoms remitting under antibiotic treatment or surgical drainage, without any complications. However, in some cases complications may occur such as extraocular muscle palsy, high intraocular pressure, pupil mydriasis or visual loss due to optic nerve damage [**2**].

Dental infections or interventions that have an important risk of spreading through paranasal sinuses to the orbital cavity are very rare and are associated with low prognosis [**4**].

Odontogenic orbital inflammation is a rare and severe condition, comprising only 2%-5% of all orbital cellulitis cases, and is associated with high risk of vision loss [**5**]. The inflammation spreads to the orbit infiltrating the apex of the dental roots, infecting the maxillary sinus and finally reaching the lower orbit infiltrating the inferior orbital fissure or through a defect of the orbital floor. The mechanisms of vision loss involve impairment of the anterior segment of the eye (exposure keratopathy), of the optic nerve (ischemic optic neuropathy), or of the retina (exudative retinal detachment). Odontogenic orbital inflammation involves a multidisciplinary and imagistic approach, antibiotic therapy and surgical treatment [**6**].

Material and methods

This is a retrospective case-series study, conducted between December 2018 and January 2020, on 3 patients aged between 16 and 55 years, in the Ophthalmology and Oro-Maxillo-Facial Clinics of "Sf. Spiridon" Emergency Hospital, Iaşi, Romania. The following investigations were made in all selected cases: visual acuity (VA), ocular motility examination, anterior segment examination at slit-lamp, fundus examination, intraoral clinical examination, sinus and orbital involvement on computed tomography (CT) imaging, pathogens involved. Dental extraction and transalveolar drainage were performed in all the cases.

Results

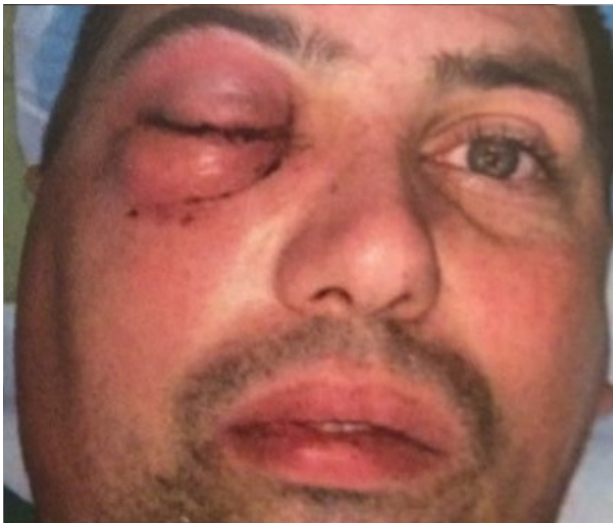
All three patients presented swelling of the genic and periorbital regions, conjunctival chemosis, hyperemia of the conjunctiva, proptosis, pain, decreased vision and extraocular movement restriction, with normal pupillary reactions and no detectable afferent pupillary defect (**Fig. 1**). There was no audible bruit on auscultation in any of the eyes. Fundus evaluation after pupillary dilatation with Tropicamide and Phenylephrine eye drops revealed pale borders of the optic disk (**Fig. 5a**). Patients did not have any history of ocular trauma.

All the patients had an initial investigation by computed tomography that confirmed the diagnosis – orbital and periorbital cellulitis and ethmoidal expanded maxillary sinusitis or in other cases pansinusitis (**Fig. 2a, b**). Dental radiography diagnosed a maxillary abscess unraveling the odontogenic origin.

They were admitted in the Oro-Maxillo-Facial Clinic or in the Ophthalmology Clinic, where the antibiotic treatment was started – Ceftriaxone, Clindamycin or Vancomycin, associated with Dexamethasone. The patients were evaluated daily by both specialists.

In one case, the culture from the external orbital angle indicated *Streptococcus constellatus*, (a bacteria from *Peptostreptococcus family)*, a saprophyte originated in the oral mucosa, but in other cases, the microbiological examination for aerobic bacteria revealed the absence of growth at 48 hours.

Dental extraction, transalveolar drainage (**Fig. 3**) and orbital decompression (**Fig. 4**) were performed in all three cases. In one case, the patient also had retrobulbar injection with Dexamethasone and Vancomycin. Post-operative, the patients started to show improvement in ocular movements and reduced proptosis. Visual acuity remained poor in one case due to total optic nerve atrophy (**Fig. 5b**). All the patients were kept under observation with monthly follow-up up to six months to rule out local recurrence. The evolution was favorable with remission of proptosis, edema of the genic and periorbital regions and conjunctival chemosis (**Fig. 6**).



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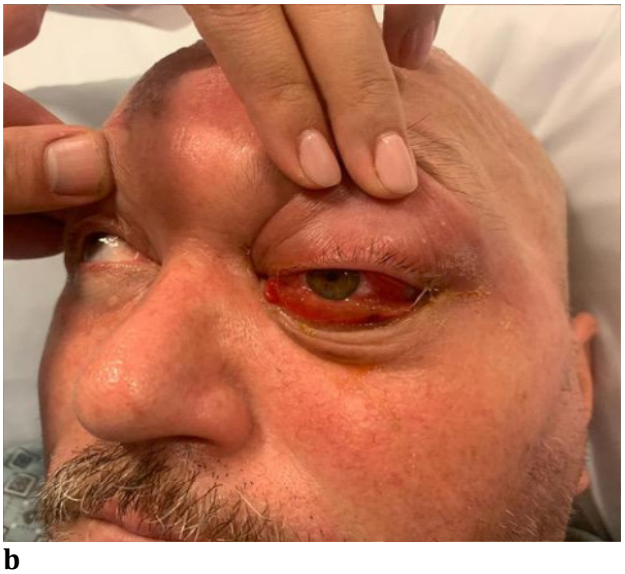

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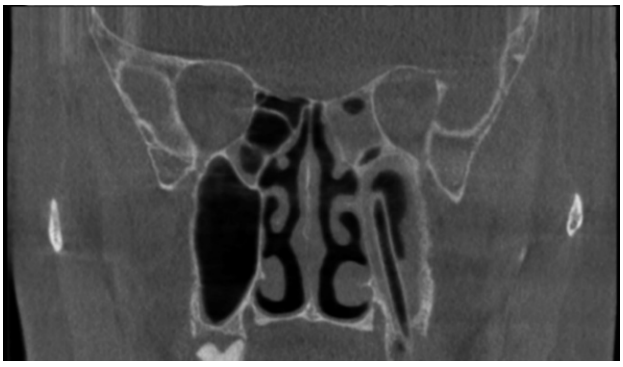
Fig. 1 Initial appearance upon admission – (a) Case 1, (b) Case 2



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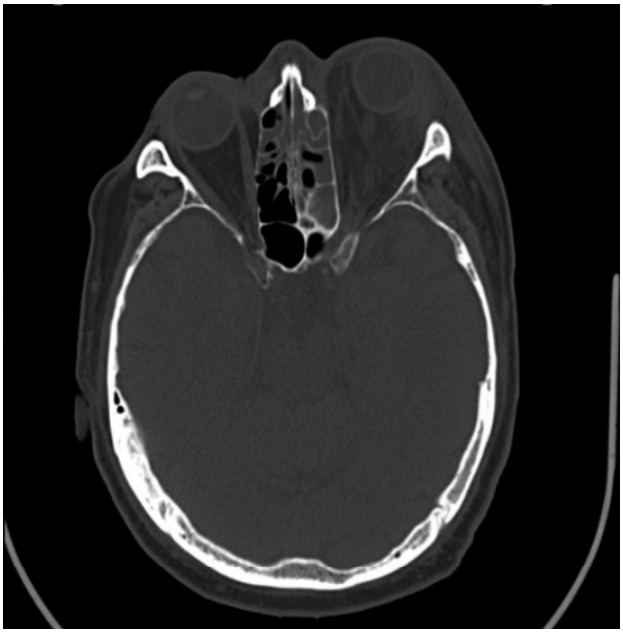

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Fig. 2 Sinus and orbital involvement on CT

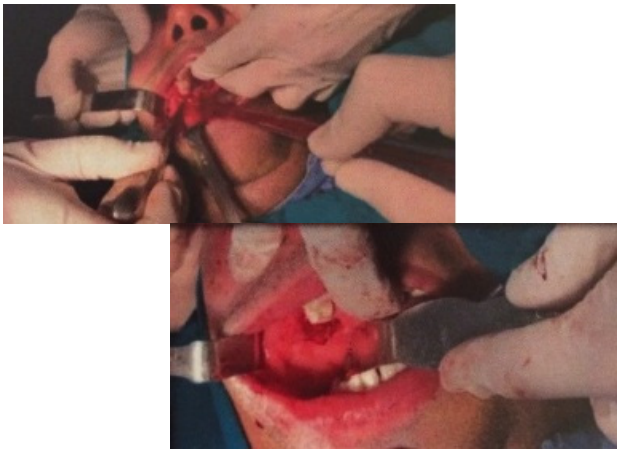


Fig. 3 Dental extraction and transalveolar drainage

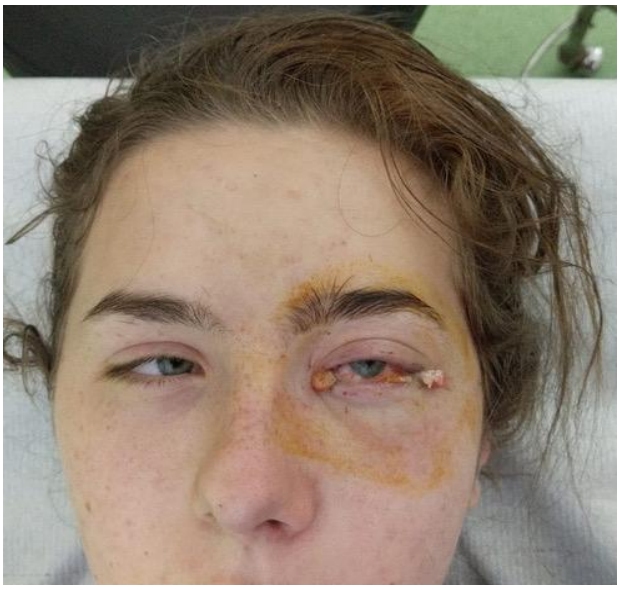
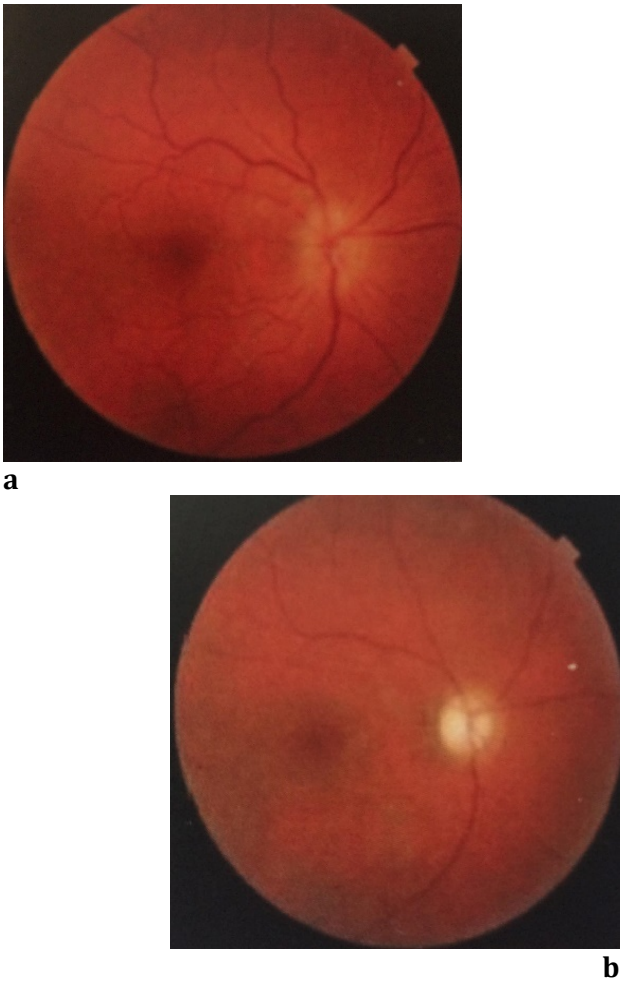


Fig. 4 Orbital decompression – Case 3



a

b

Fig. 5 RE: Fundus appearance on admission (a) and on last examination (b) – Case 1

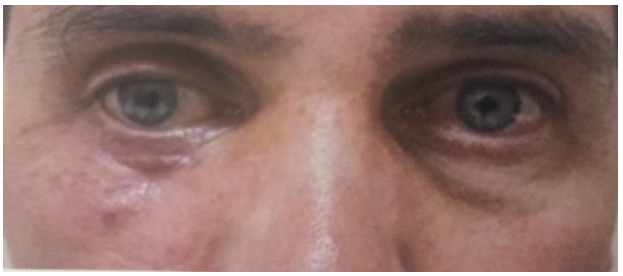


Fig. 6 RE: Appearance of the periocular region on last examination - Case 1

Three weeks after the surgical drainage and antibiotic treatment, the acute maxillary sinusitis became chronic in all the cases. The chronic maxillary sinusitis was cured at the same time with the closing of the oro-antral communication (due to the transalveolar drainage) through a Caldwell-Luc approach.

Discussions

The most frequent symptoms of orbital affection are represented by swelling of eyelids and conjunctiva, hyperemia, epiphora, discomfort or displacement of the eye.

Bacterial orbital inflammation represents a critical infection affecting the soft tissues at the back of the orbital septum making it life-threatening. It does not depend on age but it is more frequent in children. The more frequent pathogens are *Streptococcus pneumoniae, Staphylococcus aureus, Streptococcus pyogenes* and *Haemophilus influenzae*. Typically, the origin of the infection is from the paranasal sinuses [**7**]. Fungal infections are always a possibility, especially in immunodepressed patients. The most common source of orbital cellulitis is bacterial rhinosinusitis. Approximately 86-98% of the cases with orbital cellulitis have coexisting rhinosinusitis [**8**]. Origin of the infection can also be preseptal cellulitis, dacryocystitis, midfacial skin or dental infection and posttraumatic, even any type of ocular surgery. The condition usually develops with fever and peripheral leukocytosis and the diagnosis is indicated by CT scan or MRI [**7,8**].

Odontogenic orbital cellulitis (OOC) is a rare and severe cause of orbital infection, with a bad evolution [**9**].

In a prior series, 45.8% of the patients with OOC had a final vision of light perception or worse. In our study, only one patient had a visual acuity uncertain light perception, the others had a best corrected VA > 0.1. It is important to always evaluate for potential complications such as the development of intracranial extensions, destructive sinus disease, orbital abscess or vision loss [**10**], as the case of our patient who presented optic disc edema on admission and permanent vision loss due to secondary optic nerve atrophy.

The OOC infection spreads most frequently through the paranasal sinuses, and less frequently through the premaxillary soft tissues reaching the orbit [**11**], all our patients having a confirmed diagnosis of sinusitis. All the patients had no history of trauma or skin infection, but all had maxillary sinusitis or pansinusitis.

Odontogenic orbital infection of the orbit is a rare condition. Apical osteitis or infected tooth sockets after surgical teeth removal or trauma can be the reason of odontogenic infection. The infection spreads through the maxillary sinus, the canine fossa with a thrombophlebitis of the angular vein or the pterygopalatine fossa and infra-temporal fossa both reaching the orbit by means of the inferior orbital fissure [**12**].

Clinically, orbital cellulitis is dominated by swelling and pain. Patients with odontogenic orbital inflammation present with symptoms or history that are highly suggestive for this condition's etiology [**13**]. This study identified the most common initial presentations such as proptosis, chemosis, vision loss, reduced eye movements. Even though orbital cellulitis is usually associated with diplopia and RAPD (relative afferent pupillary defect), this study did not reveal patients with any of these symptoms. Secondary to the incomplete growth of the paranasal sinuses and the thin bony barrier between the orbit and the anterior skull base present in young patients, the condition is more frequent in this age group [**14**].

Many reports in literature identified the bacteriologic aspect of the acute orbit. *Staphylococcus aureus*, *Streptococci pneumoniae*, and *Hemophilus influenza* are predominantly responsible for these infections. Anaerobic bacteria are present in chronic sinusitis and are rare in the acute orbit caused by sinusitis [**12**]. In our cases, one culture indicated *Streptococcus constellatus* and the microbiological examination for aerobic bacteria revealed the absence of growth at 48 hours for the other.

Most cases with orbital cellulitis have a favorable prognosis and can be treated with oral or intravenous antibiotics. In our study, all the cases were managed with antibiotics such as Ceftriaxone, Clindamycin or Vancomycin. Dental extraction and transalveolar drainage were performed for all patients, with a favorable evolution.

Management of odontogenic orbital inflammation in immunocompromised patients includes surgical procedures and medical therapy in a multidisciplinary approach [**15**].

Our study had a small number of patients, but the data was pertinent to the general ophthalmologists and maxillofacial surgeons who need to be aware of typical clinical features and the most common etiologies.

Conclusions

Late treatment of dental infections can lead to severe ocular manifestations such as orbital cellulitis. Orbital inflammation diagnosis is expensive and time-consuming needing complex investigations such as CT imaging or sinus cone beam computed tomography (CBCT). Odontogenic orbital inflammation management involves a long-term and multidisciplinary approach.

Disclosures

None.

Conflicts of interest

None.

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GENERAL ARTICLE

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Results in keratoconus correction with Kerasoft 3 Contact lenses

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Abstract

Introduction: The purpose of the paper was to evaluate the indications, fitting, advantages and functional results of Kerasoft 3 contact lenses in keratoconus.
Material and method: A retrospective single center study was performed at Oculens Private Clinic in Cluj-Napoca, Romania. Our study included 61 eyes of 35 patients diagnosed with keratoconus in different stages of evolution fitted with Kerasoft 3 lens. The study was undergone between August 2015 and January 2019.
Results: In our study, the mean age of the patients was 26.36±8.69 years. The group of study included 80.32% males and 19.62% females. Regarding previous surgeries, CXL was performed in 25 eyes, ICR in 1 eye, CXL and ICR in 15 eyes. The mean BCVA habitual was 0.38±0.19 logMar and with the lens 0.22±0.23 logMar ($p<0.01$). Spherical equivalent (SE) at baseline was -5.78 and after fitting the lens it decreased to -0.46. Comfort and tolerance level were maximum in all cases. No significant complications were noted with the use of contact lens.
Conclusions: Kerasoft 3 contact lenses provide many of the benefits of RGP lenses (avoiding RGP's discomfort and allergic reactions), along with excellent comfort, visual acuity, high oxygen permeability and longer wearing times.
Keywords: contact lenses, Kerasoft 3, keratoconus
Abbreviations: CXL = cross-linking; ICR = intrastromal corneal ring; BCVA = best corrected visual acuity; SE = spherical equivalent; RGP = rigid gas permeable contact lenses

Introduction

Keratoconus (Kc) is a corneal progressive and degenerative disorder that appears in the second to the third decade of life, characterized by a conical shape of the cornea (thinning, ectasia) inducing an irregular astigmatism, myopia and corneal protrusion. In late stages, corneal scars develop.

The early management of Kc consists in the prescription of glasses, contact lenses (CL) and cross-linking–UVA therapy (CXL) in order to stop or arrest the progression of the disease. The use of CL continues to play a major role in the management of Kc. Contact lenses include the rigid ones (Rigid gas permeable), soft spherical and toric silicone hydrogel, scleral and

piggyback. In late stages, intracorneal rings (ICR), penetrating keratoplasty (PKP) and deep anterior lamellar keratoplasty (DALK) are indicated [**1,2**].

Soft lenses, designed specifically for Kc, have a useful role in correcting corneal irregularities in the early stages of the disease or when the patient does not tolerate RGP.

Kerasoft lenses (Ultravision, UK) are two types: conventional hydrogel and silicone hydrogel lenses. These lenses are marked with a laser sign at six o'clock position. Keratoconus and post graft fitting can be treated with the soft lens KeraSoft®3. These lenses have a toric design on the front surface and they contain 74%* Definitive™ Silicone Hydrogel. This enables them to provide a prolonged usage, better visual acuity and they are also easy to wear.

The characteristics of the lens can be seen in **Table 1**.

Table 1. The KeraSoft®3 lens characteristics

Material	Definitive™ Silicone Hydrogel 74% water content*
Modulus	0.38 MPa (Typical of mid water content materials)
Base Curves	Series A (8.00mm), B (8.20mm), C (8.40mm), D (8.60mm)
Diameter	14.00mm 14.50 mm 15.00mm
Lens design	Front Surface Asphere or Aspheric Toric prism ballasted with balanced overall thickness. Wavefront Aberration Control
Power Range	Sphere: +30.00DS to -30.00DS (in 0.25 steps) ** Cylinder: -0.50 to -11.00DC (in 0.25 steps) Axis: 0° to 180° (in 1° steps) Add up to +3.00 (in 0.25 steps)
Handling Tint	Clear
DK	60×10^{-11} $(cm^2/sec)[ml0_2/(ml \times mmHg)]$
Modality	3-monthly lenses for daily wear
Pack size	Single lens, 2-pack, 4-pack

KeraSoft®3 has an aspheric anterior zone to maintain a toric design with a prism ballasting.

With wearing of KeraSoft®3 lenses, it has been demonstrated that the patients do not have as many complications as other common lenses due to the 74% water content. For this reason the lens can be more comfortable in various meteorological conditions.

The purpose of the paper was to evaluate the indications, fitting, advantages and functional results of Kerasoft 3 contact lenses in keratoconus.

Material and method

A retrospective single center study was performed at Oculens Private Clinic in Cluj-Napoca, Romania. Our study included 61 eyes of 35 patients diagnosed with keratoconus in different stages of evolution fitted with Kerasoft 3 lens. The study period was between August 2015 and January 2019.

The inclusion criteria took into account: age- over 18 years old, any gender, diagnosed Kc (corneal topography) of stage 1 or 2 (according to Krumreich classification), Vogt striae, CXL or ICR performed previously and RGP in tolerance area.

The exclusion criteria included: the presence of systemic disease affecting ocular health, use of any systemic or topical drugs that could affect ocular physiology or lens performance, refractive astigmatism more than 5 D, atypical scar or neovascularization within the central 4mm of the cornea, aphakia and pregnancy or currently breast-feeding.

Before fitting, a complete ophthalmological examination was performed including: uncorrected and best corrected visual acuity (UCVA, BCVA), refractometry (Topconauto refracto-keratometer, KR 8900), corneal topography with pachymetry (Pentacam® HR Premium; Oculus Optikgerate GmbH, Wetzlar, Germany), keratometry and slit lamp examination (Slit Lamp BX 900, Haag-Streit AG) (**Fig. 1**).

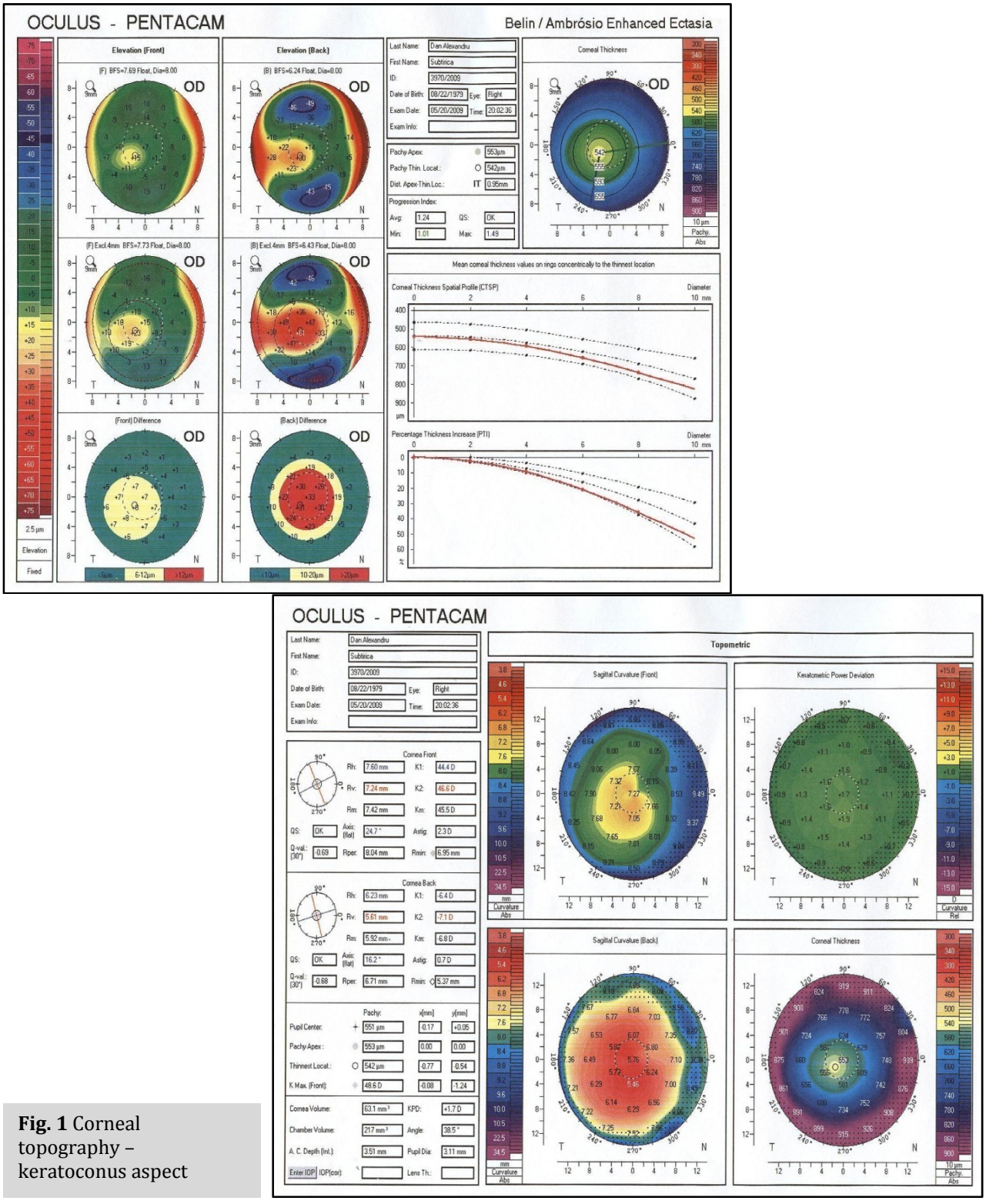

Fig. 1 Corneal topography – keratoconus aspect

Visual acuity was examined on Snellen charts and then for scientific purpose transformed in logMar.

Before starting fitting, we chose the proper CL for trial from the set trial consistent with keratometry and the stage of keratoconus. For early stages, we used the -2 or plan D, 8.6, 14.5 mm CL, for moderate stages we used -6/-4, 8.4, 14.5 mm CL and for advanced stages we used -10/-8D, 8.2, 14.5 mm. We left the patient 30 minutes with the contact lens on the eye and rechecked the visual acuity (VA), contact lens mobility (1-2 mm movement was acceptable), comfort and over-refraction. In cases of increased or decreased motility, we changed the CL with a smaller or a higher curvature respectively. The fitting assessment of the lens included the evaluation of the VA with the lens. Poor VA indicated a poor lens fit. After 3 months of wearing the prescribed contact lenses, we performed the reevaluation of the patient (VA, over-refraction, mobility, comfort) and prescribed the final contact lens. The follow–up period was at 6 months.

Regarding statistics, the follow up measurements made at 6 months after fitting were compared with baseline values, and statistical analysis was performed using a 2-tailed paired sample Student t test. A p-value <0.05 was considered statistically significant.

Results

In our study, the mean age of the patients was 26.36±8.69 years. The group of study included 80.32% males and 19.62% females. CXL was performed as previous surgery in 25 eyes, ICR in 1 eye, CXL and ICR in 15 eyes.

Baseline refractive characteristics regarding the spherical equivalent, cylinder and keratometry are shown in **Table 2**.

Table 2. Baseline refractive characteristics

Sphere	K avg		
	<45.00	**45.00-50.00**	**>50.00**
No. of patients	14	29	21
Mean	-1.02	-3.19	-7.31
SD	2.44	2.86	4.88
Cylinder	K avg		
	<45.00	**45.00-50.00**	**>50.00**
No. of patients	14	29	21
Mean	-3.25	-3.32	-3.10
SD	1.61	1.26	0.95
Curve	K avg		
	<45.00	**45.00-50.00**	**>50.00**
No. of patients	14	29	21
Mean	8.56	8.46	8.34
SD	0.10	0.17	0.19

Mean BCVA habitual was 0.38±0.19 logMar and with the lens 0.22±0.23 logMar (p<0.01) (**Table 3**, **Fig. 2**).

Table 3. Values of BCVA habitual and with lens in logMar

	BCVA habitual	**BCVA with lens**
Mean	0.38	0.22
STDV	0.19	0.23

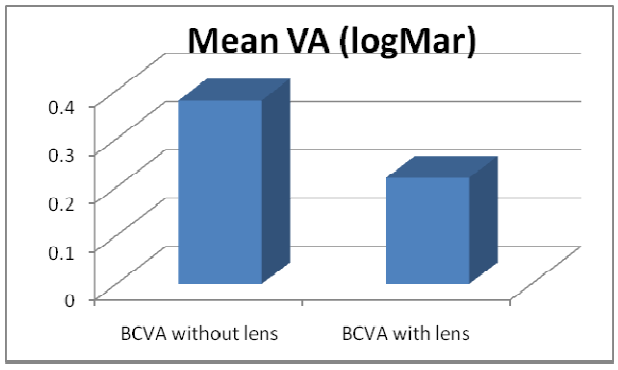

Fig. 2 Values of BCVA habitual and with lens in logMar

The difference of spherical equivalent (SE) between baseline and after fitting the lens is shown in **Fig. 3**.

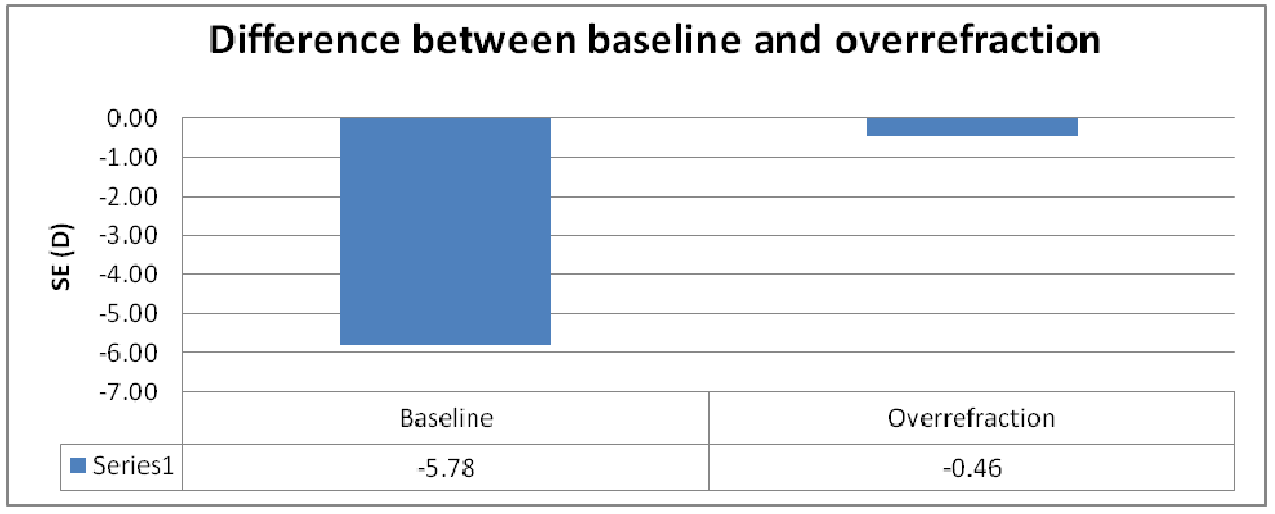

Fig. 3 The difference of SE between baseline and over-refraction

The safety of these CL was established at 12 months by slit lamp examination. In most of the cases, no findings, corneal infiltrates, corneal vascularization, epithelial microcysts, bulbar congestion were observed and limbal injection grade was 0-21%. The abandon of the CL because of financial reasons was registered in three cases.

Discussions

Contact lenses continue to play a role in the non-surgical management of Kc [**3**]. Soft lenses have a limited role in correcting corneal irregularities, offering a poor visual acuity. However, soft contact lenses designed specifically for keratoconus, such as Kerasoft 3, may be useful in the correction of mild or moderate keratoconus [**3**].

The indications of soft contact lenses are represented by: Keratoconus stage I, II, III, hard CL intolerance or after Cross linking therapy and Ferrara rings implantation.

In our study, the mean age presentation was 26.36±8.69 years. Similar data were offered by Crews et al. [**4**] in a retrospective study and found that the mean age at referral was 28 years. Seema Das et al. [**3**] noted in their study that the mean age at presentation was 25.3 years. Nevertheless, it was very difficult to establish the age onset of the disease because some of the patients paid attention to their decreased visual acuity only when both eyes were affected or when they were examined by the optometrists. There are studies that highlighted the same idea [**5**].

In our study, males were affected predominantly (80.32%). Similar outcomes were shown by several studies [**6-8**] during time.

Contact lenses normally offer the patient a better visual acuity in comparison with glasses, by acting against the irregular astigmatism

induced by Kc. Moreover, the progression of the disease may often require the change of glasses prescription and sometimes, even with best correction, it is not possible to obtain a good visual acuity. In our study, we obtained a significantly statistical difference regarding the habitual VA and VA with the lens ($p<0.01$). Similar results were demonstrated by Seema Das et al. [**3**] and Frederick et al. [**9**].

Even more, in our study we took into account not only the stage of Kc but also the keratometric readings. That is why we used Kerasoft 3 in mild and moderate stages of Kc, under 50D values of the corneal curve. Seema Das et al. [**3**] used soft lenses in Kc correction in 6% of the cases. In eyes with a keratometry above 50D, studies showed that RGPs are indicated and, in advanced cases, Rose K or Kerasoft IC lenses are the proper choice [**10,11**].

When prescribing soft contact lens for Kc, we have to take into account not only the keratometry but also the advantages offered by the lens: simple fitting, excellent comfort, very good tolerance and good mobility.

Conclusions

1. Kerasoft 3 CL provides many of the benefits of RGP lenses, (avoiding RGPs discomfort and allergic reactions), along with excellent comfort, visual acuity, high oxygen permeability and longer wearing times.

2. This CL offers a solution regarding the mechanical stress of the cornea, a major factor that contributes to keratoconus.

3. The Kerasoft 3 provides a very important opportunity for ophthalmologists to overcome the many difficulties of fitting keratoconus.

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Disclosures

None.

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GENERAL ARTICLE

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The pathogenesis of cataract in professional workers exposed to solar radiation in marine environment

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Abstract

In this article we presented the results on the cataract obtained in patients recruited during a period of two years in the social and labor ophthalmology ambulatory of Sapienza University in Rome. The first of two homogeneous populations (regarding the number of patients, age, profession, constant exposure to sunlight, same living habitat, geographical areas with similar intrinsic and extrinsic risk factors) involved the areas of the gulf of Pozzuoli and the gulf of Olbia, both of which are located at 40.5-41 degrees north latitude on the sea. The first place is located on the European continent and the other one on a medium-large island with particular genetic factors. The second of the two homogeneous populations involved the island of Ischia (NA) and the maritime professional activities carried out in Villasimius (CA) and surroundings, respectively at 40- and 39-degrees north latitude on the sea. The first is a medium-small island and the second one is located on a medium-large island, but both are in the middle of the Mediterranean Sea and are characterized by a certain degree of genetic isolation.
Keywords: cataract, professionally exposed workers, solar radiation

Introduction

The enrolment period of the current year was from the beginning of June to the end of July, with the maximum intensity of the solar radiation and also the major number of hours of radiation at our latitudes. We selected 2 homogeneous populations of port workers, nautical moorers, seafarers and lifeguards, who have been exposed for several years (at least 10) to the sun rays during the central hours of the day in the afore-mentioned period. The inclusion criteria were also a natural bilateral vision equal to or greater than 5/ 10, no past eye diseases and the sub-continuous use of protective sunglasses during their work having no graduated or specified construction technical characteristics [**1**]. The choice of the 2 geographical areas was dictated by the presence of the maximum solar radiation in summer, which is increased by the natural reverberation of sandy and marine surfaces, as widely reported in international literature [**2,3**]. Moreover, the density of the local population that is substantially autochthonous and sedentary and the relative lack of polluting industrial activities in these areas made it possible to verify whether or not there was a genetic predisposition for senile and pre-senile cataracts in the island populations considered [**4**].

Materials and methods

The two populations of workers studied in 2019 were composed of 68 subjects from the Ischia group and 72 subjects from the Villasimius group with an age ranging between 41 and 50 years. The subjects were free of refraction defects linked to cataract problems and other chronic ocular pathologies such as myopia, their work time of exposition to sunlight was 6-8 hours a day for 6 days a week, the professional categories were fishermen, boatmen, mooring workers and lifeguards [**5-6**]. By means of a Snellen optotype, a refraction test was performed on all these workers, and only those who had a natural visus for at least 5/ 10 per eye were enrolled in this study. A portable slit-lamp biomicroscope was used to examine the anterior segment with a particular attention to the degree of opacity of the crystalline lens due to sclerosis. A classification in three degrees was preferred for the opacities of the crystalline lens: incipient cataract, intumescent cataract and mature cataract, although the latter was never found in the sample examined, as they were relatively young subjects, who also had a relatively easy access to health services, due to living in a European country, even though they reported that they were not periodically examined by a competent doctor, based on Legislative Decree number 81/ 08 and subsequent amendments, consequently to the precariousness and autonomy of their work [**5-7**].

Results

As previously mentioned, no worker examined had such a lens opacity that it could be classified as a mature cataract, even though none of the subjects examined in both studied populations were free from these opacities [**8**]. The problem was limited to incipient and intumescent cataracts. For the cohort of Ischia, 90 eyes of 53 people and 81.81% of the total sample were affected by the incipient cataract, while the cohort of Villasimius included 115 eyes with 61 incipient cataracts and 79.86% of the total sample. The remaining eyes of both studied cohorts were categorized as intumescent cataract. Despite the relatively young age of the sample, these subjects had a higher incidence of progression of crystalline sclerosis than the health statistics for cohorts of the same age, although there were no statistically significant differences between the two groups studied, probably due to the constant exposure to sunlight in a strongly reflecting marine environment. The specific genetic factors on Sardinia island, which favor Mediterranean anemia or other congenital or acquired diseases, as well as on the island of Ischia, where fetal and neonatal malformations appear to be statistically favored, do not seem to be important in the case of the pathogenesis of cataracts [**9,10**].

Discussion

According to the Italian National Institute of Statistics (ISTAT), cataracts affect 8.5% of the population in Italy between 70 and 74 years old, 12.4% of the following five years and 17.1% of those over 80 years old, but, in the younger population, there are no reliable data on the matter. According to the World Health Organization (WHO), it is the world's leading cause of blindness and low vision, although it is almost always reversible [**9**]. According to the latest available data, it is also responsible for 53% of the cases of visual disability (but it is often operable or reversible), mainly concentrated in developing countries, while in many cases, there are no resources to carry out the cataract operation [**10**]. Genetic factors play an important role and the processes of aging of the body also occur in crystalline lens [**11,12**]. Among the acquired forms of cataract, we recognized the senile cataract that was 90% of all forms, with the onset usually after the age of 50. Age is the main risk factor, while environmental, metabolic or genetic factors can have a cumulative effect [**13**]. According to its location, senile cataract is divided into cortical, nuclear and posterior subcapsular. Cortical cataract is the most frequent form, it can be isolated or associated with nuclear opacity, can affect the anterior cortex, the posterior cortex or more frequently both. The main cause involved in its formation is a hydro electrolytic imbalance that induces hyper hydration and liquefaction of the lenticular fibers. Cortical opacity is usually wedge-shaped and originates from the periphery of the lens with centripetal direction. This type of

cataract generates a reduction in visual acuity of varying magnitude and a loss of contrast sensitivity that causes glare from point and intense light sources more pronounced at night; is also particularly penalizes near vision. Diagnosis is made by slit-lamp biomicroscopy, showing radial cuneiform opacity of generally equatorial origin. These signs are better recognizable in backlighting [**14,15**]. Nuclear cataracts occur due to the opacification of the nucleus of the lens by the accumulation of insoluble proteins of high molecular weight with a consequent increase in nuclear density. This phenomenon, called nuclear sclerosis, does not initially involve a reduction in visual capacity, but generates an increase in the refractive index of the nucleus with myopization of the eye, which increases as a result of the evolution of nuclear opacification. The related symptoms are myopia with reduction of visual acuity for distant and more marked in mesopic vision (at sunset), occasionally associated with diplopia or monocular polyopia due to a prismatic effect of different parts of the nucleus. The diagnosis by biomicroscopic examination with a direct beam of light (placing the light at 30° and 45°) shows the loss of transparency of the nucleus with a grey-greenish color in the initial phases (initial cataract) and yellow-brown in advanced phases (intumescent cataract). However, when this is associated with the cortical cataract, it is defined as total [**16**]. The posterior subcapsular cataract usually starts at the posterior pole of the lens in the form of fine granular opacity, with the tendency to propagate towards the periphery, constituting a plaque opacity. This type of cataract is very common in diabetic subjects or after a prolonged treatment with corticosteroids. Impairment of vision is particularly severe because the site of opacity is very close to the nodal point. Consequently, there is a difficulty in the near vision with daytime glare, while in the early stages, night vision is quite good. The development of monocular diplopia is then possible due to localized changes in the refractive index. At the slit lamp examination, posterior subcapsular cataract is highlighted as a dark area by placing the light beam in backlight. In an advanced stage, it appears as a thick calcific-like area [**17**]. Cataracts benefit from a single and exclusively surgical approach. The operability is entrusted to a medical and/ or functional criterion. The first one takes into account the mature state of the cataract and the risk of associated complications, the second one is based on the decline in visual acuity and the consequent implications in daily life. The opacification of the lens can also be acquired, as in the case of traumatic cataracts secondary to penetrating traumas that generate a continuous solution of the capsule, the metabolic cataract, linked to systemic diseases, such as galactosemia, Fabry's disease, Lowe syndrome (also called oculocerebrorenal syndrome) and Wilson's disease. A secondary toxic cataract is also possible for the prolonged use of topical corticosteroid drugs or for the systemic use with formation of a posterior subcapsular cataract, miotic anticholinesterases and phenothiazines that cause starry brownish deposits under the anterior capsule. The prevalence of senile cataract associated with visual defect varies from northern Italy to the southern, being higher in the south. The prevalence quotient in the population over 40 years old is between 4.7 and 7.2% in the South, with a maximum increase in prevalence in the population over 70 years old [**18,19**]. In this scientific work dealing exclusively with cataracts acquired in a young population and favored by the intense exposure to ultraviolet radiation present in sunlight, we made a classification of the acquired cataracts, according to the topographic criterion, into nuclear, cortical, rear and mixed subcapsular cataracts. According to the density of the opacity of the lens, the cataract is classified into incipient cataract, intumescent cataract, mature cataract, hyper-mature cataract (or morgagnian cataract), and, within the latter, white, brunescens and nigra cataracts are differentiated. However, as it can be observed from the data collected in the present study and described above, no statistically significant factors emerged in the two-year study made on the existence of genetic factors predisposing to cataracts in the populations of southern Sardinia especially and Campania islands, consequent to the exposure to intense summer sunlight in a marine environment, although there is obviously a simple aggravation of sclerosis of the lens itself, when compared to the same age groups not professionally exposed [**18-20**].

Conclusions

The study in question, carried out on four homogeneous populations in terms of visual conditions, age and profession, during the weeks of the year in which the sun's ultraviolet radiation is most intense, has not statistically demonstrated the existence of genetic factors in the isolated populations of Sardinia and Ischia, capable of playing a role of a real "melting moment", or rather of an efficient and decisive factor in the pathogenesis of the cataract opacity.

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GENERAL ARTICLE

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Correlations between corneal biomechanics and specular microscopy in patient with cataract

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Abstract

This study aimed to analyze the connection between corneal biomechanics (corneal hysteresis, CH) and endothelial cell density of cornea (mean endothelial cell density, MCD) in patients diagnosed with cataract.

This retrospective, observational study was performed in the Ophthalmology Clinic of the University Emergency Hospital in Bucharest. Of 60 patients (120 eyes) with cataract, who were included in this study, we analyzed the CH values obtained using with the Ocular Response Analyzer (ORA) and the MCD values obtained using the specular microscopy. The study groups comprised both men and women with ages ranging from 45 to 63 years.

Patients were divided into three study groups according to CH values. In each batch, the CH values obtained with the Ocular Response Analyzer (ORA) were correlated with age, gender and MCD, then the subgroups were compared. All the data gathered showed no correlation to be statistically significant regarding the biomechanical properties of the cornea and the corneal endothelial cell density in patients with cataract.

Keywords: corneal endothelial cell density, specular microscopy, corneal biomechanics, corneal hysteresis, Ocular Response Analyzer

Introduction

This study aimed to determine a possible relationship between the biomechanical properties of the cornea and the corneal endothelial cell density in patients with cataract.

Cataract is a clouding of the lens of the eye that leads to a progressive loss of vision. This is a common ophthalmological disorder that is caused by opacification of the lens and it generally develops in both eyes, but not evenly.

Numerous studies suggest that corneal hysteresis (CH), an indicator of corneal viscoelasticity, is associated with biomechanical properties of the cornea. Some studies showed that CH may be related to the biomechanical characteristics of peripapillary sclera and lamina cribrosa, as they are embryologically developed from the mesoderm and also because the collagen fibers continue with the collagen fibers from the corneal stroma [**1-8**].

The ORA (Ocular Response Analyzer) is a tool that determines corneal hysteresis (CH) at the indentation by a rapid jet of air. Corneal hysteresis is defined as the difference between the tension at which the cornea bends inward

during an air jet applanation and the tension at which it bends out again. The two pressure values (P1 and P2) are obtained at the end of the measurement period, which lasts approximately 20 milliseconds.

Thus, ORA can be used for the assessment of corneal biomechanics in vivo [**9,10**].

Corneal hysteresis (CH) represents the difference between the two pressure determinations, P1 and P2, reflecting the capacity for absorption of kinetic energy in the tissue, an indicator of corneal viscosity. The mean of the two pressure measurements (P1 and P2) determines the Goldmann correlated intraocular pressure (IOPg) [**11-13**].

Specular microscopy is a photographic, noncontact technique for visualizing and analyzing the shape, size and number of the population of endothelial cells, by computer-assisted analysis of endothelial morphology. The instrument projects light onto the corneal surface and captures image from the endothelial/ aqueous interface.

Specular microscopy is a noninvasive method for analyzing the corneal endothelium and facilitates the rapid and correct diagnosis of corneal endotheliopathy affecting the structure and physiology of this corneal layer [**14-17**].

Although there have been several studies analyzing the relationship between eyes with cataract and the biomechanical properties of the cornea or endothelial cell density, the results are still under debate.

Materials and methods

This retrospective, observational study was performed in the Ophthalmology Clinic of University Emergency Hospital in Bucharest, during the year 2019.

All patients involved in the study were informed about the use of personal data, and the study was organized in accordance with the ethical principles stated in the Declaration of Helsinki, developed by the WMA (World Medical Association) [**18**].

60 patients were included in this study, patients known with changes of transparency of the lens in any of its layers, of at least 3+, pathology for which they underwent surgery. All subjects included in the study were Caucasian, aged between 45 and 63 years, with an equal gender distribution.

Data was gathered from medical records, including a complete patient history, as well as visual acuity with or without correction, refraction, biomicroscopic examination of the anterior segment and posterior pole, keratometry, pachymetry, specular microscopy, tonometry with the help of Goldman applanation and Ocular Response Analyzer (ORA).

Another inclusion criterion was a normal value of intraocular pressure (12–22 mmHg).

The exclusion criteria from the study were the following: positive history for the administration of topical eye medications and/ or for rigid or soft contact lenses use, glaucoma or glaucoma suspect, inflammation and/ or ocular infection in the background, dystrophies/ corneal pathology (Fuchs endothelial dystrophy, keratoconus, pellucid marginal corneal degeneration, bullous keratopathy) and last but not least, without any other ocular surgery procedures performed in medical history, as for example refractive surgery or laser ablation of the cornea and lens, corneal cross-linking (CXL) and intrastromal corneal ring segment (ICRS).

Paraclinical investigations were performed using the equipment of the Ophthalmology Clinic in the University Emergency Hospital, Bucharest.

Images reflecting endothelial cell density were captured using a specular microscope (Topcon, SP-3000P). Three consecutive measurements were made with a specular reflex light, a correct centering of the fixation target, with a calibration and a favorable image resolution. The measurement technique used was the center to center method. 45-50 corneal endothelial cells were counted and cell density (CD) was calculated by automatic analysis. The average of the three CD values was considered.

In vivo data of corneal biomechanics was obtained using the Ocular Response Analyzer (Reichert Ocular Response Analyzer G3 AutoTonometer, evaluation software v.1.01). The correct positioning of the patient was verified throughout the examination and three consecutive measurements (Single Measure) were performed. The average of recordings with

a score higher than 7 (Waveform Score) was taken into consideration.

Goldmann applanation tonometry (GAT) was performed for IOP measurements.

This study included 60 patients, aged between 45 and 63 years, females and males, with cataract. We analyzed and compared the following parameters: corneal hysteresis (CH) and mean endothelial cell density (MCD) in both eyes.

Patients have been divided into three distinct study groups, according to the value of corneal hysteresis: batch no. 1 CH at RE = 8.33 ± 0.29 mm Hg and LE CH = 8.48 ± 0.26 mmHg, batch no 2. CH at RE = 9.33 ± 0.275 mmHg and CH at LE = 9.46 ± 0.275, batch no. 3 CH at RE = 10.62 ± 0.345 and LE CH = 10.55 ± 0.266.

SPSS statistics package 20 was used for statistical analysis.

Pearson's correlation coefficient is the test statistics used to measure the statistical relationship, or association, between CCT (central corneal thickness), mean corneal endothelial cell density and the properties of corneal biomechanics.

For statistical significance we have considered P values ≤ 0.05.

Results

60 patients aged between 45 and 63 years, equal in proportion, women and men, were included in the study group.

Three groups were realized according to corneal hysteresis (CH) values. The data in **Table 1** represent the description of the parameters analyzed in the study.

Table 1. Parameters analyzed

Parameters	RE			LE		
	Mean ±SD	AM	Min-Max	Mean ±SD	AM	Min-Max
CH Batch 1	8.33 ± 0.29	8.2	8-8.9	8.48 ± 0.26	8.5	8-8.9
MCD Batch 1	2199 ± 327.18	2106.5	1814-2805	2232.5 ± 349.34	2078	1800-2872
CH Batch 2	9.33 ± 0.275	9.3	9-9.9	9.46 ± 0.275	9.5	9-9.9
MCD Batch 2	2077.2 ± 328.84	1991.5	1668-2688	2093.3 ± 345.93	2002.5	1612-2805
CH Batch 3	10.62 ± 0.345	10.7	10.1-11.2	10.55 ± 0.266	10.5	10.1-11
MCD Batch 3	2110.25 ± 327.47	2007.5	1707-2812	2141.6 ± 319.05	2101	1602-2713

There were correlations between corneal hysteresis and endothelial cell density (MCD) in each batch. Most variables had a non-parametric distribution according to the Shapiro-Wilk test (p <0.05) (**Tables 2-4**, **Fig. 1-6**).

Table 2. Correlation between corneal hysteresis and endothelial cell counts in patients in group 1

Correlation	p*
CH RE (p=0.005**) x MCD RE (p=0.011**)	0.972, R=0.008
CH LE (p=0.284**) x MCD LE (p=0.019**)	0.633, R= -0.114

**Shapiro-Wilk Test, **Spearman's rho Correlation Coefficient*

Table 3. Correlation between corneal hysteresis and endothelial cell counts in patients in group 2

Correlation	p*
CH RE (p=0.062**) x MCD RE (p=0.007**)	0.962, R= -0.011
CH LE (p=0.192**) x MCD LE (p=0.200**)	0.906, R=0.028***

**Shapiro-Wilk Test, **Spearman's rho Correlation Coefficient, ***Pearson Correlation Coefficient*

Table 4. Correlation between corneal hysteresis and endothelial cell counts in patients in group 3

Correlation	p*
CH RE (p=0.094**) x MCD RE (p=0.108**)	0.350, R= -0.221
CH LE (p=0.368**) x MCD LE (p=0.265**)	0.897, R=0.031***

**Shapiro-Wilk Test, **Pearson Correlation Coefficient*

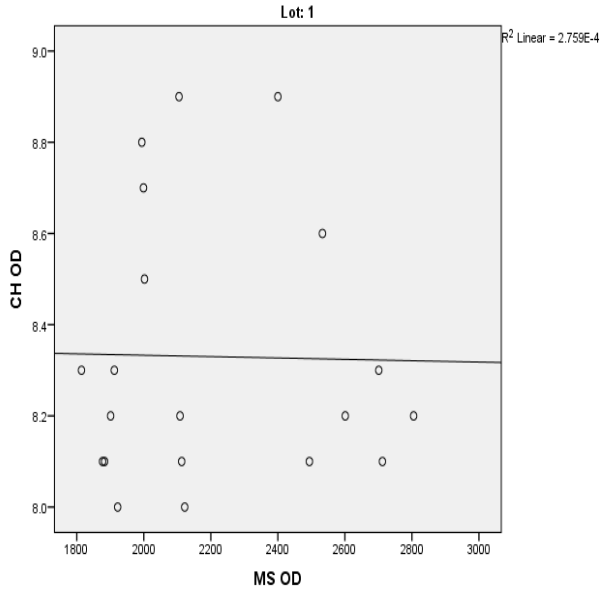

Fig. 1 Correlations between CH RE and MCD RE in batch 1

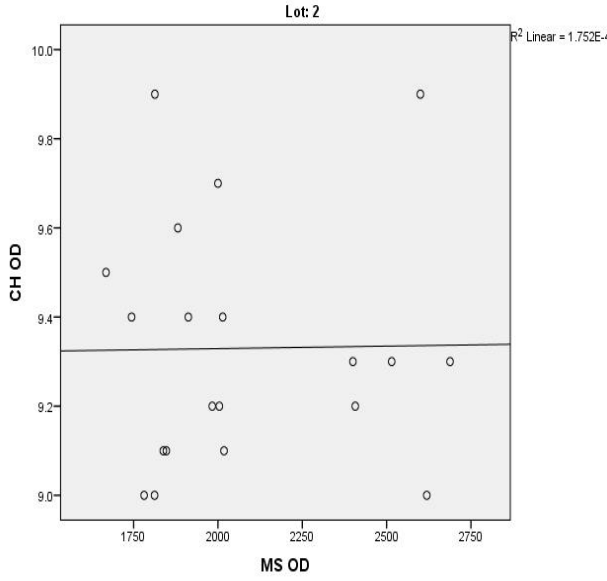

Fig. 3 Correlations between CH RE and MCD RE in batch 2

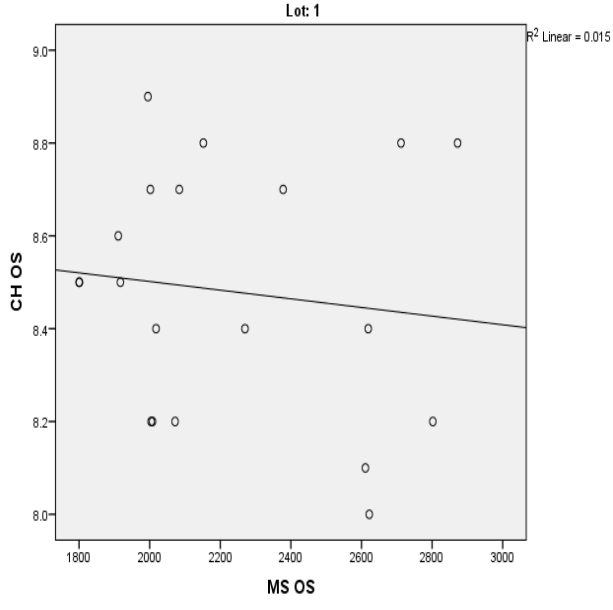

Fig. 2 Correlations between CH LE and MCD LE in batch 1

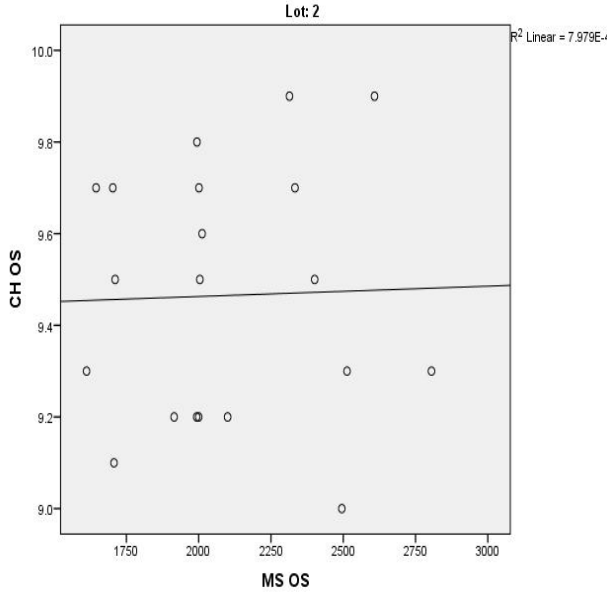

Fig. 4 Correlations between CH LE and MCD LE in batch 2

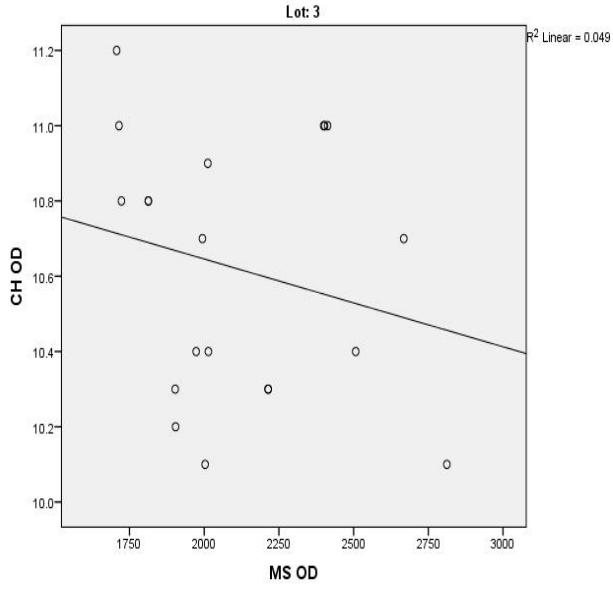

Fig. 5 Correlations between CH RE and MCD RE in batch 3

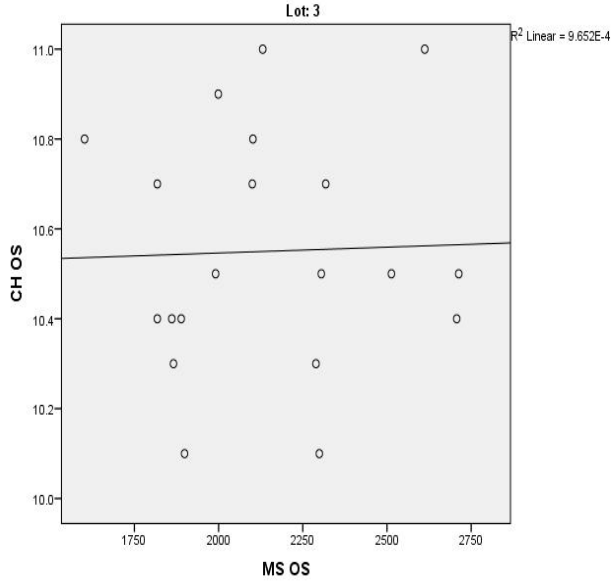

Fig. 6 Correlations between CH LE and MCD LE in batch 3

According to the correlations established using Spearman's rho coefficients, the association between corneal hysteresis and endothelial cell density was not statistically significant in the right or left eye for patients in group 1, 2 or 3.

The data in **Tables 5-7** compare the groups together by analyzing corneal hysteresis and endothelial cell density from patients in group 1, group 2 and respectively 3. The variables were tested for distribution according to the Shapiro-Wilk test (**Fig. 7-18**).

Table 5. Correlations between corneal hysteresis and endothelial cell density in patients in batch 1 vs. batch 2

Correlation	p*
CH RE L1(p=0.005**) x MCD RE L2 (p=0.007**)	0.525, R= -0.151
CH LE L1 (p=0.284**) x MCD LE L2 (p=0.200**)	0.626, R= -0.116***
CH RE L2 (p=0.062**) x MCD RE L1 (p=0.011**)	0.052, R= 0.441
CH LE L2 (p=0.192**) x MCD LE L1 (p=0.019**)	0.056, R= -0.434

**Shapiro-Wilk Test, **Spearman's rho Correlation Coefficient, ***Pearson Correlation Coefficient*

Table 6. Correlations between corneal hysteresis and endothelial cell density in patients in batch 1 vs. batch 3

Correlation	p*
CH RE L1 (p=0.005**) x MCD RE L3 (p=0.108**)	0.636, R= -0.113
CH LE L1 (p=0.284**) x MCD LE L3 (p=0.265**)	0.069, R= 0.415***
CH RE L3 (p=0.094**) x MCD RE L1 (p=0.011**)	0.684, R= 0.097
CH LE L3 (p=0.368**) x MCD LE L1 (p=0.019**)	0.697, R= 0.093

**Shapiro-Wilk Test, **Spearman's rho Correlation Coefficient, ***Pearson Correlation Coefficient*

Table 7. Correlations between corneal hysteresis and endothelial cell density in patients in batch 2 vs. batch 3

Correlation	p*
CH RE L2(p=0.062**) x MCD RE L3 (p=0.108**)	0.102, R= -0.376***
CH LE L2 (p=0.192**) x MCD LE L3 (p=0.265**)	0.018, R=0.522***
CH RE L3 (p=0.094**) x MCD RE L2 (p=0.007**)	0.765, R= -0.071
CH LE L3 (p=0.368**) x MCD LE L2 (p=0.200**)	0.116, R= 0.363***

**Shapiro-Wilk Test, **Spearman's rho Correlation Coefficient, ***Pearson Correlation Coefficient*

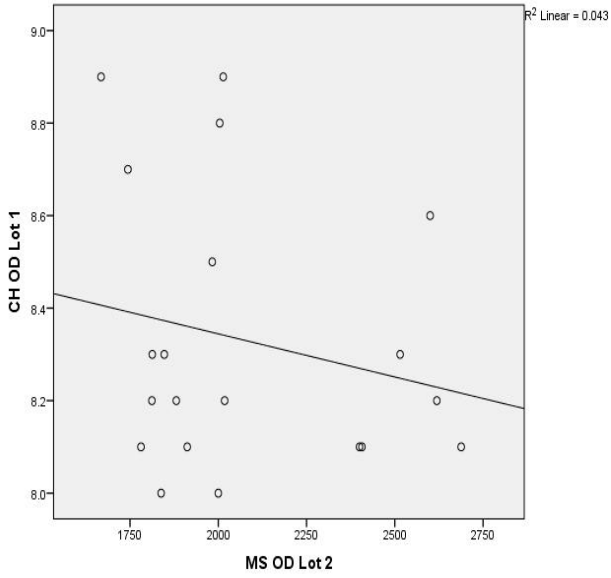

Fig. 7 Correlation between CH RE Batch 1 and MCD RE Batch 2

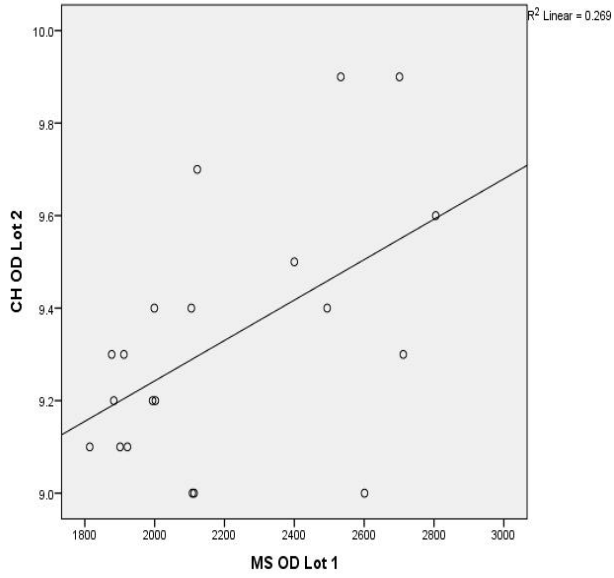

Fig. 9 Correlation between CH RE Batch 2 and MCD RE Batch 1

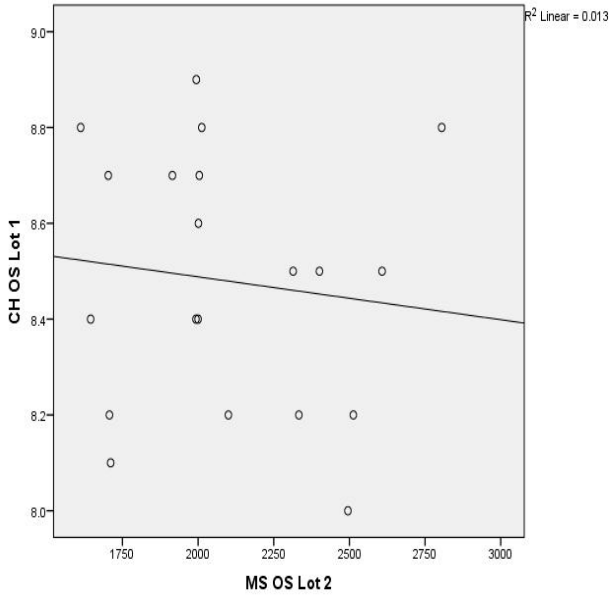

Fig. 8 Correlations between CH LE Batch 1 and MCD LE Batch 2

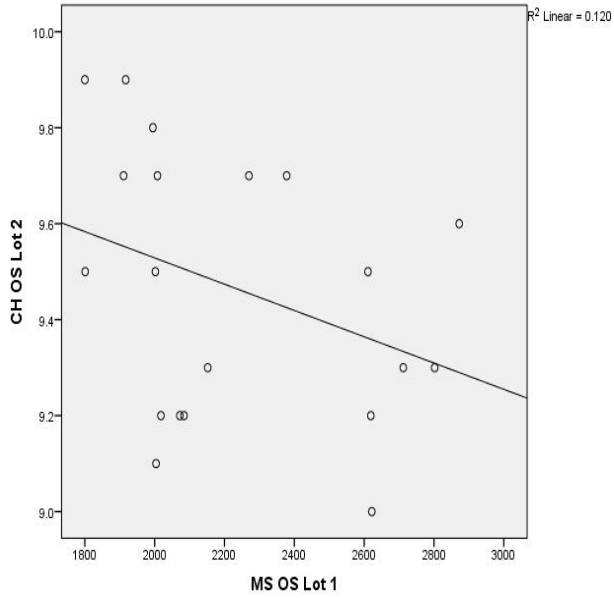

Fig. 10 Correlation between CH LE Batch 2 and MCD LE Batch 1

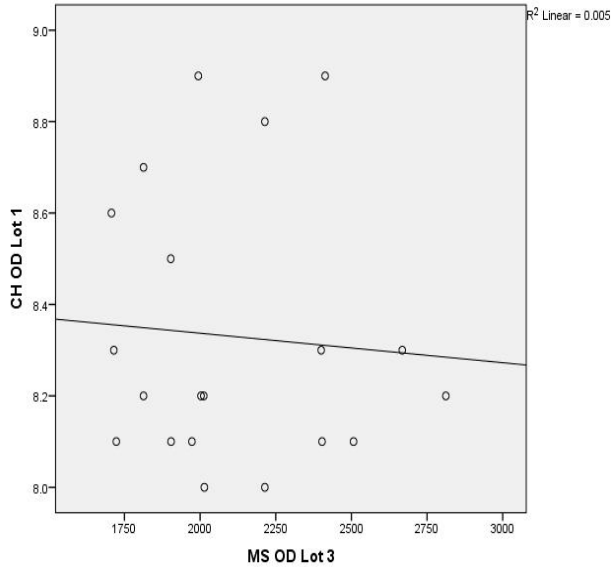

Fig. 11 Correlation between CH RE Batch 1 and MCD RE Batch 3

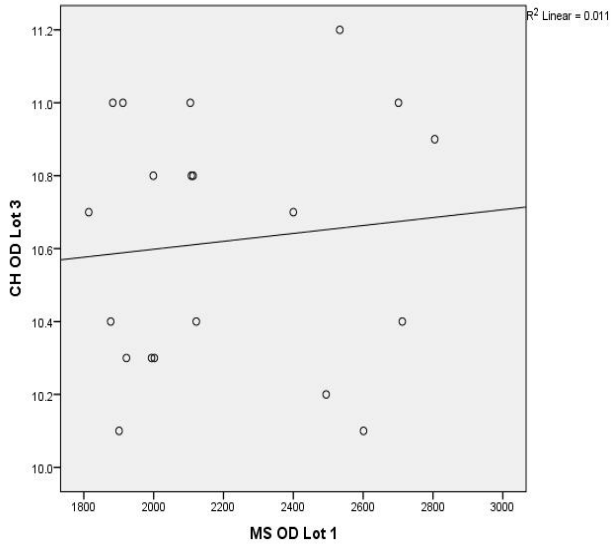

Fig. 13 Correlation between CH RE Batch 3 and MCD RE Batch 1

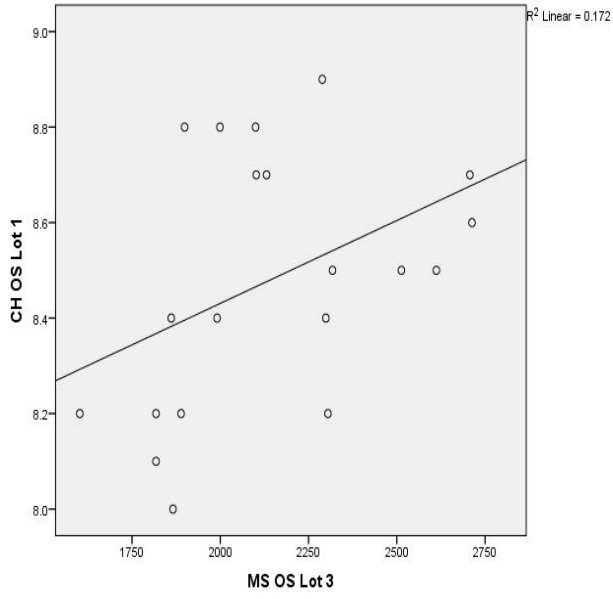

Fig. 12 Correlations between CH LE Batch 1 and MCD LE Batch 3

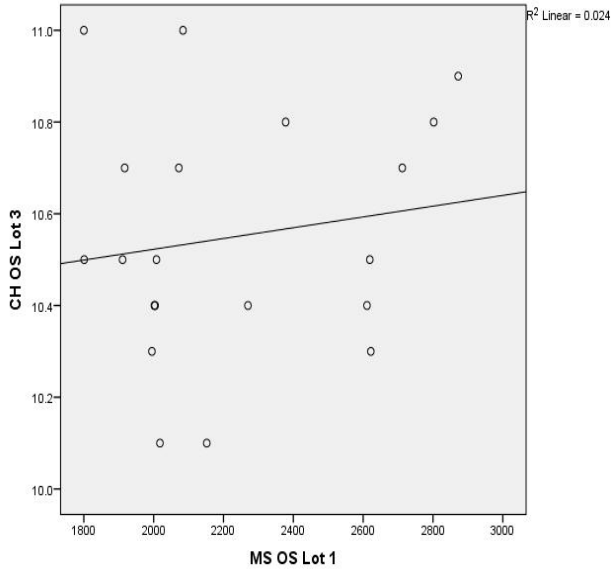

Fig. 14 Correlation between CH LE Batch 3 and MCD LE Batch 1

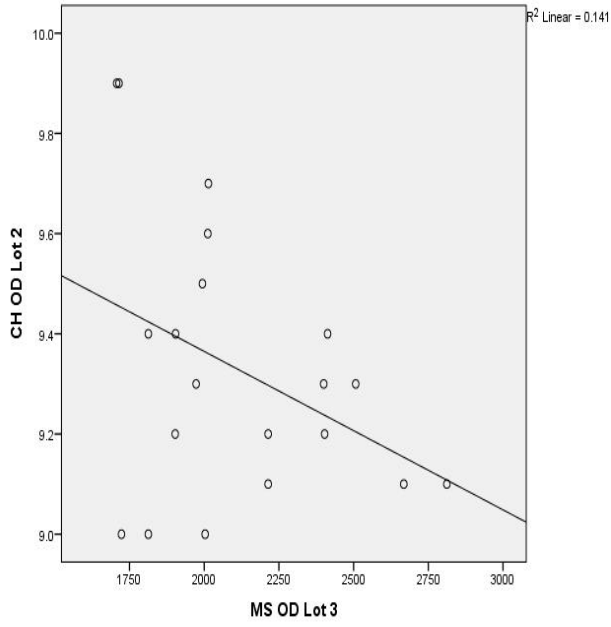

Fig. 15 Correlation between CH RE Batch 2 and MCD RE Batch 3

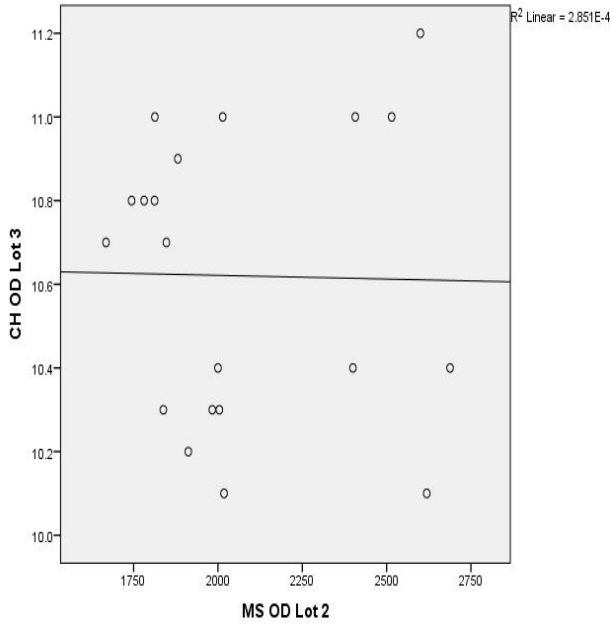

Fig. 17 Correlation between CH RE Batch 3 and MCD RE Batch 2

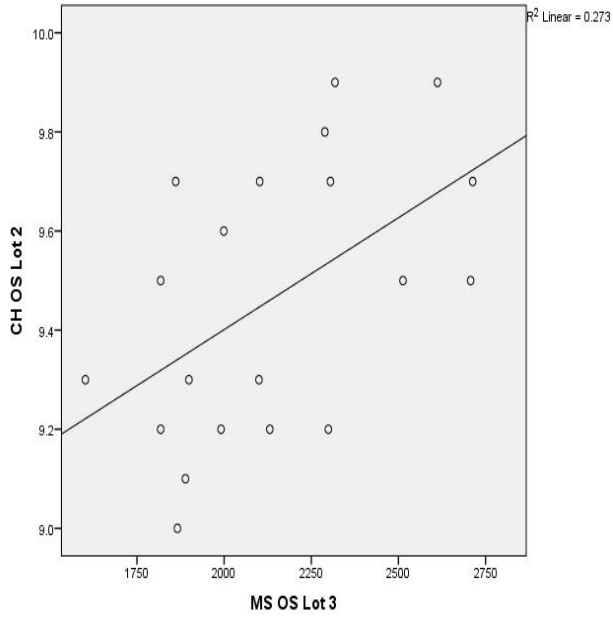

Fig. 16 Correlations between CH LE Batch 2 and MCD LE Batch 3

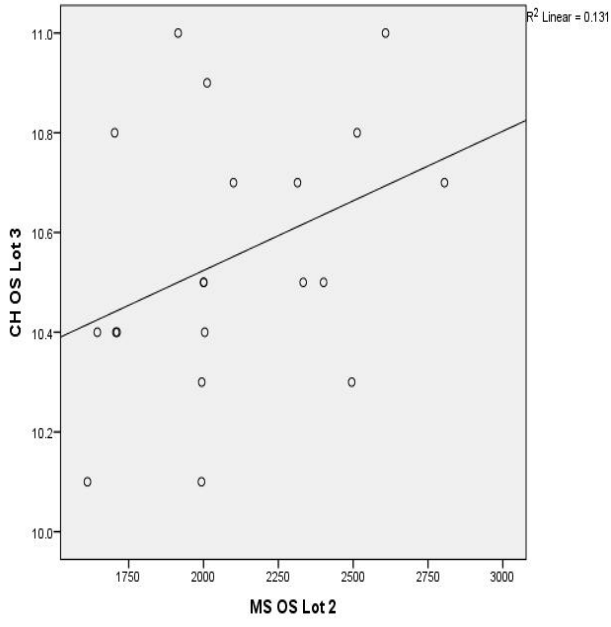

Fig. 18 Correlation between CH LE Batch 3 and MCD LE Batch 2

According to the correlations established using Spearman's rho/ Pearson coefficients, the associations between corneal hysteresis and endothelial cell density were not statistically significant. The exception was the correlation between the corneal hysteresis value in the left eye for group 2 of patients and the value of the number of cells in the left eye in group 3 of patients (p = 0.018, R = 0.522), thus showing a small value of CH from LE in group 2 of patients (close to 9 mmHg), which was significantly associated with a low value of the number of endothelial cells from LE in group 3 of patients and vice versa.

The data in **Table 8** and **Fig. 19,20** represent the correlation between corneal hysteresis and endothelial cell density in patients throughout the study group. According to the Shapiro-Wilk test (p <0.05), all variables had a non-parametric distribution.

Table 8. Correlation between corneal hysteresis and endothelial cell density in patients from the entire study group

Correlation	p*
CH RE (p=0.002**) x MCD RE (p<0.001**)	0.233, R= -0.156
CH LE (p=0.009**) x MCD LE (p=0.008**)	0.429, R= -0.104

**Shapiro-Wilk Test, **Spearman's rho Correlation Coefficient*

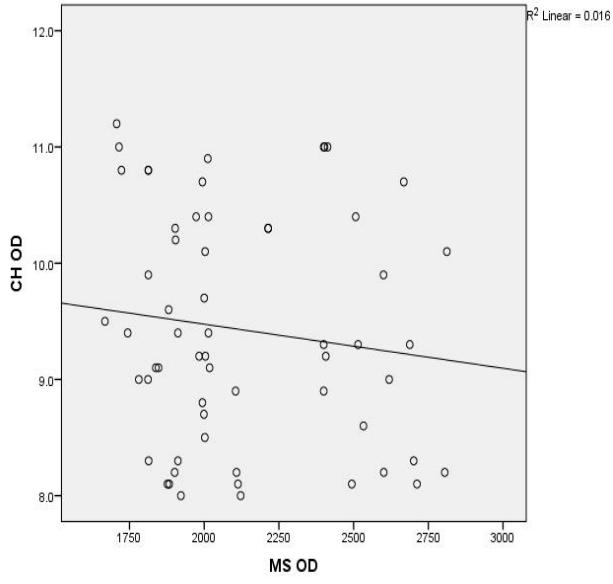

Fig. 19 Correlations between CH RE and MCD RE throughout the study group

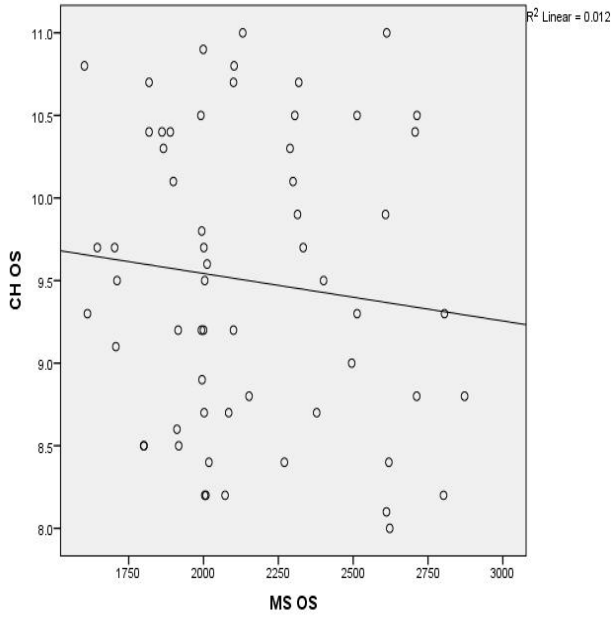

Fig. 20 Correlation of CH LE and MCD LE across the study group

Taking into account the correlations established using Spearman's rho coefficients, the association between corneal hysteresis and endothelial cell density was not statistically significant in the right eye (p = 0.233) or the left eye (p = 0.429) for patients in the entire study group.

There were correlations between the age/ sex of the patients with the values of corneal hysteresis and the density of corneal endothelial cells. According to the Shapiro-Wilk test (p <0.05), the distribution of variables was non-parametric (**Table 9-16**, **Fig. 21-28**).

Table 9. Right eye: relationship between CH and patients age

Correlation	p*
Age (p=0.015**) x CH RE (p=0.002**)	0.127, R=0.199

**Spearman's rho Correlation Coefficient, **Shapiro-Wilk Test*

Table 10. Left eye: relationship between CH and patients age

Correlation	p*
Age (p=0.015**) x CH LE (p=0.009**)	0.084, R=0.225

*Spearman's rho Correlation Coefficient, **Shapiro-Wilk Test

Table 11. Right eye: relationship between MCD and patients age

Correlation	p*
Age (p=0.015**) x MCD RE (p<0.001**)	0.388, R= -0.114

**Spearman's rho Correlation Coefficient, **Shapiro-Wilk Test*

Table 12. Left eye: relationship between MCD and patients age

Correlation	p*
Age (p=0.015**) x MCD LE (p=0.008**)	0.369, R= -0.118

**Spearman's rho Correlation Coefficient, **Shapiro-Wilk Test*

Table 13. Right eye: relationship between CH and patient gender

Gender	Mean ± SD	Median Rank	p*
Female (p=0.075**)	9.39 ± 0.985	29.92	0.790
Male (p=0.021**)	9.465 ± 1.015	31.12	

**Mann-Whitney U Test, **Shapiro-Wilk Test*

Table 14. Left eye: relationship between CH and patient gender

Gender	Mean ± SD	Median Rank	p*
Female (p=0.026**)	9.51 ± 0.946	30.89	0.859
Male (p=0.263**)	9.482 ± 0.848	30.09	

**Mann-Whitney U Test, **Shapiro-Wilk Test*

Table 15. Right eye: relationship between MCD and patient gender

Gender	Mean ± SD	Median Rank	p*
Female (p=0.004**)	2197.84 ± 313.26	35.74	0.016
Male (p=0.001**)	2055.66 ± 329.51	24.9	

**Mann-Whitney U Test, **Shapiro-Wilk Test*

Table 16. Left eye: relationship between MCD and patient gender

Gender	Mean ± SD	Median Rank	p*
Female (p=0.033**)	2208.84 ± 322.43	33.71	0.141
Male (p=0.076**)	2099.1 ± 349.84	27.07	

**Mann-Whitney U Test, **Shapiro-Wilk Test*

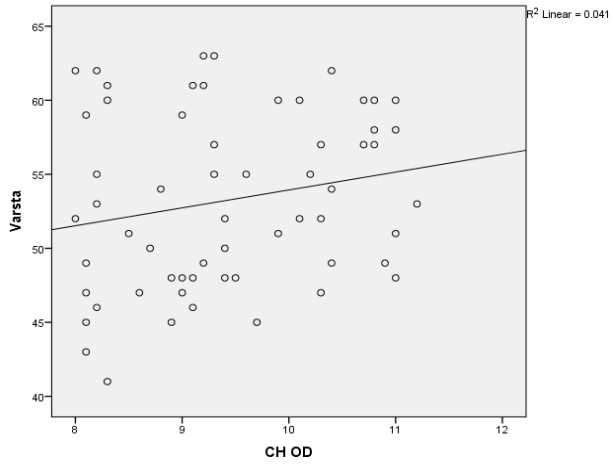

Fig. 21 Right eye: relationship between CH and patients age

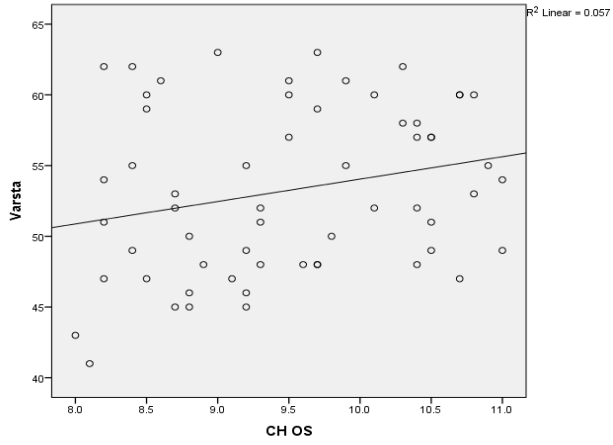

Fig. 22 Left eye: relationship between CH and patients age

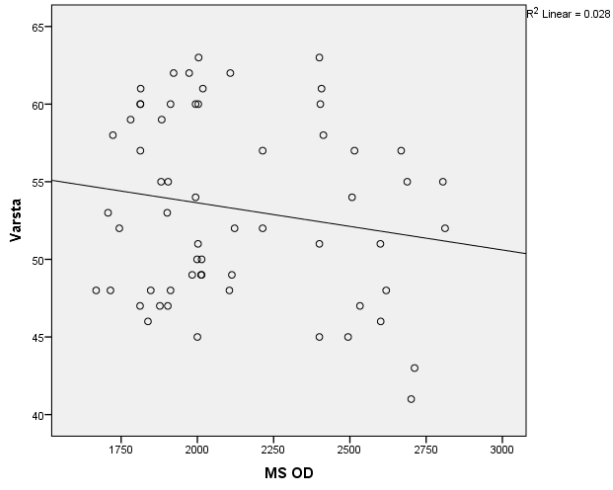

Fig. 23 Right eye: relationship between MCD and patients age

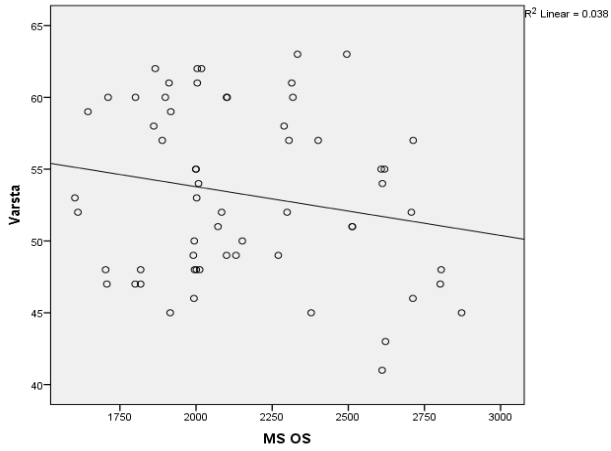

Fig. 24 Left eye: relationship between MCD and patients age

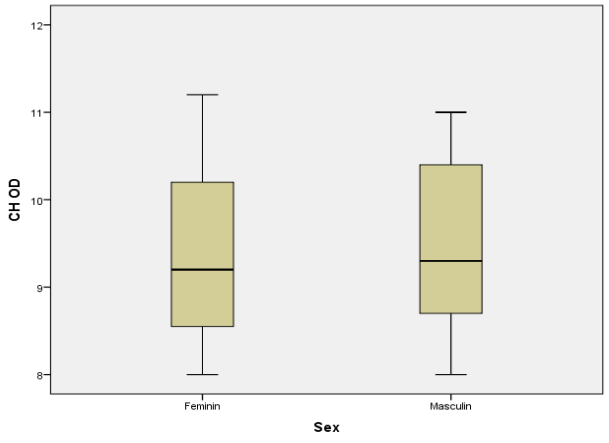

Fig. 25 Right eye: relationship between CH and patient gender

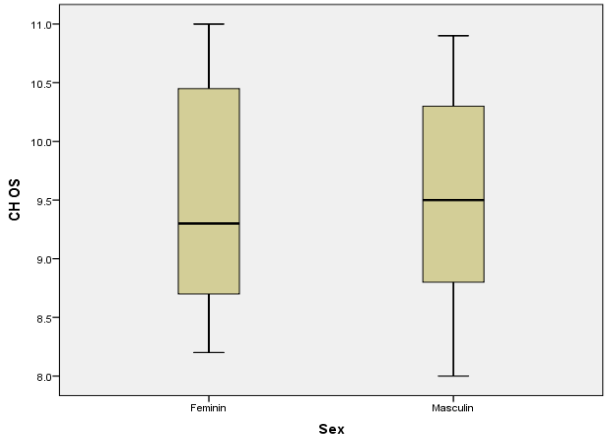

Fig. 26 Left eye: relationship between CH and patient gender

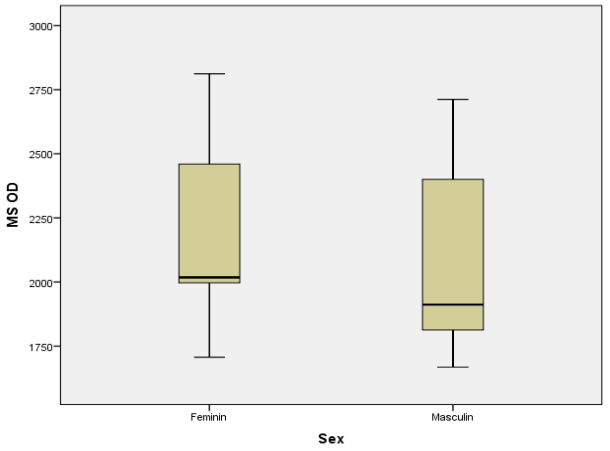

Fig. 27 Right eye: relationship between MCD and patient gender

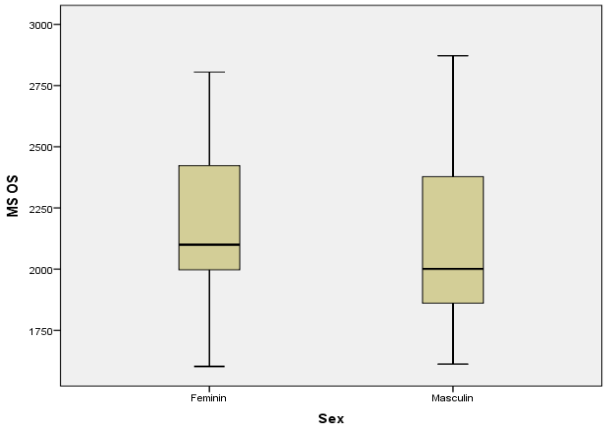

Fig. 28 Left eye: relationship between MCD and patient gender

According to Spearman's rho correlation coefficient, these associations were not statistically significant. According to the Mann-Whitney U test, the differences between women and men were not statistically significant for corneal hysteresis values, but the women in the study had significantly higher corneal endothelial cells (mean range = 35.74) than men (mean range = 24.9) (p=0.016).

Discussions

Many medical studies have underlined a link between the lower values of CH and different corneal pathologies like keratoconus, corneal dystrophy, corneal edema, post LASIK status, etc. These conditions reflect the

disorganization of the collagen fibers at the corneal stroma level.

Low values of the CH have also been identified in patients with primary open-angle glaucoma and normal-tension glaucoma. Thus, they sustain the hypothesis that changes at the Lamina Cribrosa level are directly linked with the corneal biomechanical alteration. Because of this, the CH measurements are useful in the normal-tension glaucoma and early keratoconus [**19-22**].

Numerous studies have found a clear correlation between corneal hysteresis and CCT (central corneal thickness). The hypothesis that the corneal thickness growth is associated with viscosity growth is a consequence of the fact that CH reflects the viscoelastic properties of the cornea.

Concerning open angle glaucoma patients, many studies have pointed out the link between the CH and the intraocular pressure (IOP). For these patients, the CH value has been significantly lower than the control group. After the IOP decrease under 27 mmHg, the CH level has been partially normalized. Another observation of the authors was that, while in normal, physiological conditions, CH modifications were not correlated with IOP, for IOP values of over 21 mmHg CH modifications being associated.

This is justified by the structural modifications of the collagen fibers that suffer a significant elongation under high IOP values, thus the difference between the P1 and P2 parameters at ORA is decreasing [**23-26**].

Age-related changes have shown there is a positive correlation between viscoelastic properties of the cornea and CCT (central corneal thickness). Thereby, the CH and CRF (corneal resistance factor) values are decreasing, this being linked directly with the augmentation of the corneal hydration after a certain age [**27-30**].

For hyperopic and for female patients, higher values for CRF have been observed. For highly myopic patients, other studies have registered lower values of the CH and CRF and higher values of IOPcc (Corneal Compensated Intraocular Pressure) and of IOPg (Goldmann Correlated IOP value) compared to the emmetropic, hyperopic patients or patients with medium or low myopia [**31-34**].

The recent studies (since 2015), which have analyzed the mechanical corneal properties in relation with the cell density of the corneal endothelium, have been unable to show a statistically significant correlation [**35,36**].

The IOP growth during the cataract surgery can justify the biomechanical properties of eye globe appearing after surgery. In cataract surgery, the IOP value in the anterior chamber can grow up to approximately 50-60 mmHg; these high pressures predispose the eye tissue to degradation [**37-39**].

The cataract intervention through phacoemulsification leads to important endothelial corneal damage, which is extremely significant in patients with a low number of endothelial cells. Specular microscopy records a leakage of approximately 14% (11.4% -16.6%) of corneal endothelial cells.

The thickness of the central cornea grows significantly after cataract surgery for the first seven days but after that period, up to 3 months, it decreases to a value smaller than the one pre-surgery [**40,41**].

In the studies undergone until present, significant differences have been observed between the biomechanical corneal values pre- and post-surgery. The CH value has decreased in the immediate post-surgically period and went back to the pre-surgically level in 1-2 weeks; no statistically significant change has been identified in the CRF values [**42-44**].

Conclusions

During this study, we have analyzed the following parameters: corneal hysteresis (CH) and the mean endothelial cell density (MCD) in the right and the left eye in 60 patients, males and females, aged between 45 and 63 years, with cataract.

There were no statistically significant variations of the corneal hysteresis for the right eye and for the left eye ($p = 0.204$) and there were no statistically significant differences between the cell count for the right eye and the left eye ($p= 0.138$) in all the study groups.

According to the Pearson correlation coefficient in the study batch no. 1, the correlation between the corneal hysteresis value (CH) and the mean endothelial cell density

(MCD), was not statistically significant (RE p = 0.972 and LE p = 0.633).

Like batch 1, batches 2 and 3 have shown no statistically significant relationship between the value of the CH and MCD (batch 1: RE p = 0.962 and LE p =0.906, batch 2 RE p=350 and LE p=0.897).

Applying the Pearson correlation coefficient in order to determine if there was a statistically significant association between study group no. 1 and no. 2, we found that in RE p > 0.05 and in LE p > 0.05, therefore the association was not statistically significant.

There was no statistically significant association between study group no. 1 and no. 3 (RE p > 0.05 and LE p > 0.05), according to Pearson correlation coefficient.

However, we found a statistically significant correlation (p = 0.018, R = 0.522) between the CH of the LE measured in batch no. 2. and the MCD in LE in the study group no. 3.

According to the Pearson correlation, we did not find any statistically significant associations (RE p = 0.233 and LE p = 0.429) between the CH and the MCD in patients in groups no. 1, 2 and 3 in one place.

In conclusion, there was no statistically significant correlation between the biomechanical properties of the cornea and the endothelial cornea cell in patients with cataract.

Acknowledgements

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GENERAL ARTICLE

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Canalicular lacerations in a tertiary eye hospital: our experience with monocanalicular stents

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Abstract

Introduction: Canalicular injury is commonly encountered in lid trauma. A multitude of techniques and stents are available to manage canalicular lacerations. Monocanalicular stents offer a simple, technically easy and cost-effective solution for managing such cases.

Objective: This is a retrospective review of the patients presenting with canalicular lacerations to a tertiary eye hospital from January 2014 to September 2017. We evaluated factors like time of surgery, cause of injury, time of stent removal and their association with the surgical outcome. Additionally, we also reviewed the current data available in literature on the exclusive use of monocanalicular stents for the management of all types of canalicular injuries.

Methods: Retrospective patient file review.

Results: We evaluated 30 cases of canalicular injuries in 30 patients. The majority of our patients were males (24, 80%), and the mean age was 32.11±15.09 (4-59) years. The mode of injury was road traffic accidents (RTA) in 20 (66.7%), assault with sharp edged weapons in 8 (26.7%) and dog bite in 2 (6.6%) cases. The mean time of repair was 17.2±9.37 (6-36) hours after injury and the mean time of stent removal/ extrusion was 3.5±0.99 (0.5-5) months. The cases were divided based on time of repair i.e., within 24 hours (21 cases) or after 24 hours (9 cases) from the onset of injury. The extrusion rates were 14.3% (3) and 44.4% (4) respectively in the two groups. Our overall anatomical success rate was 86.7% and functional success rate of 76.7%.

Conclusions: Overall failure rate was 23.3% (7 out of 30). Delay in surgery (>24 hours) and dog bites were associated with a poorer prognosis of canalicular repair using monocanalicular stents.

Keywords: canalicular injuries, monocanalicular stent, eyelid injury

Abbreviations: FDDT = Fluorescein dye disappearance test, SPSS = Statistical Package for Social Sciences, RTA = Road Traffic Accident

Introduction

Canalicular lacerations are present in approximately 16% of all eyelid injuries [**1**]. The lacrimal canaliculi are located within the medial aspect of the eyelid and this area is different from the rest of the eyelid as it lacks a tarsal substructure. This leads to an increased propensity of avulsion due to a force that displaces the eyelid from its strong attachment at the medial canthal tendon, lacrimal, and maxillary bone [**2**].

Based on the mechanism of injury, canalicular lacerations are classified into direct, indirect and diffuse injuries. The direct type occurs mostly with sharp objects, indirect type due to blunt tangential forces or blows and the diffuse injury refers to extensive lid trauma associated with orbital fractures, globe rupture and other body injuries [**3**].

In cases in which lid trauma is inadequately managed, complications like lid margin notching, lagophthalmos, traumatic ptosis, epiphora, hypertrophic scars and wound granuloma formation can occur [**4**] (**Fig. 1**). The role of temporary intracanalicular stents in the restoration of continuity and patency of lacerated canalicular system is well documented and established [**5,6**]. Literature has also demonstrated that meticulous eyelid and medial canthal tendon repair, irrespective of the technique, accounts for optimal cosmetic and functional outcomes [**5,7-9**].

However, there is a wide range of functional success rates reported, from 61.1 to 100% [**6,10-12**]. Previously, the distance of the laceration from the punctum has been evaluated as a factor that determines post-operative success [**10**]. However, we believe that additional factors like time of surgical intervention, duration of intubation and mode of injury also influence the outcome of surgery. We undertook this study to further evaluate these factors to determine the success rate of canalicular repair using monocanalicular stents.

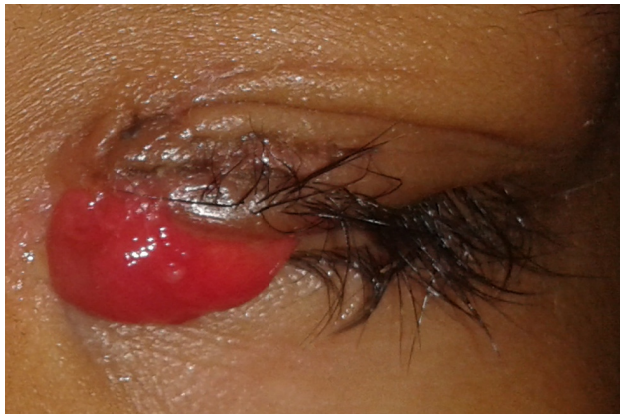

Fig. 1 Development of granuloma and hypertrophic scar in a case without lid laceration repair

Methods

In this retrospective study, medical records of 220 patients with eyelid lacerations presenting from January 2014 to September 2017 were reviewed. Of 220 patients with eyelid lacerations, 34 (15.45%) had co-existing canalicular lacerations. We included 30 patients, 4 were excluded due to different surgical techniques/ nature of implant that was used for canalicular repair. Our study strictly adhered to the tenets of the Declaration of Helsinki and the clinical review and documentation was conducted after obtaining the Institutional Ethics Committee approval. The details of clinical history, laterality, time of presentation, type of canalicular injury, method of repair, follow up and the outcome were analyzed. All surgeries were performed by a single surgeon under local/ general anaesthesia as per need. The punctum was dilated with Nettleship's punctum dilator. Medial lacerated end of the canaliculus was located using direct visualization under an operating microscope. In case of non-visualization of the medial cut end, different non-traumatic assisted techniques (air injection, viscoelastic and dye injection) were used to locate the lacerated end of the canaliculus. All canaliculi were repaired using monocanalicular stents (Mini Monoka, FCI Ophthalmics, Marshfield Hills, MA, USA) and peri canalicular tissue was repaired with 8-0 vicryl interrupted sutures, followed by closure of muscle,

conjunctiva, and skin. Bi-canalicular lacerations were also repaired using monocanalicular stents (**Fig. 2**). Adequate instructions were given to the patients about the medications, stent care, and postoperative visits.

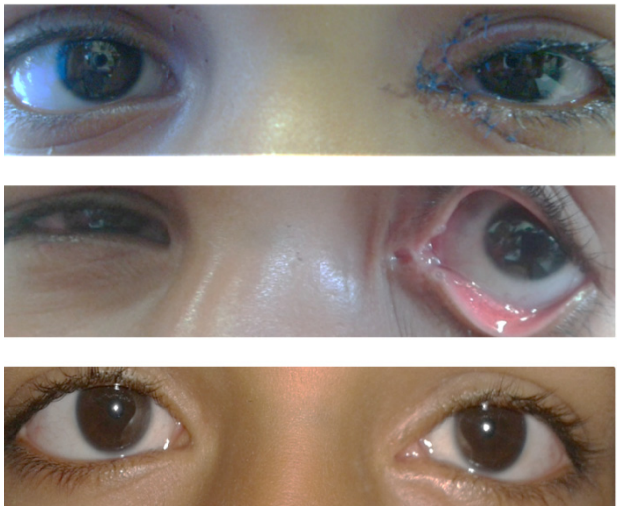

Fig. 2 Sequential images of Bi-canalicular laceration repair at 1-day post op, 1 month and 6 months (top to bottom)

After the examination on the 1st postoperative day, all patients were reviewed at 1st, 4th, 8th, 12th, and 24th week. Standard post-operative regime was followed in all patients and consisted of oral/ topical antibiotics and artificial tear preparations. At each follow-up visit, the lacrimal punctum, position of the stent and ocular surface were evaluated. The stents were removed after 12-14 weeks during slit-lamp office examination, after the assessment of the patient condition (epiphora, inflammation, patient compliance and complications). In cases of stent extrusion, the time period was also noted based on patient disclosure of the episode.

After stent removal, all the patients underwent a standard fluorescein dye disappearance test (FDDT) to access the functional patency of the repaired lacrimal system. After FDDT, a gentle lacrimal irrigation with 2ml saline was performed to check the anatomical patency using a 27-gauge straight lacrimal irrigation cannula. The irrigation findings were categorized as patent (no fluid regurgitation), stenosis (patency confirmed by the patient but partial fluid regurgitation) and blocked (complete fluid regurgitation). No attempt was made to probe the canaliculus to avoid any iatrogenic injury. Complete success was defined as patent lacrimal irrigation with negative FDDT, partial success as patent irrigation or stenosis with positive FDDT and failure as blocked irrigation with positive FDDT. Both lacrimal irrigation and FDDT were repeated after 1 month of stent removal. Minimum post stent removal follow-up of 24 weeks (6 months) was ensured. Statistical analysis was performed using SPSS software (version 24, IBM, New York, USA).

Results

Thirty eyes of 30 patients with a mean age of 32.11±15.09 (4-59 years) with canalicular injuries were included of which 80% (24) were men. The most common mode of injury was road traffic accidents (RTA) in 20 (66.7%), followed by assault with sharp edged weapons in 8 (26.7%) and dog bite in 2 (6.6%) cases. The upper canaliculus was involved in 6 (20%), lower in 20 (66.7%) and both canaliculi in 4 (13.3%). Associated medial wall fracture along with multiple orbital injuries was present in 5 (16.7%) cases. The mean time of repair was 17.2±9.37 (6-36) hours after injury. The mean time of stent removal/ extrusion was 3.5±0.99 (0.5-5) months.

The cases were divided based on time of repair i.e., within 24 hours or after 24 hours from the onset of injury. **Table 1** shows the rate of surgical success in the 2 groups. **Table 2** shows the details of the cases with tube extrusion. Most of our cases underwent early surgery and had good post-operative outcomes. 95.2% had anatomical patency on syringing and 85.7% had a physiological function with negative FDDT. The patients who were operated early also had a lower extrusion rate as compared to those who were operated late. Dog bites and delayed surgery appeared to be associated with a higher extrusion rate.

Table 1. Surgical success and time of surgery (n=30)

Time of Surgery	Number of cases	Number of Tube Extrusions	Anatomical Success (Syringing)	Functional Success (FDDT)
Within 24 hours	21	3 (14.3%)	20 (95.2%)	18 (85.7%)
After 24 hours	9	4 (44.4%)	6 (66.7%)	5 (55.6%)
Combined	30	7 (23.3%)	26 (86.7%)	23 (76.7%)

Table 2. Tube Extrusion: Causes and Surgical Success (n=7)

Time of Surgery	Tube Extrusions	Nature of Injury	Time of Extrusion (weeks)	Cause	Anatomical Success (Syringing)	Functional Success (FDDT)
Within 24 hours	3	RTA	4	Punctal Splitting	Yes	No
		RTA	8	Spontaneous Extrusion	Yes	Yes
		Assault	8	Spontaneous Extrusion	No	No
After 24 hours	4	Dog Bite	4	Spontaneous Extrusion	Yes	No
		Dog Bite	6	Spontaneous Extrusion	No	No
		RTA	8	Wound Granuloma	No	No
		Assault	1	Spontaneous Extrusion	No	No

Discussion

In our study, most of the cases were young males, this being similar to the previous studies [**11,13,14**]. The lower canaliculi were involved in 20 (66.7%) cases, this trend being also similar to reports published earlier [**11,14**] (**Table 3**).

Table 3. Summary of studies exclusively using monocanalicular stents for canalicular laceration repair

Author	Study Population (Number, Gender, Age)	Canalicular Involvement	Mechanism of Injury	Type of Stent	Extrusion Rate	Anatomical Success	Complications
Naik et al. [11]	24, 20 males (83.3%) 16 years (10 months-52 years)	Upper: 8 Lower: 13 Bi-Canalicular: 3	Blouse hook fastener: 20.8% Metal Rod: 20.8% Bicycle Handle: 16.7%	Mini Monoka	3 (11.1%)	Anatomical Success: 18 (90%) Functional Success: 20 (100%)	Spontaneous Extrusion: 3
Lee et al. [13]	36, 26 males (72%), 34 years (1-64 years)	Upper: 10 Lower: 26		Mini Monoka	2 (6%)	Anatomical Success: 16 (94.12%) Functional Success: 14 (82.35%)	Spontaneous Extrusion: 2, Punctal Slits: 2
Eo et al. [21]	15 patients, 17 eyes			Monostent and Mini Monoka	1 (5.88%)	Anatomical Success: 16 (94.12%) Functional Success: 14 (82.35%)	Stent Extrusion: 1

Chowdhury et al. [14]	61, 46 males (75%), 27 years (1-89 years)	Upper: 11 Lower: 46 Bi-Canalicular: 4	Punch 28%, Falls 12%, Broken Glass 10%	Mini Monoka	9 (15%)	Functional Success: 56 (92%)	Stent Extrusion: 9 Symptomatic Failure: 5
This study	30, 24 males (80%), 32 years (4-59 years)	Upper: 6 Lower: 20 Bi-Canalicular: 4	RTA: 20, Assault: 8, Dog Bite: 2	Mini Monoka	7 (23.3%)	Anatomical Success: 26 (86.7%) Functional Success: 23 (76.7%)	Spontaneous Extrusion: 5, Punctal Splitting: 1, Granuloma: 1

The primary mode of injury was trauma due to road side accidents in our study, this being similar to the study of Singh et al. who demonstrated a comparable demographic and surgical success profile like the one in our study [**10**]. In a study of 36 patients, they reported RTA in 47.22% of the patients. Monocanalicular stents were used in 91.67% of their cases and they reported an anatomical and functional success rate of 77.78% and 61.11% respectively.

For the identification of the lacerated medial end of the canaliculi, we used magnification on the operating microscope to locate the other end. In case of non-visualization, non-traumatic assisted techniques like air injection, viscoelastic and dye injection were employed from the other end to identify the proximal end of the laceration [**12**]. These techniques are usually required only in cases in which repair is delayed beyond 24 hours, due to tissue retraction and canalicular collapse. We have used the technique previously described by Naik et al. in the repair of bi-canalicular lacerations [**15**]. In our experience, the monocanalicular stents are effective, less invasive, patient friendly and technically easy to remove than conventional bi-canalicular stents (**Fig. 3**).

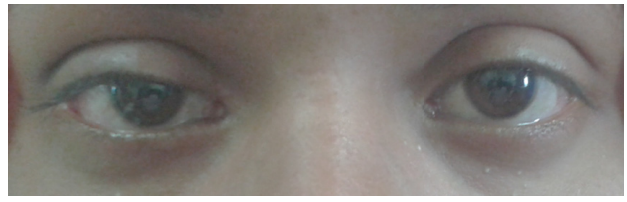

Fig. 3 Sequential images of Monocanalicular laceration repair at presentation, 1 week and 3 months (top to bottom)

Previously, authors have described associated ocular injuries in patients with canalicular lacerations like subconjunctival haemorrhage, traumatic hyphaema, retinal oedema, orbital wall fracture, traumatic optic neuropathy and traumatic cataracts [**13**]. In our study, 5 cases (16.7%) had medial orbital wall fracture and 1 (3.3%) had simultaneous globe perforation that was surgically repaired [**11**]. There were 2 cases with dog bite related injuries and it was a significant factor for surgical failure ($P<0.001$). It has been shown that in cases of periocular dog bite wounds, 66% involve the canaliculi [**16**]. In such cases, it is important to prevent other serious and potentially life-threatening complications like sepsis, arthritis, osteomyelitis, compartment syndrome, loss of a limb and rabies [**17**]. In our study, we had anatomical success in one case, while functional success could not be achieved in any of the cases. Both cases were children (4 and 6 years old), had associated mid facial lacerations, were operated after 24 hours from the injury and later developed spontaneous tube extrusion at around 2 weeks from surgery. This occurred despite broad spectrum systemic antibiotics and regular follow up. Wound infection in dog bites is well known and still remains an important cause of surgical failure [**16**]. Early detection of specific

canine oral pathogens and institution of targeted treatment may however give better results [**18,19**].

Murchison et al. have previously shown that the success rate for canalicular laceration repair is dependent on surgical skill [**20**]. In our study, a single experienced surgeon performed all the surgeries under local/ general anaesthesia. The distal location of the canalicular laceration from the punctum has also been shown to have a better surgical success rate, however, we did not assess this parameter in our study [**10**].

Our study has an anatomical success rate of 86.7% and a functional success rate of 76.7%, which is similar to the studies published earlier [**9,12-14**]. Bivariate analysis of the data using Spearman correlations indicated that the anatomical success ($S=0.381$, $P<0.05$) and functional success ($S=0.711$, $P<0.01$) was correlated with surgery when performed before 24 hours. The age, gender, laterality, canalicular location, time of tube removal and presence of associated injuries were not statistical predictors of surgical success ($P>0.05$). Our results indicated that the time of surgical intervention is an important predictor of final surgical success. Chowdhury et al. have previously reported that 77% of the repairs were conducted within 24 hours from injury; 15% were within 2 days and 8% later on. Subsequently, on analyzing their failure cases (5, 8%), all except one case were repaired on the first day. Of the 5 patients 3 suffered glass injuries, 1 a fall, 1 was kicked and canalicular repair was performed by a fellow in 4 of 5 cases [**14**]. However, in our study, all the patients were operated by an experienced surgeon, yet underwent surgical failure, indicating a role of mechanism of injury/ timing of surgery in determining the final surgical outcome. Nonetheless, further studies are needed to assess this association.

Yet, there are certain limitations of our study including the lack of a control group, small and unequal sample size and a retrospective nature. But, the epidemiological profile of the canalicular lacerations makes it difficult to design a prospective study.

Conclusion

This study is a novel attempt to assess the outcome predictors of canalicular laceration repair using monocanalicular stents in a tertiary eye hospital. These stents can also be used successfully in cases with bi-canalicular lacerations. However, it is imperative to take up such cases at the earliest to optimize easy canalicular visualization without much mechanical intervention like the use of probes or need of bi-canalicular stents. However, dog bites are still a challenge for surgeons and need patient optimization with adequate antibiotic coverage before intervention.

Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

An informed consent was obtained from all individual participants included in the study.

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GENERAL ARTICLE

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Medical legal validity of the use of the anomaloscope in the dyschromatopsia of aspiring civil and military aircraft pilots

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Abstract

Color blindness is a condition of altered color perception, scientifically defined as "dyschromatopsia". Color blindness affects 8% of the world population.
Color blindness is caused by an alteration of the cones that influences the vision of the color self (red, green, blue). A comparative study was conducted in dischromatopsic subjects identified during the course of the ordinary investigations directed towards the civil aero-navigating personnel by the Ophthalmology Department of the Air Force, between March 2019 and January 2020, at "Aldo Di Loreto" Institute of Aeronautical and Space Medicine of Rome. 10 subjects aged 20 to 50, with dyschromatopsia found at Ishihara's pseudoisochromatic tables, were submitted to Oculus HMC-Anomaloscope with a manual execution program and then a CAD test. Thus, in 2 out of 10 cases of dyschromatopsia, the Anomaloscope would have guided the medical judgement, while the CAD test would have oriented towards a judgment of full fitness despite the same lack of chromatic sensitivity however, underlined by both tests. In conclusion, the CAD test confirmed a highly sensitive and specific method of determining the presence and depth of the chromatic perception deficit but also the method was able to prevent the unjust refusal of certain air navigation activities to the aspirant staff.
Keywords: dyschromatopsia, anomaloscope, CAD

Introduction

Color blindness is a condition of altered color perception, scientifically defined as "dyschromatopsia". The word with which it is best known comes from the name of the British scientist John Dalton (affected by "chromatic blindness", another expression used to indicate the same disorder), who was the first to describe its fundamental characteristics in the Article "Extraordinary facts related to the vision of colors". Color blindness affects 8% of the world population [**1,19**].

Blindness is a disease that is mostly congenital, linked to a genetic mutation that afflicts the X chromosome. To be able to understand the mechanisms of transmission and manifestation of color blindness it is necessary to keep in mind the concepts of genetic inheritance related to the chromosome of women and men: nature attributes two X chromosomes (XX) to women, and one X chromosome and one Y (XY) to men.

When color blindness is hereditary, it is bilateral (affects both eyes). there are, However, there are cases in which it is monolateral. This is

the case of patients who are not born with the abnormality (i.e. theirs is an extragenetic "color blindness") but acquire it because of other diseases or conditions, such as:

- multiple sclerosis: since it is a disease affecting the cells of the nervous system, it may also involve the optic nerve or areas of the cerebral cortex that are responsible for the interpretation of visual signals;
- cataract: opacification of the lens abnormally filters light, causing partial insensitivity to blue;
- alcoholism: in alcoholics, color sensitivity is generally reduced;
- head trauma: traumatic brain damage is a condition that can reduce the ability to color discrimination;
- other eye diseases: maculopathies or other eye diseases may cause a color perception deficit.

Color blindness is caused by an alteration of the cones that influences the vision of the color self:

- red: the vision of this color may be impossible (protanopia) or difficult (protanomaly);
- green: the correct perception of green can be prevented (Deuteranopia, the type of color blindness that John Dalton suffered, and also the most common) or hindered (deuteranomaly/ teranomaly)
- blue: this color may not be perceived (tritanopia) or it is distinguished with difficulty (tritanomaly).

The diagnosis of color blindness is made by the ophthalmologist after a medical examination which consists of the recognition of colors. The best new tests are Anomaloscope of Nagel and CAD test [**2,21**].

The anomaloscope of Nagel is a microprocessor-controlled device for diagnosing color vision accuracy in the red/ green area (Rayleigh equation) [**3,4**] and the blue/ green area (Moreland equation) with integrated neutral automatic adaptation.

In its most frequent use, the principle in Rayleigh equation is based on the comparison, on a screen, of a yellow-orange reference light (lower hemisphere, wavelength of 589 nm, whose luminance can be adjusted) with a light (upper hemisphere) made up of an addition of a certain intensity of red (671 nm wavelength) and green (546 nm wavelength) [**5-7**]. The device is set with two knobs on the sides of the device for a normal match (yellow=15, red-green=40).

The evaluator is asked to describe the appearance of the colors seen in the tool [**8,9**]. Several lots are offered for evaluation and they are asked to describe the appearance of the colors seen. The evaluator is requested to adjust the knob that controls the luminance of the test field [**10,11**]. This way, the centre and range of combinations are determined and recorded [**12,13**].

Normal subjects are sensitive to red and green and regulate these two intensities (more red than green) to obtain a yellow comparable to the reference light.

Dyschromatic "less red" subjects regulate this light only by modifying the intensity of the green, and dyschromatic "less green" by modifying the red.

Materials and methods

The CAD test measures the size of the red/ green (RG) and/ or yellow/ blue (YB) signals needed only to see a color-defined target moving diagonally across a square made of checks that vary randomly in luminance every 50 to 80 ms. A "chromaticity chart" (CIE 1931 (x,y) - chromaticity diagram) is used for convenience and the color signal strength is measured as the distance away from the "neutral" grey background for each of the colors examined. Colored pixels have the same luminance as the gray background. During this test, the subject will see a colored target move diagonally along a central square in one of the four possible directions (top right/ left – bottom right/ left). The Response Box has 4 buttons arranged to form a square. The task of the subject is to press the right button to indicate the corresponding angle where the colored target ends and then the direction of the movement. To get a better result, the subject should be instructed to keep the view focused on the center of the square and not follow the moving target. It is designed to prevent the unjust refusal of medical

certification to individuals with slight deficits in color perception [**1-3**].

It is important to underline that if the new limit of color, based on experiments, passed/ failed in the military requirements, 36% of the deutan subjects and 30% of the protan subjects would be classified as safe for flying.

During this test, the subject will see a colored target moving diagonally across a central square in one of four possible directions (i.e., ending top-right, top-left, bottom-right, or bottom-left). The response box provided has four buttons laid out to form a square and a central button that is not used in the CAD test. The subject's task is to press the appropriate button (i.e., top-right, top-left, bottom-right or bottom-left) to indicate the corresponding end point and hence the direction of movement. A sharp beep follows the end of each stimulus presentation and indicates the subject to respond by pressing one of the four buttons. When unsure, the subject has to make the best guess without any hesitation. For best results, the subject should be instructed to maintain fixation on the centre of the square and not to track the moving target [**6,8-10,14,15**].

Pilot Study

A comparative study was conducted in dischromatopsic subjects identified during the course of the ordinary investigations directed towards the civil aero-navigating personnel by the Ophthalmology Department of the Air Force, between March 2019 and January 2020, at "Aldo Di Loreto" Institute of Aeronautical and Space Medicine of Rome. 10 subjects aged 20 to 50, with dyschromatopsia found at Ishihara's pseudoisochromatic tables, were submitted to Oculus HMC-Anomaloscope with a manual execution program and then a CAD test. The control group consisted of 10 subjects with normal color perception, who were subjected to the same examinations. The civil aero-navigating team is subjected to its reference legislation EASA (European Aviation Safety Agency), which are the Acceptable Means of Compliance (AMC) MED B 075 of 2019 for both the first and the second class, and the Acceptable Means of Compliance ATCO MED B 075 of 2015 for the third class. While the military personnel are sent to the anomaloscope only in case of mistakes in the pseudoisochromatic tables, those sets of rules imply that the ophthalmologist must choose between one of the following tests, in order to get a second level assessment: -anomaloscope (Nagel or equivalent);

- CAD test;
- lanterns test (spectrolux, Beynes, Holmes-Wright) [**11,16**].

Discussion

In the case of civil aircrew, the reference EASA (European Aviation Safety Agency) is the acceptable means of compliance (AMC) MED B 075 of 2019 for the 1st and 2nd class and the acceptable means of compliance ATCO MED B 075 of 2015 for the 3rd class. The legislation in question for the military staff, for which only the execution of the anomaloscope in the case of errors to the pseudoisochromatic tables is previewed, obliges the examiner to choose one of the following options as a level II finding:

- anomaloscope (Nagel);
- CAD test;
- lanterns test (Spectrolux, Beynes, Holmes-Wright).

The first two examinations have been the subject of discussion during the course of this article; the tests of the lanterns, although they are still provided in the current legislation, are practically not used at national and international level because the instrumentation is technologically obsolete, outdated and no longer commercially available. The notification of Alternative Means of Compliance to the European Aviation Safety Agency by ENAC on 11.12.2019 is relevant in this regard, the National Civil Aviation Authority communicating that it will no longer accept cases whose visual requirements relating to color safety for Class 1 and Class 2 of medical certification have been determined based on the lanterns, admitting only the anomaloscope (Nagel and CAD test) [**17,18,20**].

According to a French study, both the anomaloscope with manual execution and the CAD test have high sensitivity and specificity, negative predictive value and positive predictive value identical (in both cases all values are 1.00).

The subjects in the control group were normal trichromatic in the anomaloscope test with "normal" assessment. Overlapping evidence

was found in the CAD test with similar results and with "pass" assessment. The descriptive difference in the result between the two tests is inherent in the original purpose for which the two tests were designed. In fact, in the case of the anomaloscope, the instrument identifies and quantifies anomalies in chromatic perception on the red/ green axis and on the blue/ green axis, while in the case of the CAD test, the instrument not only identifies the presence of deviations in color perception but provides the operator with indications as whether or not the candidate, who had a certain color deficit, may be suitable for the civil pilot license first class, second class or achievement as an air traffic controller (CTA third class). Therefore, in this second case, the algorithm of the software is able to diversify the protocol of investigation and the sequence of the chromatic targets given depending on the class to be reached. The study led to the conclusion of the test with assessment "pass" or "fail" in the case of color perception deficit, which is not compatible with the tasks to be performed.

Therefore, it is clear that the word "pass" in the CAD test does not mean that the candidate is absolutely free of color perception deficit, but it means that even in the presence of some slight forms of dyschromatopsia, the pilot candidate or air traffic controller will be able to safely carry out all the tasks foreseen in the task to be performed. This is confirmed by the EASA regulation, which establishes the CAD test that for deuteranomaly is a threshold below the 6 standard units (SN), for protanomaly a threshold below the 12 standard units (SN) and for tritanomaly a threshold higher than the 2 standard units (SN).

On the contrary, the results of the anomaloscope should be interpreted in a more rigid way, bound to the evidence of deuteranomaly, protanomaly or tritanomaly, while the standard actually allows the operator a margin of flexibility, considering suitable the candidate with a matching range equal to or less than 4 units of scale, that is to say with a mixing light value of 40 ± 4 and a reference light of 15 ± 4.

In the light of the different construction characteristics and the different interpretation in the results of the two electro-medical products, the main question, which is the subject of this discussion, is the selective cut-off. In other words, the purpose of this article was to find out whether the two tests, considered as equivalent from the point of view of the regulation and therefore of the medical-legal ophthalmology, are also equivalent from the point of view of selection of the candidate staff. The analysis of the results in the 10 dyschromatic subjects led to the detection of 8 deuteranomalous and 2 protanomalous subjects.

As explained above, both tests showed the same sensitivity and specificity. But in practice, in selecting aero-navigating personnel, out of the two cases of deuteranomaly confirmed both to the anomaloscope, and to the CAD, the latter proved more flexible in granting the required forensic suitability.

In fact, in the case of the anomaloscope, the matching range was far more outside the requirements of the current legislation for extremely low mixing light values in both eyes (mean values of 26.08 with an average of units of scale less than 13.9 compared to the values allowed by AMC MED EASA); in the case of the CAD test, while confirming the deuteranomaly deficiency, the threshold was found to be below the 6 normal standard units (SN) (mean value 3,9 standard units), justifying the "pass" assessment of the test.

Thus, in 2 out of 10 cases of dyschromatopsia, the anomaloscope would have guided the medical judgement, while the CAD test would have oriented towards a judgment of full fitness despite the same lack of chromatic sensitivity, which was underlined by both tests.

In conclusion, the CAD test confirmed a highly sensitive and specific method of determining the presence and depth of the chromatic perception deficit, but the method was also able to prevent the unjust refusal to certain air navigation activities of the aspirant staff. Within the framework of the study carried out, it was observed that 20% of the subjects who would have been judged unfit if subjected to the anomaloscope, have passed the CAD test and could therefore continue the certification process undertaken. Previous studies have shown that the percentages could rise to 35% in air traffic controllers (ATCO).

Moreover, the analysis of the findings suggested that in the EASA legislation currently in force at international level in the countries of the European Community showed that a rational criterion does not appear to be followed in

allowing the free choice of the second level test to be administered in the dyschromatic subjects, by placing highly different tests between them on the same level, whose interpretation could discard persons who, on the contrary, if CAD tests are carried out, might have a better chance of being judged suitable [**19,20**].

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GENERAL ARTICLE

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Evaluation of safety and efficacy of different protocols of collagen cross linking for keratoconus

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Abstract

Introduction: Collagen cross-linking is a well-established modality that could stop the keratoconus from progressing. Off late, newer protocols have been suggested for progressive keratoconus, which include the use of hypoosmolar riboflavin for thinner corneas and the use of accelerated CXL protocol to reduce the effective treatment time.
Objective: To assess the safety and efficacy of different protocols of conventional CXL, hypoosmolar CXL and accelerated CXL in patients with keratoconus.
Materials & methods: It was a prospective, interventional study with minimum of 12 months follow-up. Patients were divided into 3 groups; conventional CXL, CXL using hypotonic riboflavin and accelerated CXL group. Primary outcome measures - For efficacy, Sim Kmax and Sim Kmin (Progression (Kmax $\geq$ +1 D), stabilization (Kmax +1 D to -1 D) and regression (Kmax $\geq$ -1 D). For safety - endothelial count evaluation (decrease >10% amounted to compromise the safety of the procedure). Secondary outcome measures - BCVA and adverse events.
Results: 32 eyes underwent isotonic CXL treatment. Pre-treatment and post-treatment BCVA were 0.16 +/- 0.15 and 0.10 +/- 0.11 log MAR; specular counts 2782.81 +/- 307.25 (cells/ mm2) and 2708.5 +/- 263.27 (cells/ mm2) (p=0.05); KMax values 55.31 +/- 4.12 D and 53.9 +/- 3.77 D (p=0.0001).
16 eyes underwent hypotonic CXL treatment. Pre-treatment and post-treatment BCVA were 0.15 +/- 0.13 log MAR and 0.14 +/- 0.14; specular count 2701.19 +/- 243.25 (cells/ mm2) and 2713.5 +/- 369 (cells/ mm2) (p= 1) and KMax values 54.74 +/- 7.44 D and 52.74 +/- 6.76 D (p = 0.002).
15 eyes underwent accelerated CXL treatment. Pre-treatment and post-treatment BCVA were 0.16 +/- 0.15 and 0.10 +/- 0.12 log MAR; specular counts 2967.53 +/- 356.48 and 2893.07 +/- 336.55 (cells/ mm2) (p = 0.78) and KMax values 55.19 +/- 5.46 D and 54.24 +/- 5.33 D (p = 0.337).
Conclusion: All three protocols appeared safe and efficacious as therapeutic regimen for progressive keratoconus.
Keywords: keratoconus, cornea, cross linking, CXL, accelerated CXL, hypo-osmolar riboflavin

Background

Keratoconus is a clinical condition associated with conical shape of the cornea due to its thinning and subsequent protrusion [**1**]. The process is described as non-inflammatory and progressive, without cascade of cellular infiltration and vascularization.

Treatment options available for keratoconus include spectacle corrections, rigid contact lenses, and intracorneal ring segments as a means to improve the vision and rehabilitation [**2-4**]. The resistant disease that continues to progress, requires lamellar or penetrating keratoplasty as the potential treatment modalities [**5,6**]. In recent years, the goal of keratoconus treatment also included prevention of further disease progression, beside the improvement in visual acuity of the patients. The latest treatment modality that focuses on the corneal disease pathology and biomechanically increases its rigidity, thereby preventing the advance in disease severity, is cross-linking (CXL) of the corneal collagen.

This technique was first described in Dresden in Germany and it includes photo polymerization of collagen fibers of the stroma, which is induced by the combination of a photo-sensitizer (Vitamin B2/ Riboflavin) and ultraviolet rays (UV) [**7,8**]. These rays increase the quantity of intra-fibrillar and inter-fibrillar covalent bonds, thereby increasing the stiffness of the cornea and in this process, also enhancing the resistance of collagen against degradation by enzymes [**9,10**]. For safety purposes, the minimum corneal thickness of 400 microns after epithelial removal is necessary for the effective treatment of keratoconus by CXL [**11**]. This is quantified by pachymetry and this limit has been established in order to avoid endothelium damage.

However, in progressive stages of keratoconus, thinning of the cornea, causes a residual stromal thickness lesser than the minimum of 400 microns. So, the efficacy of CXL in such cases remains unclear. Hypoosmolar Riboflavin solution has been shown to increase the pretreatment thickness of such corneas, by Hafezi and associates, after which CXL could be used for further treatment [**12**].

The standard CXL therapy requires a minimum of 1 hour of exposure time for the patients. At present, only Dresden's protocol has documented safety and efficacy profile for corneas with thickness >400 microns using this therapy. Nowadays, accelerated CXL has been described as another mean of fast-tracking the process with higher irradiance, thereby decreasing the overall period of exposure [**13**].

Safety and efficacy regarding the use of this accelerated CXL therapy in corneas thinner than 400 microns has not been documented yet. Whether or not this accelerated therapy can work for such corneas pretreated with hypoosmolar Riboflavin has not been clearly documented. The present study was conceptualized to evaluate the outcomes of accelerated CXL in such cases of keratoconus.

Materials and methods

The present study is a prospective, non-randomized, interventional case series conducted at a tertiary eye care hospital in India. The patients were enrolled over a period of 12 months and then followed up over another 12 months. Approval was taken from the institutional ethics committee and the study was performed in accordance to Helsinki Declaration.

The patients were included as per predefined criteria of inclusion and exclusion. All patients, regardless of their sex, who were 12 years old or older, having mild to moderate progressive keratoconus (defined as an increase in Sim K values by 0.5 D in 6 months or 1 D in 1 year) with BCVA 20/ 40 and a minimum follow-up of one year, were included in the study.

Exclusion criteria included patients who had ocular pathologies like vernal keratoconjunctivitis, corneal scar, corneal dystrophy, corneal degeneration and corneal hydrops. Patients having inflammatory conditions, posterior segment pathologies, ultrasonic pachymetry <350 microns and endothelial cell count <2000 cells/ sq mm were also excluded. In addition, all patients with systemic diseases like diabetes, thyroid dysfunction, collagen-vascular disorders and auto-immune disorders were not included. After informing the patients about the standard and the other modified protocols available for treating keratoconus, an informed consent was taken and patients were allocated into their respective groups. Patients having a corneal thickness of >400 microns were given a choice between the standard and the accelerated protocols, while those having a pachymetry of <400 microns were treated with hypotonic riboflavin only.

Finally, patients were divided into three groups:

- Eyes undergoing conventional CXL procedure using Indian made 0.1% isotonic riboflavin (K-Link Riboflavin, Appaswamy Ocular Devices, Puducherry) (epithelial debridement with 3mW UVA exposure for 30 minutes), in cornea with thickness of more than 400 microns after epithelial debridement.
- Eyes undergoing CXL procedure using hypotonic riboflavin i.e. riboflavin without dextran (Appaswamy Ocular Devices, Puducherry), in cornea with thickness of less than 400 microns after epithelial debridement.
- Eyes undergoing accelerated CXL procedure using 0.1% Riboflavin with 20% dextran (Avedro Inc., Massachusetts, USA) and KXL (epithelial debridement with 18mW UVA exposure for 5 minutes), in cornea with thickness of more than 400 microns after epithelial debridement.

The assessment was done at baseline and at 1, 3, 6 and 12 months after intervention; it included UCVA (log MAR units), BCVA (log MAR units), examination under the slit-lamp, ultrasound pachymetry (Pachy Meter SP3000; Tomey, Nagoya, Japan), video keratography (Orbscan II; Bausch and Lomb Surgical), measurement of the intra-ocular pressure with Goldmann tonometer (Haag-Streit AG, Koeniz, Switzerland) and evaluation of the endothelial cells with the Tomey EM-3000, Nagoya, Japan. Unmasked analysis was fine for all acquired images.

Reliability of the video keratography measurements, was improved by performing at least 3 consecutive ones for all eyes. If the value of Kmax differed by more than 1 D among the 3 scans, 2 more scans were further done. The scan with the median Kmax value was finally analyzed after all the visits.

Methodology

GROUP 1 (**Isotonic CXL)**: After achieving surface anesthesia with 0.5% Paracain eye drops, mechanical debridement of corneal epithelium over a zone of 8 mm was done. 0.1% Riboflavin drops were instilled onto the cornea at a rate of 1 drop/ 2 minutes for 30 minutes, followed by UV irradiation exposure at 370nm/ sec for 30 minutes. Instillation of 0.1% Riboflavin drops was continued during irradiation.

GROUP 2 (**Hypotonic CXL)**: All the steps were the same as for conventional CXL, however, instead of isotonic riboflavin, the cornea was initially saturated with hypoosmolar riboflavin by pouring hypoosmolar riboflavin over the cornea, drop by drop, at every two minutes, followed by irradiation for 30 minutes.

GROUP 3 (**Accelerated CXL)**: Calibrated KXL insert with independent power meter provided for the delivery of 18 mW/ cm^2 was selected and the cornea was exposed for 5 minutes after an initial soakage of 30 mins.

During any of the procedures, if intra-op pachymetry values went below 350 microns, as a safety precaution, distilled water was instilled drop by drop for 2 minutes to swell up the cornea beyond 400 microns, and then the procedure was continued as per protocol.

Postoperatively, topical antibiotics were given 4 times daily for 7 days. Low potency steroid drops were started 4 times daily once the epithelium healed and tapered off over a month's time. In addition, tear substitute drops were given 4 times daily for one month.

Outcome Measures

Primary Outcome measures, regarding the efficacy, were evaluated using Sim Kmax and Sim Kmin on topography with Orbscan to check for progression (Kmax $\geq$ +1 D), stabilization (Kmax +1 D to -1 D) and regression (Kmax $\leq$ -1.0 D). For safety, endothelial count was taken into consideration and any decrease in endothelial cell count >10% was considered significant and amounted to compromise in the safety of the procedure.

Secondary outcome measures were BCVA and occurrence of any adverse events (e.g. epithelial defects, corneal edema, corneal haze, keratitis, scarring, and cataract).

Statistical Analysis

Calculation of the sample size was done to detect a difference of 4% between the pre-op and post-op mean topographic value (Kmax).

This was done at a significance level of 0.05 and 80% study power, assuming 4.1% of standard deviation. An anticipated loss to follow-up rate of 10% gave a final sample size of 15 in all the groups. Statistical analysis was done with the R software (version 2.12). The mean difference between the pre-op and follow-up time point scans of corneal topography were compared by multiple comparisons of means with Dunnett Contrasts from a mixed effect model, and adjusted p value was obtained by Bonferroni method. The mean difference between the procedure at pre-op and at 12 months for Specular and for Kmax was computed by using multiple comparisons of means with Tukey Contrasts from a linear model, the adjusted p value being obtained by Bonferroni method. Comparison between the pre-op and 12 months median BCVA was done using Wilcoxon signed-rank test.

Results

A total of 74 eyes underwent CXL over a period of 12 months, of which 37 were in the isotonic CXL group, 19 in the hypotonic CXL group and 18 in the accelerated CXL group. However, 11 eyes were excluded from the study as they could not be followed-up and finally 63 eyes (32 in isotonic, 16 in hypotonic and 15 in accelerated CXL group) were taken into consideration for analysis.

Isotonic group: A total of 32 eyes underwent isotonic CXL treatment. The group had a mean age of 15.72 +/- 3.59 years. The mean pre-treatment and post treatment BCVA values at 12 months, were 0.16 +/- 0.15 and 0.10 +/- 0.11 log MAR; specular counts were 2782.81 +/- 307.25 (cells/ mm2) and 2708.5 +/- 263.27 (cells/ mm2) (p=0.05) (**Fig. 1**); KMax values were 55.31 +/- 4.12 D and 53.9 +/- 3.77 D (p=0.0001) (**Fig. 2**); KMin values were 48.59 +/- 4.15 D and 47.98 +/- 3.75 D and the pachymetry values were 438.44 +/- 31.16 microns and 426.09 +/- 47.07 microns, respectively. Out of 32 eyes, 16 eyes showed disease regression, 15 eyes were stable, while 2 eyes showed worsening.

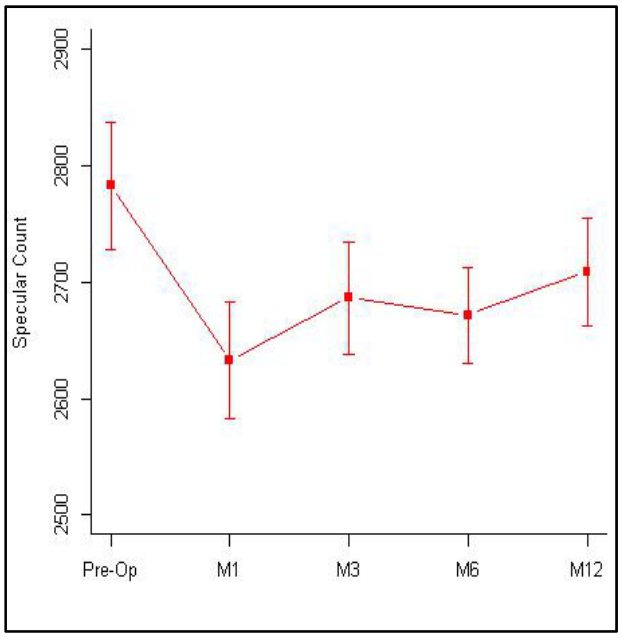

Fig. 1 Specular counts (cells/ mm2) seen at 1st, 3rd, 6th and 12-months follow-up in the isotonic CXL group. Pre-operative specular count was 2782.81 +/- 307.25 (cells/ mm2) and 2708.5 +/- 263.27 (cells/ mm2) at 12 months (p=0.05)
M = months

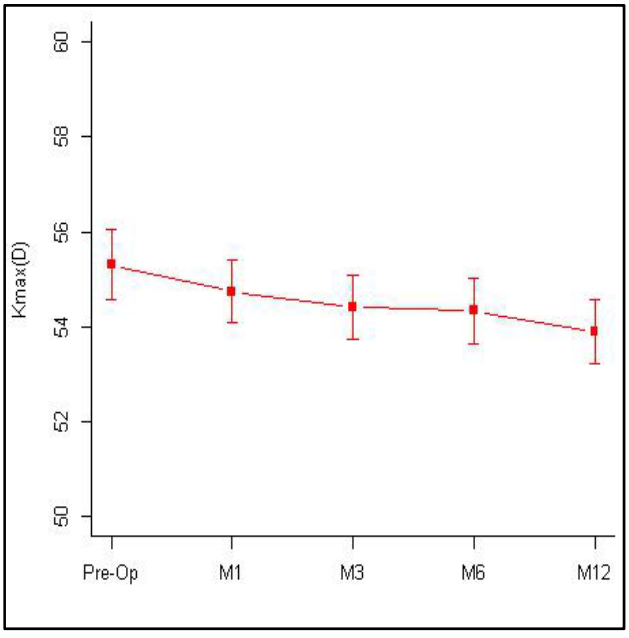

Fig. 2 Mean KMax values [Diopters (D)] seen at 1st, 3rd, 6th and 12-months follow-up in the Isotonic CXL group. Mean KMax values pre-operative was 55.31 +/- 4.12 D and 53.9 +/- 3.77 D at 12 months (p=0.0001)
M = months; D = diopters

Hypotonic group: A total of 16 eyes underwent hypotonic CXL treatment. The group had a mean age of 16.44 +/- 4.53 years. The mean BCVA pre-treatment and post treatment at 12 months were 0.15 +/- 0.13 log MAR and 0.14 +/- 0.14; the mean specular count was 2701.19 +/- 243.25 (cells/ mm2) and 2713.5 +/- 369 (cells/ mm2) (p= 1) (**Fig. 3**) and the mean KMax values were 54.74 +/- 7.44 D and 52.74 +/- 6.76 D (**Fig. 4**) respectively. The treated eyes showed statistically significant improvements with the Kmax flattening by 1.99 D at 12 months; p value of 0.002. The mean KMin values pre- and post-treatment were, 48.57 +/- 5.84 D and 47.61 +/- 6.48 D respectively and the mean pachymetry values were 397.06 +/- 9.82 microns and 371.06 +/- 14.64 microns respectively.

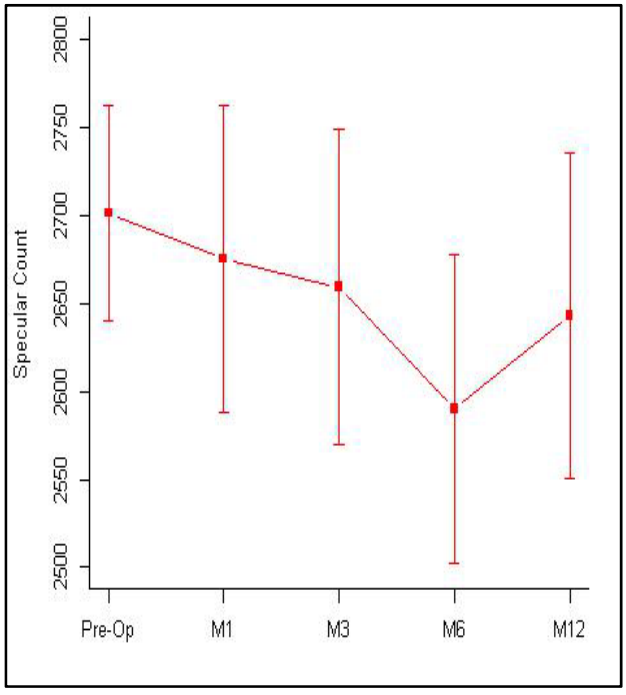

Fig. 3 Specular counts (cells/ mm2) seen at 1st, 3rd, 6th and 12-months follow-up in the Hypotonic CXL group. Pre-operative specular count was 2701.19 +/- 243.25 (cells/ mm2) and 2713.5 +/- 369 (cells/ mm2) at 12 months (p= 1)
M = months

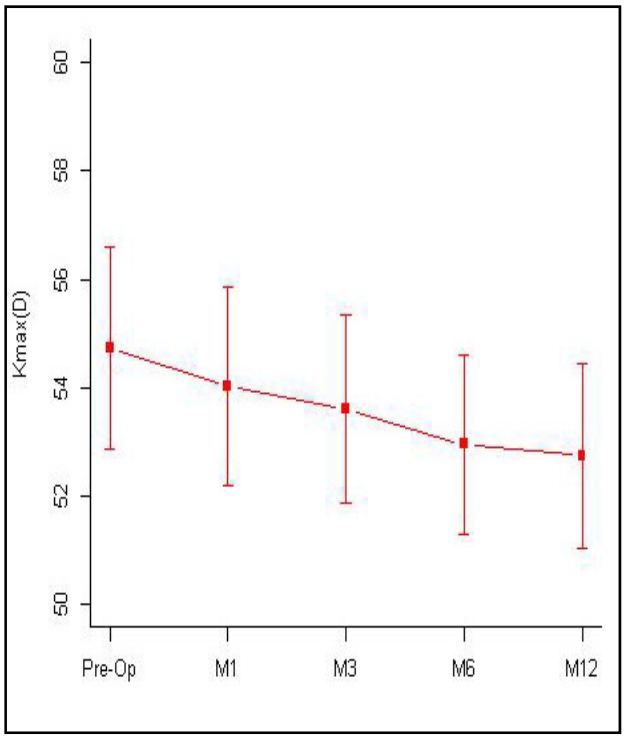

Fig. 4 Mean KMax values [Diopters (D)] seen at 1st, 3rd, 6th and 12-months follow-up in the Hypotonic CXL group. Mean KMax values pre-operatively were 54.74 +/- 7.44 D and at 12 months 52.74 +/- 6.76 D (p = 0.002)
M = months; D = diopters

Accelerated group: A total of 15 eyes underwent accelerated CXL treatment. The group had a mean age of 14.07 +/- 2.71 years. The mean BCVA, pre- and post-treatment at 12 months were 0.16 +/- 0.15 and 0.10 +/- 0.12 log MAR; the mean specular counts were 2967.53 +/- 356.48 and 2893.07 +/- 336.55 (cells/ mm2) (p = 0.78) (**Fig. 5**) and the mean KMax values were 55.19 +/- 5.46 D and 54.24 +/- 5.33 D respectively (**Fig. 6**). There was a decrease in Kmax values by about 0.95 D. However, the difference was not statistically significant (p = 0.337). The mean KMin values, pre- and post-treatment were 48.89 +/- 4.65 D and 48.75 +/- 4.49 D and the mean pachymetry values were 384 +/- 18.94 and 390.07 +/- 28.74 microns, respectively.

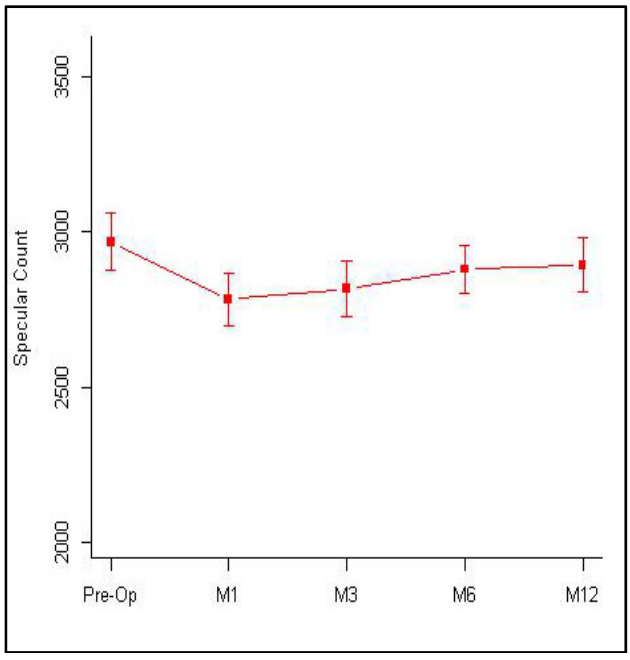

Fig. 5 Specular counts (cells/ mm2) seen at 1st, 3rd, 6th and 12-months follow-up in the Accelerated CXL group. Pre-operative specular count was 2967.19 +/- 356.48 (cells/ mm2) and 2893.07 +/- 336.55 (cells/ mm2) at 12 months (p= 0.78)
M = months

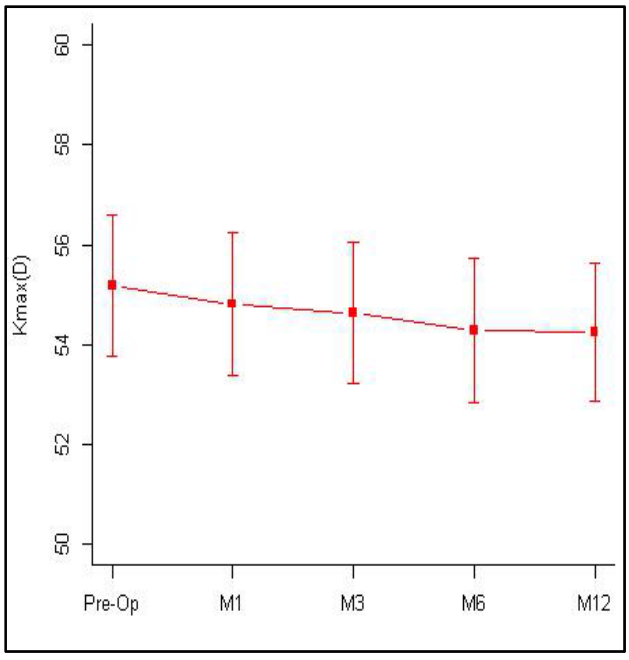

Fig. 6 Mean KMax values [Diopters (D)] seen at 1st, 3rd, 6th and 12-months follow-up in the Accelerated CXL group. Mean KMax values pre-operatively were 55.19 +/- 5.46 D and at 12 months 54.24 +/- 5.33 D (p = 0.337)
M = months; D = diopters

A comparative assessment of the Kmax values at different time intervals done in the 3 groups revealed a statistically significant flattening of the cornea in isotonic and hypotonic CXL groups, while the decrease in Kmax value in the accelerated group was not statistically significant (**Table 1**, **Fig. 7**). While comparing the change in the specular count in the 3 groups, none of them showed any significant drop in the specular count at 12 months. The accelerated group showed a significant drop in the endothelial count at the 1st and the 3rd month of the follow-up, however the counts recovered by 12 months and were comparable to the pre-operative values (**Table 2**, **Fig. 8**).

Table 1. Difference in the Kmax values at 1st, 3rd, 6th and 12-months follow-up when compared to the pre-operative Kmax values in the hypotonic, isotonic and accelerated CXL groups

	Hypotonic		Isotonic		Accelerated	
	Estimate	P-value	Estimate	P-value	Estimate	P-value
1st month	-0.7062	0.88	-0.57	0.0496	-0.37	1
3rd month	-1.125	0.20	-0.90	0.00028	-0.56	1
6th month	-1.7812	0.0079	-0.97	0.0002	-0.9	0.402
12th month	-1.9937	0.002	-1.41	0.0001	-0.95	0.337

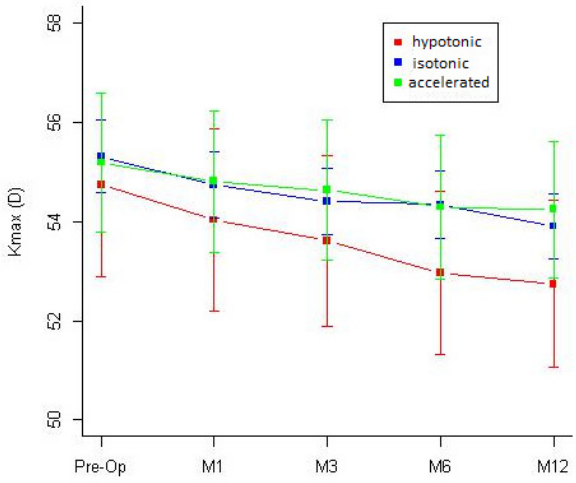

Fig. 7 Comparative assessment of the mean KMax values [Diopters (D)] seen at 1st, 3rd, 6th and 12-months follow-up in the Hypotonic, Isotonic and Accelerated CXL group

Table 2. Difference in the specular count at 1st, 3rd, 6th and 12-months follow-up when compared to the pre-operative specular count values in the hypotonic, isotonic and accelerated CXL groups

	Hypotonic		Isotonic		Accelerated	
	Estimate	P-value	Estimate	P-value	Estimate	P-value
1st month	-26	1	-150.16	0.07	-184.67	0.01
3rd month	-41.81	1	-96.12	0.21	-152.27	0.03
6th month	-111.12	0.27	-111.22	0.14	-88.27	0.5
12th month	-58	1	-74.25	0.11	-74.47	0.78

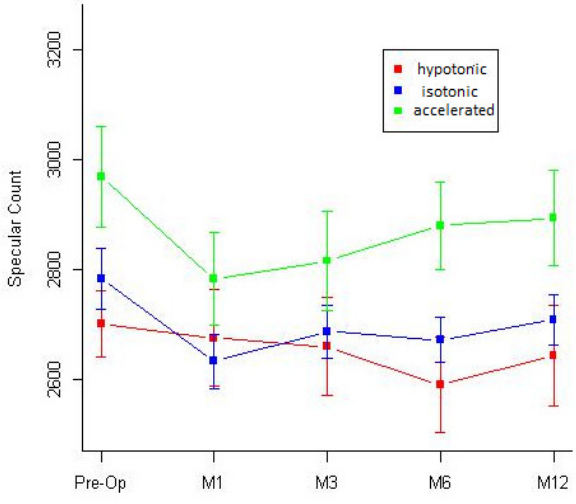

Fig. 8 Comparative assessment of the specular counts (cells/ mm2) seen at 1st, 3rd, 6th and 12-months follow-up in the Hypotonic, Isotonic and Accelerated CXL group

Best corrected visual acuity in all three groups showed a statistically significant improvement in all three groups at 12 months follow-up (**Table 3**).

Table 3. Median BCVA (inter-quartile range) in hypotonic, isotonic and accelerated CXL group at 12 months follow-up

	Pre-op	12 months	P value
Hypotonic	0.18 (0-0.3)	0.1 (0-0.18)	<0.05
Isotonic	0.1 (0-0.3)	0.1 (0-0.18)	0.005
Accelerated	0.1 (0-0.3)	0.0 (0-0.18)	<0.05

Adverse events: 5 patients in the isotonic group and 2 from the accelerated CXL group developed significant corneal haze after the procedure. While, 1 patient in the hypotonic group and 1 in the isotonic group developed sterile infiltrate.

Discussion

CXL has come up as one of the most crucial therapeutic modalities for advanced keratoconus. There has been a rapid rise in the number of publications in the literature on CXL, ever since it was first reported by Spoerl et al. in 1998 [**8**]. However, there remains a deft of strong evidence in support of extensive usage of this modality, despite an ever-increasing description in literature. The present study reports the 12-months post therapy results of CXL, and demonstrates a statistically significant improvement in Kmax values, taking into account the specular count, that, at no point in time, showed a decrease of more than 10% from the baseline, thus, rendering the procedure to be safe. We included a total of 74 patients of whom 63 completed the 12 months follow up. Our first group had a total of 32 eyes, which underwent standard CXL using Isotonic riboflavin, and these patients showed a significant difference in Kmax values, without any significant decrease in the specular count. Similar results were shown by previous reported studies.

In 2008, Snibson et al. reported that 9 eyes showed improvement (improved Kmax with a mean value of -0.74 D) after 1 year. In their 11 control eyes, the disease showed progression; mean Kmax of -1.28 D [**14**]. O'Brart et al. showed an average improvement in the value of Orbscan simulated keratometry by -0.62 D, after follow up of 1.5 years in the treatment group; P value <0.001. On the other hand, there was progression in the eyes of the control group by a mean of -0.14 D; P value < 0.3 [**15**]. In a randomized controlled trial with 1-year follow-up of treatment group and 3 months follow-up for control eyes, Hersh et al. reported an improvement in the Kmax (by mean of -2.0 D) from baseline in the treatment group. However, they reported no change in Kmax for control eyes at 3 months [**16**]. Several other studies have reported good outcomes with this technique. Caparossi et al. reported decreased mean K value in 44 eyes, by -2.24 D [**17**]. Raiskup-Wolf et al. documented 33 eyes with reduction in Kmax by a mean of -2.57 D [**18**].

The major drawback for CXL is the requirement of at least 400 microns, including a margin of safety, of the stromal thickness (excluding the epithelium of corneal). It is well described that in the advanced stages of keratoconus, there is increased thinning of the cornea, which more than often reduces the stromal thickness to less than 400 microns. Kymionis et al. studied the effect of Vitamin B2 and UV-A rays in thin cornea, using Dresden's protocol in 12 eyes and concluded that there were no immediate intra and post-operative complications, but there was a significant endothelial damage [**19**]. This made researchers look for a safer option in the thin corneas [**12**]. Pre-operatively, the usage of hypo-osmolar Vitamin B2 has been described to influence swelling of the thin corneas with a stromal thickness of at least 400 microns. This has shown no complications post-operatively.

In a similar study performed on 32 eyes, Raiskup et al. observed stability of keratoconus one year after the cross-linking procedure using hypoosmolar riboflavin [**20**]. Thus, the use of hypoosmolar riboflavin helped in the application of CXL even to those corneas that could potentially be ineligible because of they had less than the minimum required thickness. Using the same protocol as established for the treatment of thin corneas, Hafezi et al. performed CXL in a patient with a corneal thickness of 268 microns [**21**]. There was a distinct progression of 1.9 D at 3 months and 2.3 D at 6 months respectively. With this, the authors concluded that a minimal pre-op stromal thickness of 330 microns needs to be respected for successful CXL procedure in thin corneas. In their study, Kaya et al. compared the thickness of cornea using an iso-osmolar riboflavin solution plus 20% dextran with a hypoosmolar riboflavin solution with no dextran [**22**]. The authors concluded that hypoosmolar riboflavin leads to a significant swelling effect during the procedure, however, the iatrogenic swelling effect might be short acting and not durable throughout the UVA application; thereby, doubting the safety and warranting the need for continuous pachymetry measurements during the procedure.

In the present study, a total of 16 patients underwent CXL using hypotonic riboflavin. A statistically significant improvement was noted in the treated eyes with a flattening of Kmax by 1.99 D at 1 year, with a p value of 0.002. No

significant difference in the endothelial cell density was found at any point when compared with the baseline (p=1). These results were consistent with the results published in the past.

A third protocol with accelerated CXL has been described recently, as an alternative stimulator of the procedure by using higher irradiance to the patients in order to decrease the time of exposure to radiation. Alternative photoactive cross-linking agents, effective with much abbreviated UV-A exposures can be used to achieve the reduction in exposure time. In the present study, we also tested this protocol. Out of a total of 18 patients, 15 completed the 12-months follow-up. At the end of the 12-months follow-up period, the mean K-value showed a decrease of 0.95 D from the mean baseline pre-op values. In spite of this difference of not being statistically significant (p=0.337), the procedure certainly helped stabilizing the progression of the disease. The procedure showed a significant decrease in the endothelial count on the 1st and the 3rd month follow-up, however, at the end of the 12-months period, the endothelial count improved and the difference was not significant when compared to the baseline (p=0.78). The endothelial count was at no point less than 10% of its baseline values, thereby not compromising the safety of the procedure.

In a randomized study of 138 eyes with keratoconus that underwent crosslinking at radiance of 3, 9, 18 or 30mW/ cm^2, Shetty et al. observed that while there was an improvement in the corrected distance visual acuity in all groups at 1 year, the change was not significant in the 30mW/ cm^2 group and most of the improvements occurred in the group with 18mW/ cm^2 radiance. They also noted that the flattening effect of crosslinking was reduced with higher irradiation and shorter treatment duration [**23**]. Few other studies have reported a decrease in the spherical equivalent and cylinder error in both accelerated and conventional crosslinking, but with no significant difference between the 2 groups [**24-27**].

Therefore, our study is unique, evaluating all the described protocols for CXL treatment in keratoconus.

There were several transient complications we encountered in our patients. Postoperative haze was one of the major adverse effects seen after the procedure. 5 patients in the isotonic group and 2 from the accelerated CXL group developed significant corneal haze after the procedure. However, it was transient and responded well to low dose steroids. In their study, Caparossi et al. observed stromal haze in 9.8% of the eyes after CXL [**17**]. In contrast, in the present study, a mild degree of haze was observed in all the patients undergoing CXL, which resolved with time.

Sterile infiltrates have been described in 7.6% of the treated eyes [**16**]. We encountered 2 cases of clinically significant sterile infiltrates postoperatively; one was associated with corneal oedema and an infiltrate paracentrally; the second eye developed subepithelial infiltrates (1 patient in the hypotonic group and 1 in the isotonic group). The lesions healed completely with scarring, which were away from the visual axis, and showed no effect on the visual acuity.

Keratoconus runs a variable course with different grades of severity and rates of progression to advanced disease. The associated difficulties in measuring outcome parameters that are reliable and reproducible, make randomized level 1 studies essential in order to evaluate the efficacy of CXL. Long-term studies also become crucial, to monitor the persistence of the CXL effect over a long duration. Overall, the results of our trial of CXL continue to support its efficacy in progressive keratoconus, with an improvement in Kmax values at 12 months. Additionally, no significant difference was noted at any point during the follow-ups, in the density of endothelial cells when compared with the baseline values; validating all three protocols to be safe. The associated risks with the protocols are minor compared to the associated morbidity of the advanced disease. Our findings suggested that CXL must be considered as a treatment modality in progressive keratoconus and the efficacy of new accelerated protocols helped to fasten the process with an acceptable safety profile. Also, the new protocols appeared to be as efficacious as the conventional protocols in arresting the progression of keratoconus.

Conclusion

CXL is a reliable and time proven treatment modality for keratoconus. The newer protocols with hypoosmolar riboflavin and accelerated CXL can reliably be used with adequate outcomes, being at par with the conventional technique. It is a safe technique without any

significant complications and with good patient acceptability.

Conflicts of Interest

Nil.

Sources of Funding

Nil.

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GENERAL ARTICLE

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Clinical and therapeutic particularities of congenital cataracts in pediatric patients with Down syndrome

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Abstract

Objective: This study aims to identify clinical and therapeutic surgical particularities and postoperative complications encountered in children suffering from Down syndrome and congenital cataract, as well as the existence of a correlation with associated systemic anomalies.

Methods: A retrospective interventional study that analyzes cases of congenital cataracts operated on a group of 14 children with Down syndrome, respectively on 26 eyes, was performed. The age of the children at the time of the surgery, the presence of associated ocular and systemic anomalies, the employed surgical technique, the frequency and the type of postoperative complications, were examined.

Results: Cataracts present at birth, with recommendations for surgical treatment, were rare among children suffering from Down syndrome, but their frequency increased with age. Most children had systemic anomalies, but also other, usually multiple, ocular anomalies. The rate of postoperative complications was higher than among children with congenital cataracts, but without Down syndrome. In six cases, more than one complication/ case was identified. It was not possible to establish a clear correlation between the number and type of the postoperative complication and the systemic anomalies, nor was it possible to establish a correlation with the functional visual outcomes, because those children had other important ocular anomalies as well.

Conclusions: Congenital cataracts with recommendations for surgical treatment in children suffering from Down syndrome have a low incidence, but an increase in frequency can be noticed with age. The recommended surgical technique is the one that involves maneuvers for the prevention of visual axis re-opacification. Per primam implantation is definitely indicated. The risk of postoperative complications is high, in terms of both frequency and number, with the possibility that more than one complication occurs, unrelated to a particular systemic anomaly, in one patient.

Keywords: congenital cataracts, Down syndrome, congenital cataract, surgical techniques, pseudophakia, postoperative complications

Introduction

Down syndrome or trisomy 21 is one of the best-known genetic syndromes. It is caused by the presence of an additional chromosome 21 in each somatic cell, with a total of 47 instead of 46 chromosomes per cell [**1**].

Worldwide, Down syndrome frequency is about 1 case in 700-1,000 live births [**2**] and its occurrence is dependent on multiple socio-cultural factors (birth rate, mother's age, the possibility of prenatal diagnosis, legality of abortion, etc.) [**3**]. Taking into consideration the frequency worldwide, we estimate that there are approximately 30,000 people with Down syndrome in Romania [**4**].

A number of general anomalies are present in patients suffering from Down syndrome: delayed psychomotor development, facial dysmorphia (epicanthic folds, absence of the eyelid groove, upward slanting of the eyes, the so-called mongoloid appearance), heart and gastrointestinal malformations, thyroid dysfunction (hypo- or hyperthyroidism), obstructive sleep apnea, visual disturbances [**5**].

The most common vision problems in children with Down syndrome are: blepharitis, Brushfield spots [**6**], strabismus, nystagmus, various refractive errors, partial or complete congenital cataracts and very rarely congenital glaucoma [**7**]. The association of congenital cataracts with Down syndrome is rare, the existing literature estimating a frequency of 1 per 40,000 live births, but the risk of association increases with age [**2**].

Lens transparency can be affected very rarely from birth, but starting from preschool age, crystalline lens opacities increase [**8**]. Cataracts may progress to forms that require surgery or may require only monitoring in the case of non-evolving crystalline lens opacities.

Methods

A retrospective interventional study performed at the Clinical Emergency Eye Hospital, Bucharest, Romania, analyzed a group of 14 children, respectively 26 eyes, with operated congenital cataracts and Down syndrome. The same eye surgeon operated those patients between 01/01/2010 and 01/01/2018.

The exclusion criteria were children with Down syndrome and cataracts caused by other factors, namely traumatic cataracts, complicated cataracts, pathological cataracts, congenital cataracts caused by intrauterine infections (rubella, mumps). Systemic and ocular disorders, other than congenital cataracts, were not considered exclusion criteria.

14 children diagnosed with Down syndrome and congenital cataracts with recommendations for surgical treatment, aged between 2 and 17 years, were included in this study. 12 of them presented bilateral cataracts and two, unilateral cataracts.

All patients were operated under general anesthesia by an anesthesiologist with pediatric anesthesia experience, after a careful anamnestic and clinical evaluation and a complete paraclinical examination, in connection with various associated systemic diseases (congenital heart malformation, thyroid dysfunction, obesity, gastrointestinal malformation, obstructive sleep apnea) [**9**].

Results

Out of the total of 14 children suffering from Down syndrome and congenital cataracts, 10 were males and 4 females, 12 had bilateral cataracts and 2 unilateral cataracts.

The ages the patients were diagnosed with congenital cataracts at, with recommendations for surgical treatment, which was performed (clearing the visual axis by removal of the cataract-affected lens), ranged from 2 to 17 years.

The associated systemic anomalies present in those children with Down syndrome were multiple, a situation that attracted increased attention from the entire medical team. All children presented developmental delay, 8 children - congenital heart malformations, 1 patient - gastrointestinal malformation, 4 patients - thyroid dysfunction (3 patients presented hypothyroidism and one thyroid hyperfunction), 5 patients - obesity and 1 patient - obstructive sleep respiratory dysfunction (**Table 1**).

Ocular anomalies, other than congenital cataracts, were the following: refractive errors [**10**] (20 eyes, of which 2 with severe myopia in

1 patient), nystagmus (8 eyes), strabismus (6 eyes), microphthalmia (1 eye), persistence of Cloquet's canal (2 eyes) and presence of pupillary membrane (1 eye).

The preoperative ophthalmological examination identified morphopathological forms of congenital cataracts, such as the following: lamellar cataracts – 7 cases, posterior polar cataracts – 3 cases (**Fig. 1**), nuclear cataracts – 6 cases, cerulean cataracts – 4 cases and total cataracts – 6 cases.

Table 1. Age, morphopathological forms and associated ocular and systemic anomalies

Case No.	Age	Sex	Morphology	Type	Systemic anomalies	Ocular anomalies
1	2	M	Total	Bilateral	None	OD: persistence of Cloquet's canal
2	2	M	Total	Bilateral	None	OD: microphthalmia
3	3	M	Nuclear	Bilateral	CHD*	OS: presence of pupillary membrane
4	5	M	Total	Bilateral	gastrointestinal malformation	OS: persistence of Cloquet's canal
5	5	M	Nuclear	Bilateral	CHD	OU: nystagmus
6	7	M	Nuclear	Bilateral	CHD, hypothyroidism	OU: strabismus
7	11	F	Posterior Polar	Unilateral	CHD	None
8	12	F	Lamellar	Unilateral	Hypothyroidism, obesity	None
9	14	M	Lamellar	Bilateral	Obesity, Sleep apnea	OU: nystagmus, strabismus
10	14	F	Lamellar	Bilateral	CHD, thyroid hyperfunction	None
11	15	M	Cerulean	Bilateral	CHD	OU: nystagmus
12	17	M	Lamellar	Bilateral	CHD, obesity	OU: strabismus
13	17	M	Posterior Polar	Bilateral	Hypothyroidism, obesity	None
14	17	F	Cerulean	Bilateral	CHD, obesity	OU: severe myopia nystagmus

**congenital heart defect*

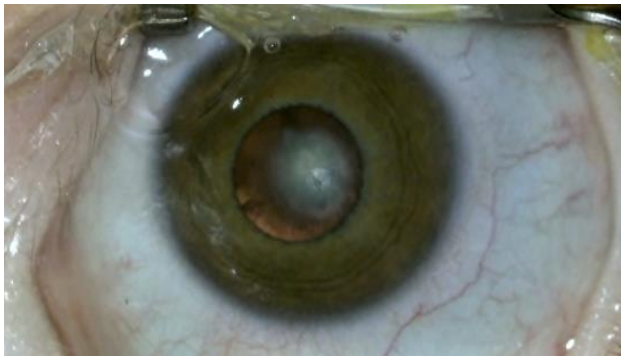

Fig. 1 Posterior polar congenital cataract in a patient with Down syndrome from our series

All 26 surgeries were performed by the same eye surgeon with pediatric cataract surgery experience. The surgical techniques were adapted to each case, depending on the patient's age, biometric measurements and associated eye anomalies. The chosen surgical treatment was related to the particularities of the children's eyes: small antero-posterior axis, more curved cornea, special elasticity of the capsular bag, intense inflammatory response to surgical aggressions [**11**].

In all cases, removal of cataract-affected lens, anterior and posterior capsulorhexis were performed, followed by per primam implantation of an IOL in 24 eyes, respectively 13 children (11 children with bilateral cataracts and 2 children with unilateral cataracts), one patient with bilateral cataracts remaining with bilateral aphakia (the patient presented severe myopia and severe horizontal nystagmus).

In this group of 26 operated eyes, 3 types of surgical methods were employed (**Table 2**). In 24 cases, per primam implantation was chosen, depending on the results of the preoperative biometric measurements. 4 eyes of patients aged

between 10 and 18 years were operated using a technique consisting in monofocal and toric IOL implantation in the capsular bag, posterior capsulorhexis and limited anterior vitrectomy.

When the integrity of the anterior vitreous allowed (10 operated eyes), a three-piece posterior chamber IOL implantation was preferred, using the optical capture method, without anterior vitrectomy. Using this surgical method, after performing the anterior and posterior capsulorhexis, the IOL haptics were positioned in the sulcus or in the bag, and the optical part in the capsular bag, but behind the posterior capsulorhexis [**12**]. The ages of the children operated by using this technique ranged from 5 to 18 years.

In children aged between 2 and 5 years (5 children, 10 operated eyes), the chosen surgical technique was BIL implantation (bag in the lens, a technique described by Marie-Jose Tassignon) (**Fig. 2**). This technique involves the implantation of a lens with a special design, after performing an anterior and posterior capsulorhexis, equal in size (5 mm), perfectly centered, so that the two remaining crystalline capsules are positioned between the lens haptics [**13**] (bag in the lens, compared to the classic technique – lens in the bag).

In one case, of a 17-year-old child, with severe myopia and nystagmus and already accustomed to wearing glasses, only the removal of the cataract-affected lens was preferred in both eyes, without IOL implantation. Postoperative refraction in this patient was a spherical equivalent = -4D.

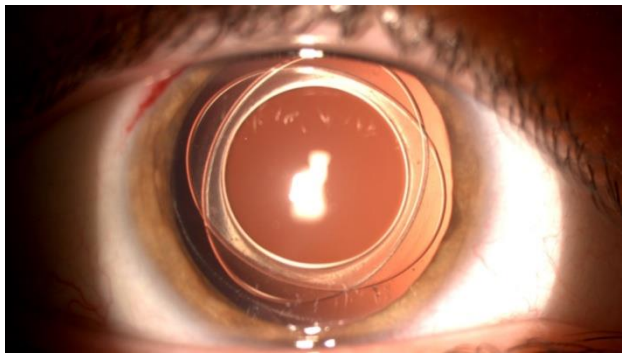

Fig. 2 Postoperative image of BIL implant in a 5-year-old patient with Down syndrome – our series

All postoperative patients received treatment with antibiotic eye drops and corticosteroid anti-inflammatory drugs for 3 months due to extremely intense postoperative inflammatory reactions. Postoperative complications included visual axis re-opacification – 7 cases (3 BIL cases, 4 non-BIL cases), secondary glaucoma – 7 cases (1 BIL case, 6 non-BIL cases), anterior pseudophakia subluxation – 1 case, severe inflammation – 6 cases (non-BIL), retinal detachment – 1 case (BIL). The described complications occurred in 16 operated eyes, respectively in 9 children. Of these, 7 children also presented systemic anomalies: 4 children with congenital heart malformation, 2 children with thyroid dysfunction and obesity and 1 child with gastrointestinal malformation.

Table 2. Surgical technique and postoperative complications

Case No.	Age	Surgical technique	Type	Postoperative complications
1	2	BIL	Bilateral	OS: Visual axis re-opacification
2	2	BIL	Bilateral	OD: Visual axis re-opacification
3	3	BIL	Bilateral	OD: Retinal detachment
4	5	BIL	Bilateral	OD: Severe inflammation, glaucoma
5	5	BIL	Bilateral	None
6	7	Non-BIL	Bilateral	OD: inflammation, glaucoma; OS: visual axis re-opacification
7	11	Non-BIL	Unilateral	OS: Visual axis re-opacification
8	12	Non-BIL	Unilateral	OS: inflammation, glaucoma
9	14	Non-BIL	Bilateral	OS: visual axis re-opacification, OD: inflammation, glaucoma
10	14	Non-BIL	Bilateral	OD: anterior lens dislocation, OS: glaucoma
11	15	Non-BIL	Bilateral	OD: visual axis re-opacification, OS: inflammation, glaucoma
12	17	Non-BIL	Bilateral	None
13	17	Non-BIL	Bilateral	None
14	17	Aphakia	Bilateral	OD: visual axis re-opacification, OS: inflammation, glaucoma

We could notice that 6 cases (eyes) developed more than one postoperative complication and all cases that showed severe inflammation also developed secondary glaucoma.

Visual axis re-opacification is the most common complication in pediatric cataract surgery and can compromise, sometimes completely, the treatment of amblyopia, that is the postoperative functional visual outcome [**14**]. For this reason, posterior capsulotomy is the current standard in congenital cataract surgery, a gesture that can considerably reduce the risk of visual axis re-opacification. Sometimes, anterior vitrectomy performed by employing a bimanual technique at the level of the limbus is necessary, because the remaining capsular epithelial cells can continue to proliferate, although curvilinear and continuous posterior capsulorhexis has been performed.

Postoperative complications encountered in the studied group were compared with data reported in other studies on pediatric patients with and without Down syndrome (**Table 3**) [**15-17**].

Table 3. Postoperative complications; case series with comparison to literature

	Down Syndrome			Without Down Syndrome
Complication	Our Study	Santoro et al. [**15**]	Gardiner et al. [**16**]	Tomkins et al. [**17**]
Visual axis re-opacification	7 (26.9%)	1 (20%)	10 (30.3%)	2 (2.2%)
Secondary glaucoma	7 (26.9%)	3 (60%)	5 (15.15%)	3 (3.3%)
Retinal detachment	1 (3.8%)	1 (20%)	2 (6%)	0
Severe inflammation	6 (23%)			1 (1.1%)
IOL decentration	1 (3.8%)			1 (1.1%)

Discussions

Congenital cataracts in children with Down syndrome account for 3%-5% of all cases of congenital cataracts. Patients usually have other ocular anomalies as well, which is why these children should be ophthalmologically monitored annually throughout childhood and adolescence, from birth, as recommended by various authors [**18**]. The frequency of congenital cataracts with recommendations for surgical treatment in these children increases with age. In our study, which included 14 patients, none of them was less than 2 years old and most were aged between 5 and 17 years (9 children). The specialized literature estimates the frequency of congenital cataracts associated with Down syndrome to range from <1% [**18**], 5% [**19**] to 50% [**20**]. Our view is that such different reports occur due to the fact that minor crystalline lens opacities, which are the most common crystalline abnormalities in pediatric patients with Down syndrome, are not reported by most authors. Other authors report frequencies of congenital cataracts ranging from 15% to 75%, but based on the study of patients with Down syndrome, regardless of age [**21**].

Modern surgical techniques require the circular and continuous capsulorhexis of the anterior and posterior lens capsule, which contributes significantly to reducing the frequency of visual axis re-opacification. The techniques that also use limited anterior vitrectomy for hyaloid removal, a procedure performing IOL optic capture or the BIL technique, provide greater safety against the risk of visual axis re-opacification. BIL technique is sometimes believed to be too difficult as a surgical technique because it requires a calibrated anterior and posterior capsulorhexis, and the using of femtosecond laser assisted capsulectomy facilitates the surgical step of capsulorhexis, and sizing is even more accurate [**13**].

Regardless of age, there are recommendations for per primam artificial lens implantation (in our study, 24 artificial lenses were implanted per primam), because these children have great difficulties in wearing spectacles or contact lenses [**22**]. Most of the

authors consulted consider the implantation of a pseudophakia a must when there are no contraindications: congenital glaucoma, microphthalmia, corneal dystrophies, absence of the photomotor reflex. The choice of dioptric power still remains unpredictable, although it is based on increasingly advanced calculation formulas that involve corrections depending on the child's age [**23**]. In the absence of general anesthesia, biometric measurements in these patients can often be only approximate or even impossible, due to lack of collaboration. When aphakia is chosen as a surgical solution in children under 5 years of age, with bilateral congenital cataracts, per secundam implantation can be considered, and until then the correction is made with spectacles [**24**]. The diopter value of the lenses can be correctly adjusted according to the objective refraction, which changes with age, being able to correct both near and distance vision.

Pseudophakia is the best therapeutic solution for the subsequent treatment of amblyopia, which must be initiated as soon as possible postoperatively [**25**]. In both bilateral and unilateral cataracts, the treatment of amblyopia must be vigorous, sustained and on long term, requiring a good collaboration with the young patient and his/ her family, an aspect difficult to achieve in patients suffering from Down syndrome.

Severe postoperative complications are more numerous than in pediatric patients with congenital cataracts and without Down syndrome, according to data provided by specialized studies (**Table 3**). In the patients we studied, the rate of postoperative complications varied between 3,8% and 26,9%, depending on the type of complication, these percentages being similar to those found in other studies, except for retinal detachment (we identified a very low rate - 3,8%) (**Table 3**). Of the 11 children with severe postoperative complications, 9 also had systemic anomalies. Children with Down syndrome have several health problems that can influence the healing process after surgery. The specialized literature shows an increased rate of complications for other types of surgery, such as cardiovascular surgery, in patients with Down syndrome [**26**].

One of the most important complications is visual axis re-opacification, which might interfere with postoperative visual rehabilitation and could induce deprivation amblyopia. That is the reason why we often perform an anterior vitrectomy. When using the BIL technique, an anterior vitrectomy is not necessary, unless a persistent fetal vascularization is present, because the tight fusing of capsular blades in the interhaptic groove of the artificial lens prevents the escape of the epithelial cells from the capsular bag and their proliferation. If possible, the anterior vitreous membrane should be kept, for it is a barrier between the anterior and posterior segments of the eye.

Secondary glaucoma is the most severe long-term complication. The reported incidence varies, but the risk is higher when the patient is younger, when cataract is associated with other ocular anomalies, severe postoperative inflammations and in the eyes that have been left aphakic [**27**]. In this study, we found 7 eyes with secondary glaucoma, 6 of them presenting aggressive anterior chamber inflammations as well.

Postoperative inflammations are more severe than in adult cataract surgery, and the incidence is higher in pediatric cataract cohort with Down syndrome than without Down syndrome. Inflammation predisposes to visual axis opacification, posterior synechiae, macular edema and secondary glaucoma. In our study, 6 children developed aggressive postoperative inflammation, never as a single complication [**28**].

Increased postoperative complications, influence the functional visual outcome. Complications encountered in this study included visual axis re-opacification, severe inflammation, secondary glaucoma, anterior pseudophakia subluxation and retinal detachment, which required other surgical procedures performed under general anesthesia in these sensitive patients, who frequently have heart anomalies. It was not possible to establish a clear link between the type and number of associated systemic and ocular anomalies and postoperative complications, the group of studied patients being too small to allow such a correlation.

Conclusions

The association of congenital cataracts with Down syndrome, with recommendations for surgical treatment, is rare, but we believe that the risk of association increases with age. In our study, we did not have any patient under 2 years old. The high frequency in the specialized literature (15%-75%) is based mainly on adult cases. It is possible to improve visual acuity through surgery in children with congenital cataracts and Down syndrome, even if followed by an increased risk of single or multiple postoperative complications. In our study, postoperative complications ranged from 3,8% for retinal detachment and IOL decentration to 26,9% for visual axis re-opacification and glaucoma. Per primam implantation is the best solution for these patients, even at a young age (2 years old), because they have major difficulties in handling contact lenses or glasses. Aphakia may also be an acceptable solution to bilateral cataracts in patients with severe myopia, as it allows them to have a good near vision. The impact on psychomotor development following surgical treatment of congenital cataracts in pediatric patients suffering from Down syndrome may be the subject of future studies.

Disclosures
None.

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GENERAL ARTICLE

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Fellow eye comparison between alcohol-assisted and single-step transepithelial photorefractive keratectomy: late mid-term outcomes

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Abstract

Objective: To compare late mid-term results of two different surgical approaches of surface excimer laser ablation for myopic and astigmatic errors in contralateral eyes of the same patients.

Methods: Prospective cohort study. A photorefractive keratectomy technique was performed on the right eye and single-step transepithelial photorefractive keratectomy on the left eye of the same patient, in 2012. Postoperative uncorrected and corrected visual acuities, manifest refraction, contrast sensitivity, objective scatter index, tear film stability assessed by serial measurements of objective scatter index and aberrometry as well as occurrence of haze, were compared between groups of eyes.

Results: Thirty-two eyes of 16 patients with a mean time of follow-up of 35.2 +/ - 5.0 months (range 30-46 months) were evaluated. No significant differences were observed in postoperative results (visual acuity, spherical equivalent, defocus equivalent, higher-order aberrations, objective scatter index, tear film stability and contrast sensitivity). Contrast sensitivity tended to be better in transepithelial photorefractive keratectomy technique, under photopic lighting conditions without glare and mesopic conditions both with glare and without glare, however, no statistically significant differences were found. No eye presented corneal haze at the last examination.

Conclusion: No statistically significant differences in visual acuity, refractive results, contrast sensitivity, objective scatter index, tear film stability or ocular aberrometry were observed between the two surface ablation techniques.

Keywords: refractive surgical procedures, photorefractive keratectomy, excimer laser, visual acuity, contrast sensitivity

Introduction

Surface ablation techniques, such as Alcohol-assisted Photorefractive Keratectomy (PRK), Transepithelial Photorefractive Keratectomy (TransPRK) and Laser-Assisted Subepithelial Keratomileusis (LASEK), have shown to be effective and safe alternatives for refractive corrections and without significant differences neither between them nor when comparing them with the techniques that include the cutting of a corneal flap [**1-4**]. Laser epithelial debridement previous to ablation of the stroma has been used from early 1990, but the technique was not popularized because it was a two-step procedure and, in addition, either the laser de-epithelization was not complete and a supplementary mechanical removal of the remnant epithelium was needed or the surgeon had to use various subtle signs (such as the dissipation of the autofluorescence of the epithelium) to determine when epithelial ablation was complete [**5-10**]. It was not until 2009 that a system was developed to perform epithelial and stromal ablation in one step in a predictable manner (Schwind Amaris, Schwind eye-tech-solutions GmbH, Kleinostheim, Germany) and this approach has been reported to have similar refractive results as PRK and possibly some advantages like less post-operative pain, less epithelial erosion-related symptoms, shorter epithelial closure time and in some studies less corneal haze [**11-26**]. The purpose of the present study was to evaluate the outcomes, comparing alcohol-assisted PRK and single step TransPRK techniques, considering refractive results, aberrometry, contrast sensitivity test, Objective Scatter Index (OSI, measured by AcuTarget®, Visiometrics SL, Cerdanyola del Vallès, Spain) and tear film stability assessed by serial measurements of OSI with a late mid-term follow-up time (minimum 30 months and a mean of 35.2 +/ - 5.0 months) using a contralateral (fellow eye) approach.

Materials and methods

This prospective cohort study included patients with myopic refractive errors, who underwent ablation on the surface of the cornea with excimer laser using two different techniques: PRK technique in the right eye and single-step TransPRK in the left eye, in 2012, at a tertiary ophthalmological center in Bucaramanga, Colombia, by a single surgeon (VG). The study followed the tenets of the Declaration of Helsinki and was approved by the institutional ethics committee.

Patients with preoperative CDVA better than 20/ 30, older than 19 years of age, with refractive stability at least during one year and who had discontinuously worn soft or hard contact lenses for at least 2 and 4 weeks (respectively) prior to preoperative assessment, were included in the study.

Patients with history of autoimmune diseases, planned ablation depth greater than 100 μm and pachymetry thinner than 490 μm, were excluded. Patients with findings of corneal ectasia at corneal tomography, amblyopia or other ocular pathologies were not recruited either.

Surgical procedures:

All surgical procedures were performed by a single surgeon (VG). In PRK technique, after proparacaine (5 mg/ ml) was instilled on the eye, a well filled with ethyl alcohol (200 mg/ mL) was placed on the central 9.5 mm of the cornea for exactly 30 seconds and afterwards the cornea was flushed with balanced saline. Then, an epithelial debridement was performed using an angled spatula.

In single step TransPRK technique, laser ablative surgery was performed by removing sequentially in one step corneal epithelium and stroma using the algorithm included in the Schwind Amaris platform (ablating 55 microns centrally, and 65 microns peripherally, in addition to the refractive stromal ablation, which corresponded approximately to epithelial thickness).

In both groups of eyes, laser photoablation was done with the Schwind Amaris 750S excimer laser (Schwind eye-tech-solutions GmbH, Kleinostheim, Germany) with a pre-established optimized algorithm that aimed to maintain the preoperative levels of higher order aberrations basically unaltered, avoiding induction of new aberrations (mainly spherical aberration), known as "Aberration-Free™" ablation algorithm. The optical zone was 6.5 mm in all eyes.

Mitomycin C 0.2 mg/ mL was applied on the ablated stroma for 30 seconds in all the eyes, followed by irrigation with balanced saline solution, and then application of moxifloxacin (5 mg/ ml). A silicone hydrogel contact lens was finally placed on the cornea for 5 to 6 days. Postoperatively, patients received topical moxifloxacin, prednisolone and carboxymethylcellulose.

Outcome measures:

The last evaluation was performed on patients between 30 and 46 months after the surgery, and the postoperative results assessed at the last check-up visit were analyzed. Outcome measures included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction, contrast sensitivity, Objective Scatter Index (OSI, measured by AcuTarget®) [**27-29**], tear film stability assessed by serial measurements of OSI [**30**], aberrometry, and safety and efficacy indices, which were compared between the study groups. Presence and grading of stromal haze were also analyzed.

Visual acuity (VA) was measured with an ETDRS chart, and then converted to LogMar notation for statistical analysis. Refractive results were analyzed using both spherical equivalent (SE) and defocus equivalent calculated from the manifest refraction [**31,32**].

The efficacy and safety indices were calculated as it follows:

- *Safety index:* The ratio of postoperative CDVA, previously converted to decimal notation, to preoperative CDVA, previously converted to decimal notation, was determined for each eye. Then, the mean and standard deviation of those values were found for each group (PRK and single-step TransPRK).
- *Efficacy index:* The ratio of postoperative UDVA, previously converted to decimal notation, to preoperative CDVA, previously converted to decimal notation, was determined for each eye. Then, the mean and standard deviation of those values were found for each group (PRK and single-step TransPRK).

Postoperative contrast sensitivity was measured using a system with microprocessor-controlled glare and luminance level (Optec® 6500, Stereo optical Company Inc., Chicago, IL, USA) under mesopic (3 cd/ m^2) and photopic lighting conditions (85 cd/ m^2), with glare and without glare.

Additionally, postoperative ocular aberrometry (KR-1W Wavefront Analyzer®, Topcon, Tokyo, Japan) was analyzed.

The intraocular light scatter was quantified postoperatively through the optical quality analysis system AcuTarget® (Visiometrics SL, Cerdanyola del Vallès, Spain) to calculate the initial Objective Scatter Index (OSI) [**27-29**], then it was measured every 0,5 seconds for 20 seconds after in order to evaluate tear film quality [**30**].

Statistical analysis:

Statistical analysis was performed using Microsoft Excel® and Stata VE 12.0® with a significance level of 5%. Qualitative variables were summarized by absolute and relative frequencies. In contrast, quantitative variables were expressed by measures of central tendency (mean) and dispersion (standard deviation) according to the frequency distribution. Normality was considered by evaluating graphic behavior, asymmetry and kurtosis. Furthermore, a descriptive analysis was carried out to identify potential differences among preoperative findings between both groups using a Student's t-test. Higher order aberrations, objective scatter index (OSI) and tear film stability values were compared using the Student's t-test. Proportion of eyes achieving a given level of visual acuity were compared using the Fisher exact test.

Results

Sixteen subjects who underwent PRK in the right eye and single step TransPRK in the left eye, were evaluated. Mean age was 29.93 +/ - 7.58 years (range 20-53) and average follow-up time was 35.2 +/ - 4.9 months (range 30-46). 10 patients (62.5%) were men.

Preoperative and postoperative visual acuity and refractive data are detailed in **table 1**. Mean spherical equivalent (SE) in PRK-treated eyes was -2.11 ± 0.91 D, decreasing after the surgery to -0.23 ± 0.65 D. Similarly, TransPRK-treated group changed from a preoperative SE of -2.10 ± 0.71 D, to -0.05 ± 0.34D. Postoperative defocus equivalent values were 0.48 +/ - 0.64 D and 0.33 +/ - 0.4 D in the right and left eyes,

respectively. No statistically significant differences were observed either in the postoperative SE (p= 0.39), defocus equivalent (p= 0.41) or in the surgically induced change on those values (p values of 0.65 and 0.90) at the last follow-up examination between the two groups of eyes.

Table 1. Preoperative and postoperative parameters in PRK and single-step TransPRK treated eyes

	Preoperative findings					Postoperative findings					Difference pre vs. postoperative		
Parameter	PRK (n=16 eyes)		TransPRK (n=16 eyes)		p value	PRK (n=16 eyes)		TransPRK (n=16 eyes)		p value	PRK (n=16 eyes)	TransPRK (n=16 eyes)	p value
	Mean ± SD	Range	Mean ± SD	Range		Mean ± SD	Range	Mean ± SD	Range		Mean+/- SD	Mean +/- SD	
UDVA LogMAR (Snellen)	0.79 ± 0.27 (20/147)	0.17 - 1.3	0.78 ± 0.24 (20/140)	0.39 - 1.3	0.913	0.05 ± 0.12 (20/23)	0.39 - 0 (20/20 - 20/50)	0.01 ± 0.03 (20/20)	0.09 - 0 (20/20 - 20/25)	0.206	0.74+/- 0.28	0.77+/- 0.23	0.743
CDVA LogMAR (Snellen)	0.006 ± 0.02 (20/20)	0 - 0.09 (20/20 - 20/25)	0.006 ± 0.02 (20/20)	0 - 0.09 (20/20 - 20/25)	1.000	0 (20/20)	0 (20/20)	0 (20/20)	0 (20/20)	1.000	0.006+/-0.02	0.006+/-0.02	1.000
Sphere (D)	-1.56 ± 1.03	-4.00 - 0	-1.66 ± 0.74	-2.75 - 0	0.755	-0.08 ± 0.63	-1.5 - 0.75	0.09 ± 0.37	-0.75 - 0.75	0.366	-1.48+/-0.91	-1.75+/-0.73	0.362
Cylinder (D)	-1.09 ± 1.13	-3.5 - 0	-0.80 ± 0.77	-3 - 0	0.403	-0.30 ± 0.41	-1.25 - 0	-0.28 ± 0.38	-1.25 - 0	1.000	-0.81+/-1.1	-0.52+/-0.62	0.366
Spherical equivalent (D)	-2.11 ± 0.91	-4.45 -0.75	-2.10 ± 0.71	-3.5 -1.0	0.973	-0.23 ± 0.65	-1.6 - 0.25	-0.05 ± 0.34	-0.88 - 0.25	0.390	-1.89+/-0.77	-2.01+/-0.71	0.65
Defocus Equivalent (D)*	2.66 ± 1.10	1 - 5.5	2.45 ± 0.87	1 - 4.25	0.554	0.48± 0.64	0 - 2	0.33 ± 0.40	0 - 1.25	0.410	2.17+/-0.97	2.13+/-0.84	0.902

** Defocus Equivalent = Absolute value of spherical equivalent + ½ absolute value of cylinder.*

75% of the eyes in the PRK group achieved postoperative UDVA of 20/ 20 at the last examination, and 87.5% of TransPRK-treated eyes reached UDVA of 20/ 20 postoperatively. No statistically significant differences were observed among the proportions of the eyes reaching specified cumulative levels of UDVA at the last postoperative follow-up (**Fig. 1**).

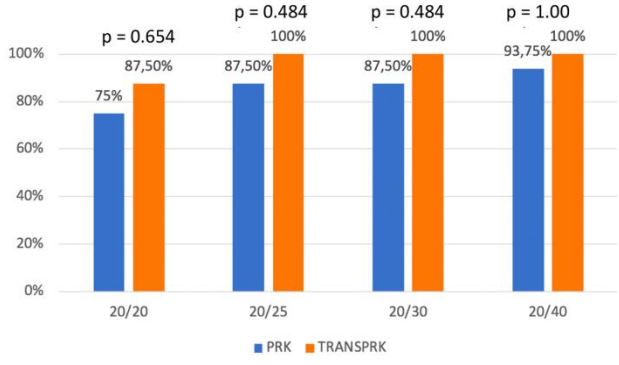

Fig. 1 Late mid-term visual results in PRK and TransPRK treated eyes: Cumulative percentages of eyes attaining specified cumulative levels of UDVA at the last postoperative follow-up (mean= 35.2 months) in the 2 groups. No statistically significant differences were found (p values shown in the figure calculated using exact Fisher test)

Efficacy index was 0.93 +/ - 0.19 and safety index 1.03 +/ - 0.09, for the PRK treated eyes, and 0.99 +/ - 0.05 and 1.02 +/ - 0.06, respectively, for TransPRK treated eyes. No statistically significant differences were observed between the two groups either in the efficacy (p=0.243) or in the safety indexes (p=0.569).

The postoperative Objective Scatter Index (OSI) value at the last visit exhibited no significant differences between the two groups of eyes (p=0.734): in right eyes, treated with PRK, it was 0.62 +/ - 0.42 (range 0.1-1.6) and in left eyes, treated with TransPRK, 0.69 +/ - 0.72 (range 0.2-3.2). Tear Film stability (OSI measured during 20 seconds) yielded a mean of 1.44 +/ - 0.92 (range 0.45- 3.14) in the PRK-treated group of eyes and 1.19 +/ - 0.73 (range 0.48-2.65) in eyes treated with TransPRK, exhibiting no significant differences (p = 0.40).

No statistically significant differences were found with regard to postoperative contrast sensitivity between the two groups of eyes (**Fig. 2**). However, contrast sensitivity under photopic lighting conditions without glare, as well as in mesopic conditions with glare and without glare, revealed a slightly better performance in TransPRK-treated compared to PRK-treated eyes (**Fig. 2**), but as mentioned, the differences were not statistically significant (**Fig. 2**).

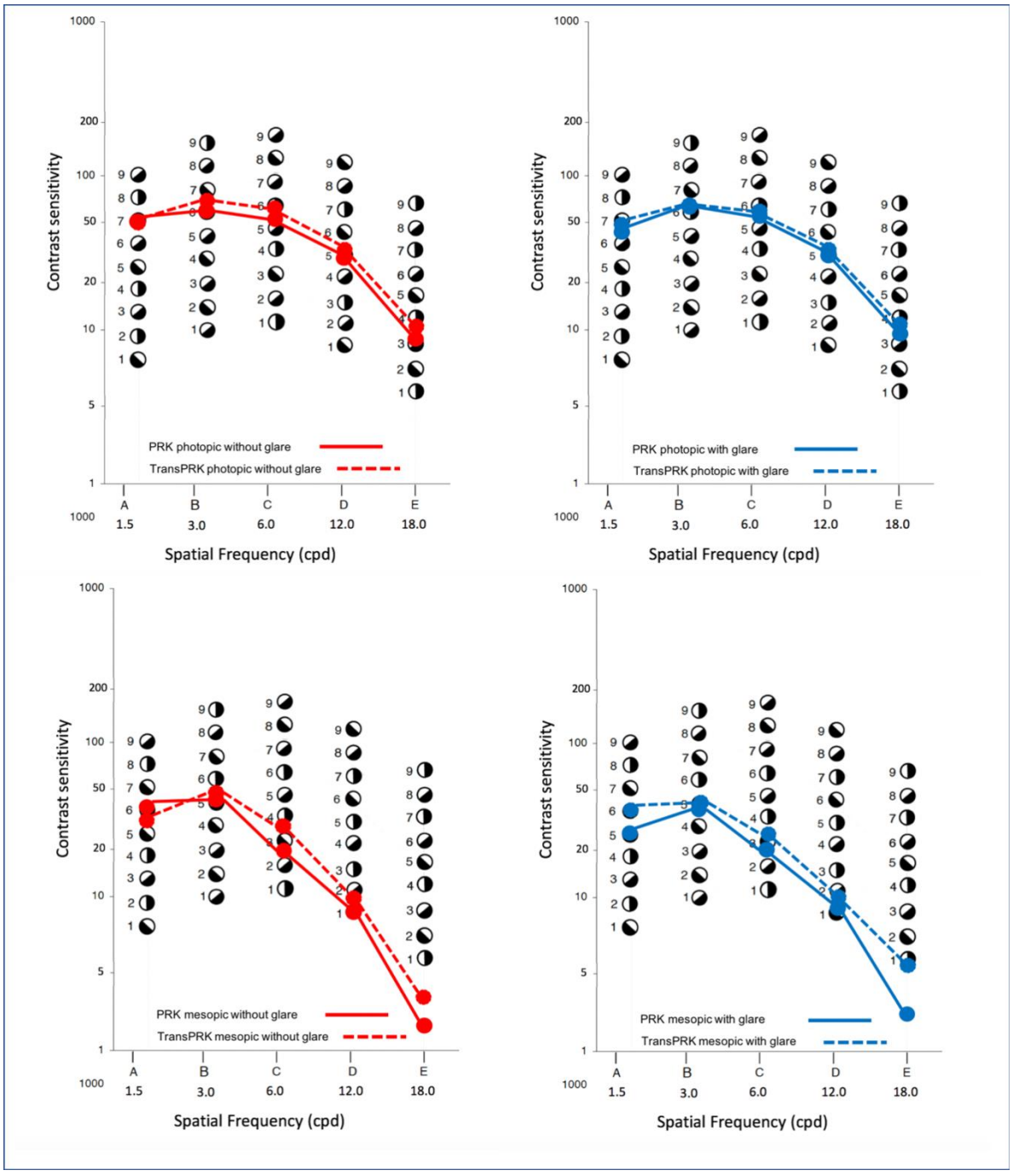

Fig. 2 Contrast sensitivity at spatial frequencies of 1.5, 3.0, 6.0, 12.0 and 18.0 cycles per degree at photopic (superior row) and mesopic (inferior row) conditions, without (left) and with glare (right), at the last follow-up examination (mean:35.2 months after surgery). No statistically significant differences were found

Postoperative aberrometry measures at 35.2 months of follow-up (with natural pupil size) are shown in the **table 2**. No statistically significant differences were observed between the two groups. However, root mean square (RMS) of coma, spherical aberration, and that of total higher order aberrations had values slightly lower in the TransPRK-treated eyes, but as mentioned, without reaching statistical significance.

Table 2. Postoperative aberrometry measurements (Topcon's KR-1W Wavefront Analyzer®)

Parameter	PRK (n=16 eyes)		TransPRK (n=16 eyes)		
	Mean	Range	Mean	Range	p value
Pupilar diameter	5.82 ± 0.65	4.55 to 7.20	5.99 ± 0.66	4.90 to 7.13	0.1332
Coma (µm)	0.27 ± 0.15	0.06 to 0.12	0.222 ± 0.171	0.04 to 0.56	0.1684
Trefoil (µm)	0.19 ± 0.15	0.06 to 0.56	0.223 ± 0.18	0.01 to 0.59	0.1717
Spherical aberration (µm)	0.07 ±0.12	-0.11 to 0.32	0.058 ± 0.137	-0.12 to 0.28	0.3227
RMS Higher order aberrations (µm)	0.45 ± 0.21	0.20 to 0.90	0.435 ± 0.229	0.19 to 0.87	0.8149
RMS Total aberrations (µm)	0.98 ± 0.47	0.44 to 2.10	0.934 ± 0.447	0.37 to 1.68	0.3936

RMS: Root mean square

Discussion

This study assessed postoperative visual outcomes after excimer laser surface ablation for correction of myopic refractive errors (both quantitative and qualitative), with an average follow-up time of 35.2 months (late mid-term), comparing PRK and single-step TransPRK techniques in contralateral eyes of the same patients.

No statistically significant differences either in visual acuity or in refractive results (represented by sphere, cylinder, spherical equivalent and defocus equivalent) between PRK and TransPRK, were found, as already reported by other previously published studies [**3,4,11-13,17,19,23,25**]. However, other researchers have reported some better results using TransPRK (especially with the new refinements of the software) including better UDVA and CDVA results [**14,18,20,21,24**]. On the other hand, in 2015, Shapira et al. evaluated 3417 patients, showing that PRK-treated eyes demonstrated better refractive outcomes at 6 and 12 months after surgery ($P < .0001$). Nonetheless, the TransPRK was not a one-step surgery (as done using the Amaris Schwind system in the present study) but a two steps procedure with a different system, first using a PTK mode ablation at a depth of 50 µm followed by mechanical completion of deepithelization with a sponge [**15**].

The present study used the comparison approach between the two eyes of the same individual, and like, in the four published contralateral studies, which had a maximum postoperative follow-up of one year, there were no significant differences in refraction and visual results between PRK and one-step TransPRK treated eyes [**12-14,23**].

It is noteworthy that, although no differences were observed in the mean of UDVA between groups, according to cumulative visual acuity, in the present fellow eye study, there were lower percentages of eyes in the PRK group with UDVA better than 20/ 30 compared to TransPRK, although, as previously indicated, the differences were not statistically significant (**Fig. 1**). This finding was in contrast to the data reported by Luger et al., also in a contralateral eye study, who reported slightly more with visual acuities better than 20/ 20 at one year in the PRK-treated eyes [**12**].

Marginally better postoperative contrast sensitivity under photopic without glare, and mesopic conditions with glare and without glare in TransPRK-treated eyes were observed in the present study (**Fig. 2**) but differences were non-significant. Similarly, in their fellow-eye study, Luger et al. did not find any statistically significant difference in contrast sensitivity [**12**].

A slightly better performance in higher order aberrations at 35.2 months of follow-up in the TransPRK treated eyes was found in the present study, but it did not reach statistical significance. Similarly, no differences in aberrometry has been published [**13,22**].

In the present study, both contrast sensitivity and aberrometry were measured only at the last check-up visit after the surgery, so we could not evaluate the surgically induced change on those values, and could therefore induce a non-intentional bias if some of the eyes in one group had better or worse values of these parameters before surgery. This is a weakness of the present study. However, on the other hand, being a fellow-eye study, it is very probable that

both eyes of the same patient had very similar characteristics on these parameters before the procedure.

Intraocular scattering measurement, the objective scatter index (OSI), has been a recently implemented parameter for the determination of optical quality and has been used with that purpose after refractive surgery [**27-30**]. The OSI as determined by the AcuTarget® (Visiometrics SL, Cerdanyola del Vallès, Spain) using a laser (wavelength of 780 nm) with a double-pass technique (i.e. recording images from a single point source of light, after reflection in the retina and a double pass through transparent optic ocular media), represents the amount of scattered light. Some studies have shown its impairment initially after corneal procedures [**28**]. According to our knowledge, there has been no previous study comparing OSI in PRK and TransPRK. In our cases, we found no difference in the late mid-term postoperative OSI between groups of PRK-treated and TransPRK treated eyes. When determining the tear film stability by sequentially measuring OSI during 20 seconds of evaluation, results were slightly better in TransPRK-treated group, but the difference again was not statistically significant.

With regard to corneal haze found at the late mid-term when the patients were examined the last time (i.e. between 30 and 46 months after surgery), none of the eyes showed clinically evident haze.

The small differences, not statistically significant, that we found in some postsurgical parameters when comparing eyes treated with PRK and those treated with single step Trans-PRK, were more probably not clinically significant either. Consequently, both techniques can be considered effective and safe for the correction of moderate myopic and astigmatic errors. Recently, Adib-Moghaddam et al. published a complete review on single-step TransPRK, and their conclusions are similar [**26**].

A limitation of the present study is the limited number of patients. Since the number of patients was small, the result was that although some of the observed differences could be real, they did not reach statistical significance. However, the importance of this work is based on the comparison of two different techniques in contralateral eyes, which allowed the homogenization features of studied samples, since many biological variables remained constant in both eyes, expecting to allow more reliable comparison in outcomes that represent the postoperative behavior of refractive surgery (v.gr. in contrast sensitivity performance), and in addition, to have the longest postoperative follow-up time that has been published in this type of comparative study (35.2 months) [**12-14,23**].

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This study did not receive any specific funding.

Compliance with Ethical Standards

The authors declare that they have no competing interest. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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GENERAL ARTICLE

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Significance of metastatic topography for the immunotherapy of cutaneous and ocular melanomas

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Abstract

PD-1 is expressed on the surface of activated T lymphocytes and belongs to the category of negative immune stimuli. Its blocking stimulates the immune response to tumor antigens. Ocular melanomas represent 3-4% of the total melanomas and have metastatic potential, especially to the liver but also to the lungs, skin, and bones. In the case of metastatic melanoma, immunotherapy has a unique role due to the lower frequencies of BRAF mutation in choroidal melanomas and consecutive exclusion from treatment with specific BRAF tyrosine kinase inhibitors. A retrospective observational study was performed in 42 patients who received immunotherapy (IT) with nivolumab for cutaneous and ocular metastatic melanomas, aimed at highlighting the association between the topography of metastases and the duration of immunotherapy until progressive disease. The results indicated the presence of liver metastases as a negative predictive factor for IT duration in patients with melanoma and the presence of lymphatic metastases as a predictive factor for longer IT in patients with melanoma under 65 years old.
Keywords: melanoma, ocular, nivolumab, metastases

Introduction

The efficient functioning of the immune system requires PD-1 ("programmed death – 1"), which is a surface receptor expressed on activated T lymphocytes. PD-1 belongs to the category of negative immune stimuli. Nivolumab binds with high affinity to the PD-1 receptor and prevents interaction with PDL-1 and PDL-2 ligands, stimulating the memory immune response to tumor antigens and the proliferation of antigen-specific T cells [**1,2**].

The mean half-life of nivolumab was estimated at 25 days, which means at least 12 weeks of treatment until a serum plateau concentration is reached [**3**]. Other estimates

provide half-lives for nivolumab of 12-20 days [**4**].

Degradation of anti-PD-1 antibodies appears to be achieved by mechanisms of proteolytic degradation belonging to liver cells or reticuloendothelial system. Degradation rates are unaffected by age, tumor size, renal dysfunction, or mild liver dysfunction. The higher rate of degradation of these antibodies correlates with a weaker response to treatment. The low level of albuminemia at the start of treatment is correlated with increased clearance of nivolumab and a weaker therapeutic response [**5-7**].

Administration of a single dose of 0.3 mg/kg of nivolumab results in a PD-1 receptor occupancy level of 65% while a dose of 3.0 mg/kg results in an occupancy level of only 69% and a dose of 10 mg/kg induced an occupancy level of 70% (estimates valid for circulating cells) [**8**].

The effects of neutralizing antibodies under treatment remain to be evaluated. Anti-nivolumab antibodies occur in 11-37.8% of the treated cases - especially in combination with ipilimumab - and neutralizing antibodies have been documented in up to 4.6% of the cases [**9**].

Risk factors for the development of ocular melanomas are: Caucasian race, light eyes (blue, green), advanced age, the association of cutaneous dysplastic nevus syndrome, oculodermal melanocytosis, presence of cutaneous or ocular nevus, exposure to natural or excessive artificial light [**10**].

Ocular melanomas represent 3-4% of all melanomas. Topographically, ocular melanoma may have as a starting point the choroid (most commonly) and uvea (especially iris). The incidence of the disease is 5 cases per year per 1 million population, and the cell of origin is the melanocyte. Ocular melanoma has metastatic potential, especially to the liver but also to the lungs, skin and bones. Sometimes, metastases are detected years after the primary disease.

The symptoms of ocular melanomas are not always present and may include: photopsia, unilateral blurry vision, diplopia, pupil irregularities, loss of peripheral vision, a growing dark spot on the iris, pain, foreign body sensation, metamorphopsia (distortion of vision) [**11**].

The rare frequency of BRAF driver mutation in choroidal melanomasis particular for ocular melanoma. The situation of iridal melanoma is different because it proves a prevalence of BRAF mutation of about 50%, comparable to the frequency of the same mutation among cutaneous melanomas of 60-65% [**12**].

Materials and methods

A retrospective observational study included patients receiving immunotherapy (IT) with nivolumab for cutaneous and ocular metastatic melanomas, which aimed to highlight the associations between the topography of metastases and the duration of immunotherapy.

Thus, 2241 hospitalizations (especially day-care) were processed for the administration of immunotherapy belonging to 220 distinct persons between 28th of June 2017 and 20th of March 2020. Among the 220 cases, 42 cases of melanoma were identified (with 527 IT administrations) of which 2 cases of ocular melanoma (4.7% of the treated metastatic melanomas).

Since the distribution of immunotherapy durations is not normal (Gaussian), the Mann-Whitney U Test (MWUT) was applied for sets of individual variables and the correlations between IT duration and various parameters were verified with Cox Proportional Hazards Survival Regression (CPHSR) which takes into account both cases still in treatment as well as those out of treatment.

Results

For the entire group of 220 patients, the mean duration of immunotherapy (discontinued due to lack of clinical benefit/disease progression/intolerance) is 163.60 days. Remarkably, 95 cases (of which 18 with melanoma) are still under treatment (they have been administered over the last 3 weeks compared to the cut-off date) (**Table 1**). Single-dose patients were counted with 0 duration of treatment. The average duration of treatment is 194.55 days if only cases with at least two administrations are considered. The maximum duration recorded is 783 days (patient with melanoma, treatment still in progress).

Table 1. Distribution of cases by cancer site

Type of cancer	Number of cases	Percentage	Average age	Number of cases still in treatment	Percentage
lung	154	70,0	61,97	66	69,5
melanoma	42	19,1	60,90	18	18,9
renal	24	10,9	59,17	11	11,6
Total cases	**220**			**95**	

The distribution of the duration of immunotherapy is a particular one, the curve of the number of cases that have gone through a specific duration of immunotherapy has a hyperbolic aspect with a secondary peak in the area of 400-449 days (**Table 2**). Out of the 220 cases, 35 underwent only one administration, and the other 21 did not exceed one month of treatment (**Fig. 1**). The median duration of treatment was 89 days

Table 2. Distribution of cases by the duration of immunotherapy

IT duration (days)	<50	50-99	100-149	150-199	200-249	250-299	300-349	350-399
number of cases	81	35	26	12	13	7	7	4

IT duration (days)	400-449	450-499	500-549	550-599	600-649	650-699	700-750	750-799
number of cases	13	7	3	4	4	1	0	3

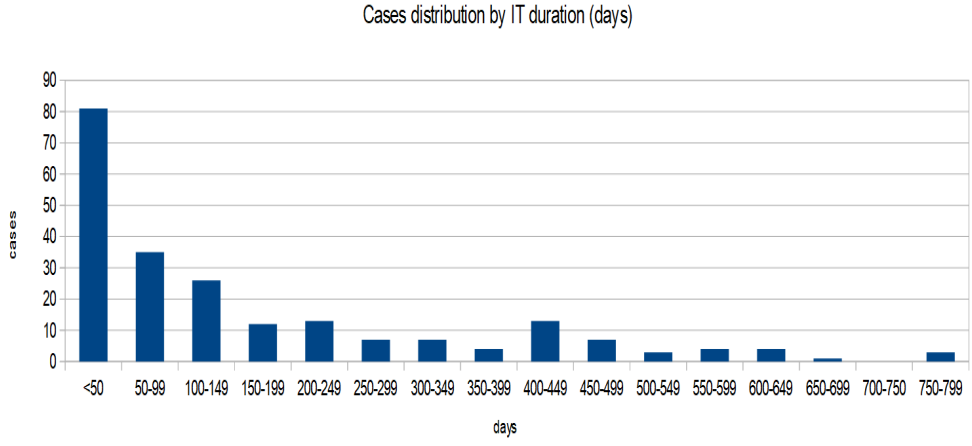

Fig. 1. Distribution of cases by the duration of immunotherapy

The mean duration of immunotherapy was longer for melanomas and renal cancer compared to lung cancer (considering only cases initiated after reimbursement of treatment for all locations) (**Table 3**). MWUT revealed a value of p = 0.05155 extremely close to the statistical validation of the significant difference in the individual durations of immunotherapy in melanomas and lung cancers.

Table 3. The average duration of immunotherapy according to the cancer site

Initiated cases for all locations	Average IT duration (days)
lung cancer	146,13
melanoma	209,75
renal	202,57

The 42 cases of melanoma were divided into 26 males and 16 females (61.9% and 38.1% of the cases, respectively). The number of IT initiations was 6 for the period of 6 months in 2017, 16 cases during 2018, 17 cases in 2019 and 3 cases in the first two and a half months of 2020, which indicated an average of 1.27 patients initiated monthly with IT for melanoma in our center. The treated cases of ocular melanoma belonged to two females, both aged 62 years at initiation, treated for 63 and 97 days, respectively, until progressive disease.

The data for the whole 220 patients group under IT revealed data similar to those presented above: the distribution by sex revealed 155 cases (70.5%) belonging to male gender and 65 cases (29.5%) belonging to female gender. The average duration of immunotherapy

was 155.12 days for males and 183.83 days for females. The CPHSR statistical test could not validate as significant the difference between the genders of the IT durations (p = 0.936). The average age of the group of patients enrolled was 61.45 years, with small differences in groups with different locations of neoplasms (**Fig. 2**).

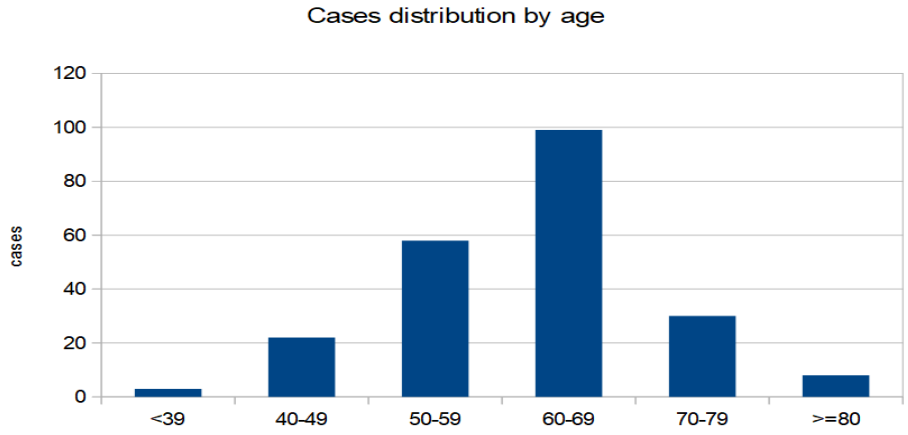

Fig. 2 Distribution of cases by age groups

The age distribution of melanoma cases (42) revealed the dominance of the seventh decade (60-69 years). Of note were two cases aged 18 and 33 years, respectively, and 4 cases initiated at the age of over 80 years (9.5% of the group) (**Table 4**).

Table 4. Distribution of melanoma cases by age groups

Distribution by age	Number of cases	Percentage
<39	3	7,1
40-49	7	16,7
50-59	6	14,3
60-69	14	33,3
70-79	8	19
>=80	4	9,5

Fractions of cases exceeding 300 days of treatment were higher for kidney cancer and melanomas (**Fig. 3**).

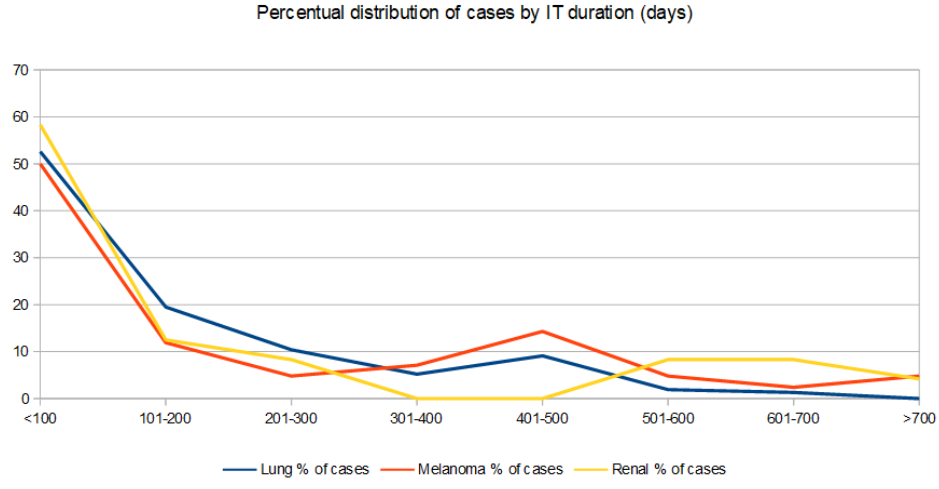

Fig. 3 Distribution of cases according to location and duration of immunotherapy

The frequency of use of mild and strong opioids (WHO category II and III) was 4.8% among melanoma cases, 8.4% among lung cancer cases and 8.3% among renal cancer cases, respectively. Opioid use was not associated with significantly reduced average treatment times (**Table 5**).

Table 5. Average duration of immunotherapy according to opioid use

Average IT duration by opioid use	Average IT duration	Cases
no opioids	163,9	203
WHO category II or III	160,4	17

An overview of the duration of IT, marking the cessation of treatment (**Fig. 4**):

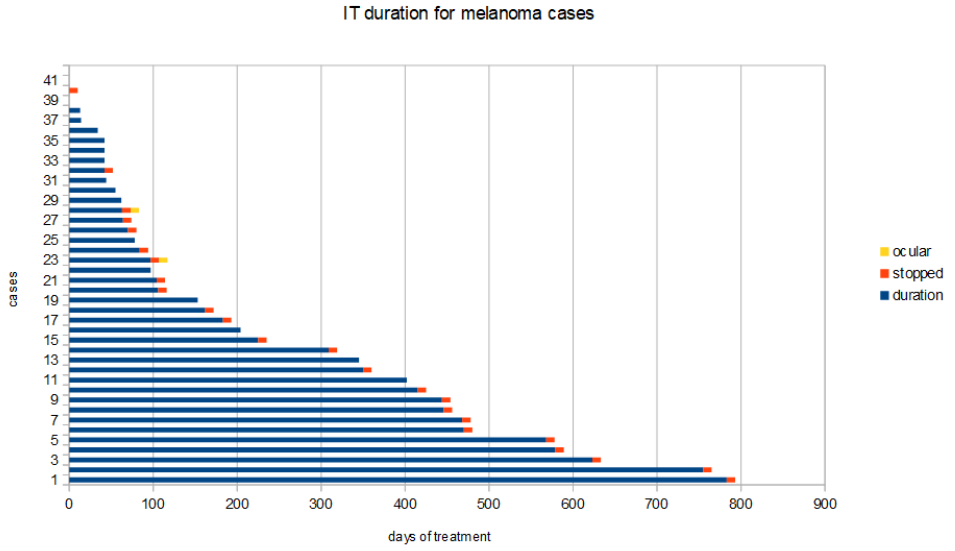

Fig. 4 Cases of nivolumab-treated melanoma stratified by IT duration

Cox Proportional Hazards Survival Regression was applied to different groups of cases, investigating the presence of liver and bone metastases. Lymphatic and adrenal glands as shorter IT risk factors in patients with melanoma (negative coefficients translate into shorter IT durations). **Table 6** includes the determinants for IT duration identified with values of p <0.1. Interpretation for the relative risk is coefficient; if the coefficients are negative: the duration of IT increases with the determinant (favorable predictive factors); positive coefficients: IT duration decreases as the determinant increases. Liver metastases were identified in 40.4% of treated melanoma patients, bone metastases in 11.2%, lymphatic patients in 57.1% and adrenal metastases in 9.5%.

Table 6. Coefficients of variation for IT duration and statistical significance by different patient groups

Patient group	Parameter	Number of cases	Coefficient	Statistical significance	Confidence interval	Risk Ratio	Confidence interval
Melanoma all cases	Liver metastases present 0/1	42	1.36	P=0.0086	0.34 to 2.38	3.91	1.41 to 10.85
Melanoma, cases > 65 years	Age (years)	18	-0.13	P=0.0773	-0.28 to 0.01	0.87	0.75 to 1.01
Melanoma, cases ≤ 65 years	Lymph node metastases present 0/1	22	-1.99	P=0.0330	-3.82 to 0.16	0.13	0.02 to 0.85

Discussions

The half-life of nivolumab of 25 days and the time required to reach the serum concentration plateau of 84 days raised the question of the usefulness of a loading dose, considering that 43% of the patients with melanoma have a treatment duration with nivolumab shorter than 84 days.

The number of cases in the analyzed subsets proved to be relatively small to allow statistical conclusions for most iterations, leading to uncomfortably wide confidence intervals.

Melanoma cases represented 19.1% of all immune treated cases. Among them, the cases of ocular melanoma, however, painted a more aggressive profile for the evolution of the disease: an average IT duration of 80 days for ocular melanoma cases compared to the average of 215 days of IT duration among the 42 cases of melanoma (even though we had extremely few cases of ocular melanoma).

Surprisingly, among the total of 220 patients, the cases following opioid treatment (WHO category II or III) revealed only slightly different averages of IT duration, the number of cases not allowing statistical conclusions to the Mann Whitney analysis or Cox regression (to be mentioned however, CPHSR revealed a coefficient of 0.4053 with a relative risk of exit from IT of 1.49 [0.85 to 2.61] for those under opioid treatment, but with a p value of 0.1539).

Conclusions

The presence of liver metastases is a negative predictive factor for the duration of IT in patients with melanoma ($p < 0.05$). Lymphatic metastases are a predictive factor for longer IT in melanoma patients under 65 years old ($p < 0.05$). It is necessary to extend the study in order to be able to validate the determinants currently close to the limit of statistical significance.

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GENERAL ARTICLE

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Anthropometry in the immunotherapy of cutaneous and ocular melanomas

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Abstract

The height of the adult individual is a balance of the expression of some genetic factors (especially the Y-M 170 haplotype of the Y chromosome) and the environment (nutrition and morbidity during childhood). Higher height is associated with a low risk of developing coronary heart disease, hypertension, gastroesophageal reflux, diaphragmatic hernia, but with a higher risk for atrial fibrillation, venous thromboembolism, intervertebral disc pathology, vasculitis and cancer. The research consisted of a retrospective observational study on patients who received immunotherapy (IT) with nivolumab for cutaneous and ocular melanoma neoplasms. We intended to highlight the associations between the duration of immunotherapy and sex profiles, age, anthropometric data (height, weight). Even though the number of available cases was relatively small (42), an inverse association between the body mass index of the subjects and the duration of immunotherapy could be proved, a more expressed association in case of male patients.
Keywords: melanoma, nivolumab, anthropometry

Introduction

The height of the adult individual is a balance of the expression of some genetic and environmental factors. The most important non-genetic factors that determine the height of the adult individual are nutrition and morbidity during childhood (factors related to socio-economic, educational conditions). A lower height correlates with a lower average educational level and a lower social position as an adult [**1**].

The IM170 Y chromosome haplotype correlates with a higher average (unusually high) height of male individuals in a given population. The determinations reveal the highest proportions for this haplogroup in the countries of northern and south-eastern Europe. The average height for men in Sarajevo is 184 cm [**2**].

Higher height is associated with a low risk of developing coronary heart disease, hypertension, gastroesophageal reflux, diaphragmatic hernia, but with a higher risk of atrial fibrillation, venous thromboembolism, intervertebral disc pathology, vasculitis, cancer (odds ratio for models epidemiological and genetic, respectively: ORepi = 1.09, 95% CI 1.08–1.11; ORgen = 1.06, 95% CI 1.04–1.08) [**3**].

The average height of European populations in the Paleolithic (<9,000 BC) was estimated at 177 cm for males and 166 cm for females (higher than today's European average), to gradually decrease to averages of 161 cm for men and 154 cm for women in the late Neolithic (5000-3000 BC) [**4**]. The change seems to coincide with the shift from hunter-gatherers to farmers.

Also, the average life expectancy seems to have decreased from 33 years in the Paleolithic to 26 years in the Bronze Age and the Iron Age (3000 BC - 650 BC). However, given the high infant and pediatric mortality, the average life expectancy at birth does not give a fair overview of the historical situation. It is considered that people who reached the age of 15 (only 60% of those born) had a life expectancy of another 39 years (a total of 54 years) [**5**].

The historical evolution of the average height of European populations reveals an increase of 11 cm for males, born in 1870 and 1980, respectively, correlated with the improvement of the health status of the population expressed by the value of infant mortality [**6**].

However, after reaching maximum heights, around 2000 (the generation born in 1982), the average heights at 18 years old for both women and men suffered stagnation and even a modest decrease, which is true even for Romania and the country with the highest average height of the population - the Netherlands [**7**].

Until the introduction of immunotherapy, melanoma was considered a refractory disease marked by the lack of effective options in the treatment of metastatic disease. It was only after 2010, with the introduction of immunotherapy (anti-PD-1, anti-CTLA-4 antibodies), that a breach in the status of an unapproachable disease of metastatic melanoma was achieved. Immunotherapy response rates in metastatic melanoma can exceed 40%, with a remarkable percentage of long-lasting responses and good tolerability [**8**].

The combination of Nivolumab + Ipilimumab (anti-PD-1 + anti-CTLA-4 antibodies) manages to provide survival rates of over 50% at 5 years for cases of metastatic melanoma [**9**].

The rarity of cases of ocular melanoma makes it more difficult to assess the benefit of immunotherapy in this situation. Published data for cases of metastatic uveal melanoma reveal response rates of the order of 7% with disease control rates of 43%, and progression-free survival between 4 and 105 weeks (median 10 weeks). All these data describe uveal melanoma as relatively refractory to nivolumab immunotherapy [**10**].

Another study for patients with uveal melanoma using the combination of nivolumab and ipilimumab obtained response rates of 17% with disease control rates of 70%, with progression-free survival of 26 weeks, median survival of 83 weeks. However, the presence of immunotherapy-specific side effects was noted in 83% of the patients, with 40% of cases with grade 3 or 4, with 10% of the cases having treatment stopped due to side effects [**11**].

Materials and methods

The research consisted of a retrospective observational study in patients who received immunotherapy (IT) with nivolumab for lung cancer, renal cancer and melanoma, seeking to highlight the associations between the duration of immunotherapy and sex, age, anthropometric data (height, weight).

Out of the 2241 hospitalizations (especially day-care) for the administration of

immunotherapy belonging to 220 distinct persons between 28.06.2017 and 20.03.2020, attention was retained to the 42 cases of treated metastatic melanoma (including 2 cases of ocular melanoma). The administration of immunotherapy for melanoma cases started on 28.06.2017 and consisted of 527 administrations.

Because verification of the distribution of immunotherapy durations did not indicate a Gaussian type, the Mann-Whitney U Test (MWUT) was applied for sets of individual variables. The verification of the correlations between the duration of IT and various parameters was verified with Cox Proportional Hazards Survival Regression (CPHSR) which takes into account both cases still in treatment and those out of treatment.

Results

Among 220 immunotherapeutic cases, the most extended recorded administration of immunotherapy is 783 days (patient with melanoma, treatment still in progress) and 35 cases benefited from only a single IT administration, another 21 cases being in treatment for less than 30 days.

Regarding the cases of cutaneous and ocular melanoma (a total of 42 cases, divided into 26 males and 16 females), the average duration of IT administration was 209 days (**Fig. 1**). Eighteen of the 42 cases of melanoma are still undergoing treatment. The mean age of the group of 42 patients with melanoma was 62 years for males and 58 years for females.

The distribution by age groups of melanoma cases indicated extreme values of 18 and 85 years, respectively, with the peak incidence located in the area of decades 7 and 8 (**Table 1**).

Table 1. Distribution of melanoma cases by age and sex

Age (years)	Male	Female	Total
≤30	0	1	1
31..40	2	0	2
41..50	5	2	7
51..60	2	4	6
61..70	7	7	14
71..80	7	1	8
>80	3	1	4

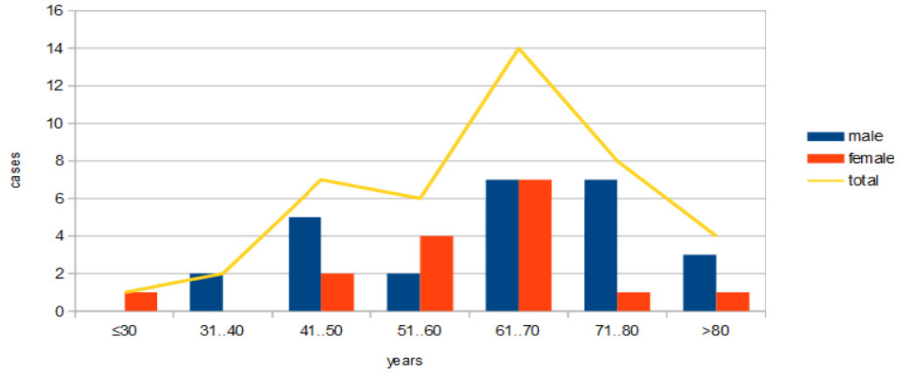

Fig. 1 Distribution of melanoma cases by age and sex

The distribution of cases according to the body mass index at the initiation of treatment reveals the dominance of patients with overweight and obesity, which had a much longer average duration of immunotherapy (**Table 2**).

Table 2. Melanoma cases and IT duration distribution by BMI

BMI (kg/m2)	Cases	Average IT duration
20..24	6	5,83
25..29	17	5,4
30..34	7	15,62

Treated ocular melanomas are represented by two female cases, both 62 years old at initiation, treated with 6 and 4 IT administrations respectively, both off treatment at present due to progression.

Of the 220 cases (lung + renal + melanoma), there were available data on the initiation weight for 174 cases, indicating an average weight of 74.15 kg (77.03 kg for males and 67.4 kg for females) (**Fig. 2**).

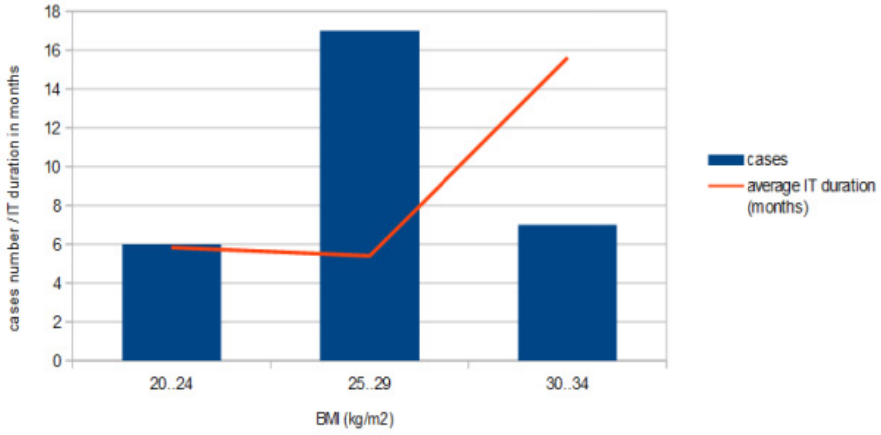

Fig. 2 Melanoma cases and IT duration distribution by BMI

For 45 cases, weight variation was recorded during treatment. The highest weight gain under treatment was + 57% (a case of kidney cancer), and the largest decrease was -22%, with an average of -1.15%. Two-thirds of cases suffered weight loss and one-third gained weight (among weight-weighted cases) (**Fig. 3**).

Among the cases of melanoma, we found 15 cases for whom the weight variation was documented and their evolution revealed a quarter of the cases with weight gain and approximately three quarters with weight loss.

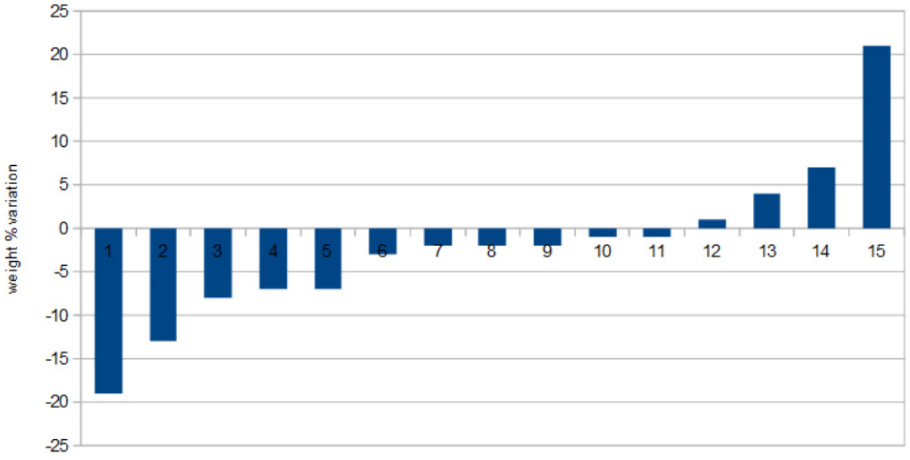

Fig. 3 Relative weight variations during IT - cases of melanoma

The average duration of immunotherapy in cases whose weight has increased during treatment was 291 days, while for patients who lost weight, this average duration was 244 days. MWUT did not qualify the observed difference as statistically significant.

Cox Proportional Hazards Survival Regression was applied to different groups of cases, researching sex, age, height, initiation weight and body mass index as risk factors for shorter IT. Determinants for IT duration identified p values < 0.05 among cases with data available for height and weight. Interpretation: negative coefficients: IT duration increases with the determinant (favorable predictive factors); positive coefficients: IT duration decreases as the determinant increases (**Table 3**).

Table 3. Coefficients of variation for IT duration and statistical significance by different groups

Patient group	Parameter	Cases number	Coefficient	Statistical significance	Confidence interval	Risk Ratio	Confidence interval
Melanoma, available weight and height data cases at the initiation	BMI at initiation	30	-0.14	P=0.036	-0.26 to -0.09	0.87	0.76 to 0.99
Melanoma, available weight and height data cases at initiation, male cases	BMI at initiation	18	-0.28	P=0.029	-0.52 to -0.02	0.75	0.59 to 0.97

Discussions

Fixed-dose administration of nivolumab in the immunotherapy of metastatic melanomas (and other cancers) would be expected to be more beneficial for anthropometrically less prominent individuals. Although a higher BMI does not automatically mean a higher clearance of the active substance, statistically we demonstrated an advantage over 10% per 1 unit increase of BMI for a longer duration of immunotherapy and implicitly for better survival. It should be noted that after the progression on treatment with immunotherapy it might be possible to continue with BRAF tyrosine kinase inhibitors (only for cases with documented BRAF mutation and if not already tried) and possibly chemotherapy (with uncertain effects on survival). A beneficial and more pronounced association of increased BMI throughout immunotherapy for male patients has been noted.

Without being able to reach statistical significance, other favorable predictors could be younger age, male gender and smaller height of the subjects but the p-value for these is between 0.19-0.25.

It seems that the dosage of immunotherapy still hides some mysteries.

Conclusion

In the case of cutaneous and ocular melanomas, **the subject's body mass index is positively correlated with the duration of IT, with statistical significance (p <0.05)**.

Prolonged surveillance or a pool of cases of immunotherapeutic melanomas could statistically prove the value of other anthropometric determinants in terms of their correlation with the duration of immunotherapy.

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GENERAL ARTICLE

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Direct and crossover effects of Phenylephrine and Cyclopentolate on foveal avascular zone and vessel density of macular capillary plexuses: an optical coherence tomography angiography study

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Abstract

Purpose: To determine the influence of phenylephrine and cyclopentolate on foveal avascular zone (FAZ) and vessel density of macular capillary plexus measurements via optical coherence tomography angiography (OCTA).

Materials and Methods: The participants were separated into 2 groups according to the administration of drops. One drop of phenylephrine 2.5% was administered on one eye of each subject in the phenylephrine group (n=30) and one drop of cyclopentolate 1% in the cyclopentolate group (n=30). FAZ parameters and vessel density values of both superficial (SCP) and deep capillary plexuses (DCP) were calculated via OCTA priorly and at 45 min following the drop administration in both eyes. Vessel density, acircularity index of FAZ, FAZ area, perimeter of FAZ and foveal density-300 were evaluated via OCTA.

Results: The vessel density values of fovea in SCP and DCP was 18.51±7.14% and 36.05±8.76% and significantly decreased to 16.16±6.26% and 33.29±9.47% respectively after drop instillation in dilated eyes in phenylephrine group (p=0.041 and p=0.032). Likewise, the vessel density values in SCP and DCP were 21.56±7.74% and 39.27±8.76% and significantly decreased to 18.89±7.32% and 35.36±5.75% respectively, after drop instillation in dilated eyes in cyclopentolate group (p=0.035 and p=0.028). However, there was no significant difference between before and after instillation of drops in terms of foveal density-300 value via FAZ assessment tool in both dilated and nondilated contralateral eyes in both groups (p>0.05 for all).

Conclusions: Mydriasis with phenylephrine and/ or cyclopentolate did not affect the foveal density-300 values while analyzing the perfusion of macula. Vessel density in foveal region should be evaluated via FAZ evaluation software of the OCTA.

Keywords: capillaries, mydriatics, optical coherence tomography

Introduction

Over the last years, optical coherence tomography angiography (OCTA) has become an important imaging technique in terms of differential diagnosis of macular disorders including senile macular degeneration, type 3 neovascularization, perifoveal telangiectasia and retinal polyps [**1-3**]. It is a safe and advanced resolution imaging modality that allows the assessment of retinal microcirculation without the need of fluorescein usage [**4**]. OCTA also allows the evaluation of foveal avascular zone (FAZ) features, capillary nonperfusion areas, vessel density in both superficial (SCP) and deep capillary plexuses (DCP) quantitatively in different retinal disorders [**5-8**]. While evaluating vessel density in foveal region, different algorithms of OCTA including density evaluation software and/ or FAZ evaluation software could be used [**5**].

Phenylephrine and cyclopentolate are two commonly used mydriatics in clinical practice. Phenylephrine, an alpha agonist, implements its mydriatic action by stimulating the iris dilator muscle and cyclopentolate, a parasympatholytic agent, which obtains pupil dilatation by limiting iris sphincter muscle activity. Moreover, cyclopentolate has a cycloplegic and long acting effect. Systemic effects of topical ocular medication mostly occur after absorption through the nasal mucosa or from the anterior segment of the eye. Both sympathomimetics and parasympatholytics have vasoconstricting effects and they may affect the measurements of the OCTA parameters. The objective of this present study was to find out the effect of phenylephrine and cyclopentolate on FAZ area and capillary density of foveal region measurements in healthy subjects using FAZ evaluation software, non-flow evaluation software and density evaluation software of OCTA.

Materials and Methods

This cross-sectional study with prospective enrollment was carried out at Ulucanlar Eye Research and Training Hospital. Written and oral informed consent were provided from all the participants. The study was approved by the Ethical Committee of Numune Training and Research Hospital (21.03.2018/ 1788) and adhered to the Declaration of Helsinki.

Examination protocol and screening

All the participants had an entire ophthalmic evaluation, including evaluation of best corrected visual acuity (BCVA), biomicroscopic examination of anterior segment, gonioscopy with Goldman three mirror lens and applanation tonometry. Axial length (AL) calculations, central corneal thickness (CCT) and OCTA measurements were also performed.

Eligibility criteria

Inclusion criteria were BCVA better than or equal to 20/ 20, less than 2 diopters of spherical or cylindrical refractive error, nonsmoking, no drug therapy, no alcohol use, nonexistence of glaucomatous evidence and intraocular pressure (IOP) levels over 21 mmHg. The exclusion criteria were anterior segment obscurity, AL < 21 millimeters and > 24 millimeters, and history of ocular intervention within 12 months before the study entry. Individuals with pathological findings (such as retinal vascular abnormalities, iridocyclitis, or vitreoretinal interface disorders) were excluded. Patients with diabetes mellitus and hypertension were also removed from the study.

Study groups

The individuals were randomly separated into 2 groups according to the application of drops as previously described by Kara and associates [**9**]:

Phenylephrine group (Group 1). The individuals took a drop of phenylephrine (Mydfrine®, Alcon, USA) 2.5% three times at 5 minutes span in one eye.

Cyclopentolate group (Group 2). The individuals took a drop of cyclopentolate (Sikloplejin®, Abdi İbrahim, TR) 1% thrice at 5 minutes span in one eye.

The left eye was assigned the study eye for phenylephrine group individuals with an even-numbered birth year and the right eye was

assigned the study eye for cyclopentolate group individuals with an odd-numbered birth year. Appropriate subjects were included in the study consecutively until group 1 and 2 achieved 30 individuals.

OCTA calculations

The same ophthalmologist performed the OCTA calculations using the via AngioVue software (Version 2017.1.0.151) of the RTVue XR Avanti (Opto-Vue, Inc, Fremont, CA) during the same period of the day (between 10-12 AM) and in aqua environmental situations. All images were of 6 mm × 6 mm scanning region centered on macula. One experienced independent observer assessed the angiography slabs. Individuals with low signal strength index (SSI <7) were excluded.

The machine placed three fovea-centered rings on the macula by using density assessment software in both SCP and DCP slabs (**Fig. 1**). Foveal zone was described as 1 mm diameter circle area, the parafoveal zone was defined as 3 mm diameter middle circle area, and perifoveal zone was described as 6 mm diameter outer circle area. Additionally, the zones were separated into two equal hemispheres (inferior and superior). Non-flow FAZ area in SCP was automatically provided using non-flow evaluation software (**Fig. 2A**), and the FAZ area in whole retina, foveal density (FD-300) (vessel density in 300 microns around the FAZ), FAZ perimeter and acircularity index (AI) of FAZ were also automatically provided using FAZ evaluation software (**Fig. 2B**).

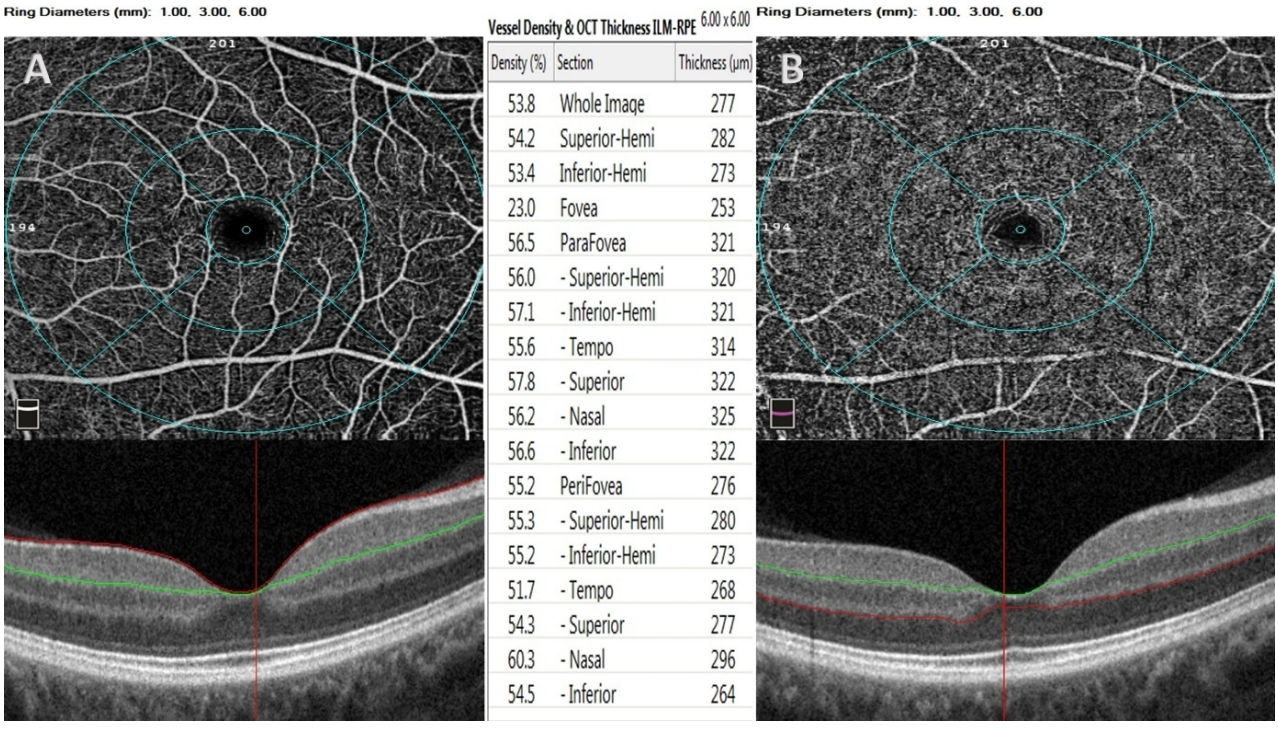

Fig. 1 The device placed three fovea-centered rings on the macula by using density assessment software in both superficial capillary plexus (A) and deep capillary plexus (B) slabs. The zones were separated to equal parts

Fig. 2 Non-flow FAZ area (mm^2) in superficial capillary plexus was automatically provided using non-flow evaluation software (2A), and the FAZ area in whole retina (mm^2), foveal density (%) (FD-300) (vessel density in 300 microns around the FAZ), FAZ perimeter (PERIM) (mm) and acircularity index (AI) of FAZ were also automatically provided using FAZ evaluation software (**Fig. 2B**)

Statistical analysis

SPSS (Statistical Package for the Social Sciences) (version 22 for Windows) was used for the statistical analysis. Kolmogorov–Smirnov test was used to evaluate the normality of the data ($p > 0.05$). Numerical variables were saved as mean and standard deviation and categorical data were saved as numbers. The categorical variables between the group 1 and 2 were evaluated via the χ^2 test. The comparisons of the FAZ area values in superficial capillary plexus and whole retina, perimeter and AI of FAZ, FD-300 and vessel density values prior and following the administration of drops were analyzed with paired t-tests. A p value less than 0.05 was considered significant.

Results

One hundred twenty eyes of 60 individuals were evaluated in this prospective study: 30 individuals in group 1 and 30 individuals in group 2, between December 2017 and June 2018. **Table 1** demonstrates the clinical characteristics and demographic data of the study individuals. The mean age in phenylephrine and cyclopentolate group was 42.10±16.72 (20-68) and 41.90±13.89 (20-66) years respectively. The mean axial length was 23.13±0.41 (22.20-23.5) mm in phenylephrine group and 23.20±0.33 (22.69-23.60) mm in cyclopentolate group. Spherical equivalent refraction was -0.14±0.98 (-2.0-2.0) diopters in phenylephrine group and 0.04±0.69 (-1.5-1.5) diopters in cyclopentolate group. The mean CCT and IOP values were 548±26.93 (505-600) µm and 14.43±2.16 (10-18) mmHg in phenylephrine group and 552±31.06 (497-624) µm and 15.60±3.10 (10-19) mmHg in cyclopentolate group respectively. Age, IOP, CCT, spherical equivalent refraction, AL and gender distribution did not show a significant difference between groups (P > 0.05 for all).

Foveal Avascular Zone and Macular Capillary Plexus Vessel Density Changes

The clinical data before and after instillation of drops in dilated eye and in contralateral eye are shown in **Tables 2-5**. The vessel density values of fovea via density evaluation software in SCP and DCP were 18.51±7.14% and 36.05±8.76% and significantly decreased to 16.16±6.26% and 33.29±9.47% respectively after drop instillation in dilated eyes in phenylephrine group (p=0.041 and p=0.032) (**Table 2**). The vessel density values in SCP and DCP were 21.56±7.74% and 39.27±8.76% and significantly decreased to 18.89±7.32% and 35.36±5.75% respectively after drop instillation in dilated eyes in cyclopentolate group (p=0.035 and p=0.028) (**Table 4**). However, this difference did not demonstrate a statistical significance in foveal region in nondilated contralateral eyes (p=0.104 and p=0.684 in group 1 and p=0.140 and p=0.284 in group 2 respectively) (**Tables 3,5**). On the other hand, the FD-300 value via FAZ assessment tool in full retinal vasculature was not affected in dilated eyes in both groups. It was 53.44±7.00 and 52.64±5.59 in phenylephrine and cyclopentolate group and decreased to 52.97±7.41 and 51.44±3.73 respectively but this difference did not demonstrate a significant difference (p=0.842 and p=0.884 respectively) (**Tables 2,4**). Moreover, perimeter of FAZ, AI of FAZ, vessel density values in parafoveal and perifoveal zones and FAZ area in full retinal vasculature and in SCP did not demonstrate a significant difference before and after instillation of drops in both dilated and non-dilated contralateral eyes (P > 0.05 for all) (**Tables 2-5**).

Table 1. Clinical and Demographic Characteristics of the Study Individuals

Variable	*Phenylephrine group*	*Cyclopentolate group*	*P**
Age (years)			
Mean±SD	42.10±16.72	41.90±13.89	0.662*
Range	(20-68)	(20-66)	
Sex (n)			
Male (%)	13 (%43)	13 (%43)	0.196**
Female (%)	17 (%57)	17 (%57)	
CCT, µm			
Mean±SD	548±26.93	552±31.06	0.096*
Range	(505-600)	(497-624)	
Axial Length, mm			
Mean±SD	23.13±0.41	23.20±0.33	0.346*
Range	(22,20-23,5)	(22.69-23.60)	
Spherical Equivalent, D			
Mean±SD	-0.14±0.98	0.04±0.69	0.894*
Range	(-2.0-2.0)	(-1.5-1.5)	
IOP, mmHg			
Mean±SD	14.43±2.16	15.60±3.10	0.112*
Range	(10-18)	(10-19)	

D = diopter; CCT = central corneal thickness; IOP = intraocular pressure; µm = micrometer; SD = standard deviation.
**: Independent samples test.*
***: χ^2 test*

Table 2. Phenylephrine group (Dilated eye)

	Before Mean±SD	*After* Mean±SD	*Difference*	*P**
FAZ area (mm²) in SCP	0.57±0.26	0.57±0.26	0.00	0.984
FAZ area (mm²) in Full Retinal Vasculature	0.30±0.13	0.30±0.12	0.00	0.216
Perimeter (mm)	2.09±0.50	2.04±0.48	-0.05	0.146
Acircularity index	1.09±0.03	1.08±0.01	-0.01	0.104
FD-300 (%)	53.44±7.00	52.97±7.41	-0.47	0.842
Vessel density in SCP (Flow)%				
Whole Image	49.78±3.41	48.45±4.19	-1.33	0.234
Superior-Hemi	49.72±3.26	48.41±3.70	-1.31	0.220
Inferior-Hemi	49.85±3.61	48.49±4.70	-1.36	0.264
Fovea	18.51±7.14	16.16±6.26	-2.35	**0.041**
Parafovea	51.29±5.56	49.56±6.27	-1.73	0.541
Perifovea	50.78±3.25	49.66±4.32	-1.12	0.304
Vessel density in DCP (Flow)%				
Whole Image	51.04±6.60	47.85±7.59	-3.19	0.086
Superior-Hemi	50.97±6.81	47.52±7.55	-3.45	0.074
Inferior-Hemi	51.12±6.52	48.19±7.96	-2.93	0.122
Fovea	36.05±8.76	33.29±9,47	-2.76	**0.032**
Parafovea	55.34±5.90	53.92±6.87	-1.42	0.105
Perifovea	52.68±7.14	49.30±8.46	-3.38	0.108

SD = Standard deviation; FAZ = Foveal avascular zone; FD = foveal density-300; SCP = superficial capillary plexus; DCP = deep capillary plexus.
**: Paired t-test*

Table 3. Phenylephrine group (Contralateral eye)

	Before Mean±SD	*After* Mean±SD	*Difference*	*P**
FAZ area (mm²) in SCP	0.61±0.34	0.53±0.12	-0.08	0.232
FAZ area (mm²) in Full Retinal Vasculature	0.33±0.16	0.29±0.11	-0.04	0.154
Perimeter (mm)	2.20±0.56	2.07±0.42	-0.13	0.191
Acircularity index	1.10±0.03	1.09±0.02	-0.01	0.135
FD-300 (%)	52.04±4.74	52.43±4.22	0.39	0.470
Vessel density in SCP (Flow)%				
Whole Image	48.87±5.43	48.59±2.44	-0.28	0.212
Superior-Hemi	48.82±5.42	48.59±2.33	-0.23	0.211
Inferior-Hemi	48.93±5.51	48.60±2.67	-0.33	0.174
Fovea	19.27±6.45	17.97±6.53	-1.30	0.104
Parafovea	50.09±7.92	49.40±2.34	-0.69	0.745
Perifovea	49.88±5.05	49.02±2.12	-0.86	0.865
Vessel density in DCP (Flow)%				
Whole Image	49.86±8.13	48.74±5.35	-1.12	0.542
Superior-Hemi	50.11±8.05	49.49±5.40	-0.62	0.546
Inferior-Hemi	49.65±8.28	47.99±5.67	-1.66	0.528
Fovea	34.33±9.63	33.87±8.20	-0.46	0.684
Parafovea	54.94±6.97	54.66±4.06	-0.28	0.260
Perifovea	50.98±8.90	50.44±5.40	-0.54	0.393

SD = Standard deviation; FAZ = Foveal avascular zone; FD = foveal density-300; SCP = superficial capillary plexus; DCP = deep capillary plexus.
**: Paired t-test.*

Table 4. Cyclopentolate group (Dilated eye)

	Before Mean±SD	*After* Mean±SD	*Difference*	*P**
FAZ area (mm²) in SCP	0.53±0,18	0.50±0.14	-0.03	0.240
FAZ area (mm²) in Full Retinal Vasculature	0.27±0.12	0.25±0.11	-0.02	0.091
Perimeter (mm)	1.99±0.51	1.90±0.45	-0.09	0.162
Acircularity index	1.09±0.03	1.08±0.04	-0.01	0.144
FD-300 (%)	52.64±5.59	51.44±3.73	-1.20	0.884
Vessel density in SCP%				
Whole Image	50.60±3.70	49.37±2.87	-1.23	0.186
Superior-Hemi	50.70±3.85	49.45±2.72	-1.25	0.554
Inferior-Hemi	50.46±3.77	49.30±3.12	-1.16	0.662
Fovea	21.56±7.74	18.89±7.32	-2.67	**0.035**
Parafovea	52.33±5.73	51.12±3.99	-1.21	0.126
Perifovea	51.50±3.73	50.19±2.87	-1.31	0.234
Vessel density in DCP%				
Whole Image	50.50±4.84	47.45±5.30	-3.05	0.146
Superior-Hemi	50.48±4.76	47.43±5.57	-3.05	0.651
Inferior-Hemi	50.53±5.13	47.47±5.21	-3.06	0.324
Fovea	39.27±6.10	35.36±5.75	-3.91	**0.028**
Parafovea	51.51±3.77	48.09±3.90	-3.42	0.670
Perifovea	52.27±5.28	49.54±6.12	-2,73	0.394

SD = Standard deviation; FAZ = Foveal avascular zone; FD = foveal density-300; SCP = superficial capillary plexus; DCP = deep capillary plexus.
**: Paired t-test.*

Table 5. Cyclopentolate group (Contralateral eye)

	Before Mean±SD	*After* Mean±SD	*Difference*	*P**
FAZ area (mm²) in SCP	0.49±0.16	0.50±0,15	0.01	0.514
FAZ area (mm²) in Full Retinal vasculature	0.26±0.09	0.26±0,10	0.00	0.511
Perimeter (mm)	1.96±0.39	1.98±0,45	0.02	0.756
Acircularity index	1.10±0.05	1.10±0,03	0.00	0.474
FD-300 (%)	54.47±4.48	53.92±5,57	0.55	0.660
Vessel density SCP%				
Whole Image	50.83±3.54	50.73±2.69	-0.10	0.831
Superior-Hemi	50.89±3.32	50.78±2.34	-0.09	0.742
Inferior-Hemi	50.77±3.88	50.68±3.12	-0.09	0.901
Fovea	21.44±7.52	20.17±6.82	-1.27	0.140
Parafovea	53.09±3.79	52.93±4.30	-0.16	0.691
Perifovea	51.40±3.60	51.27±2.63	-0.13	0.635
Vessel density DCP%				
Whole Image	51.55±6.71	51.40±5.27	-0.15	0.360
Superior-Hemi	51.63±6.75	51.36±5.34	-0.28	0.421
Inferior-Hemi	51.48±6.80	51.44±5.35	-0.04	0.324
Fovea	39.24±8.97	38.14±9.23	-1.10	0.284
Parafovea	55.80±4.55	55.74±3.68	-0.06	0.296
Perifovea	52.97±7.26	52.90±5.90	-0.07	0.346

SD = Standard deviation; FAZ = Foveal avascular zone; FD = foveal density-300; SCP = superficial capillary plexus; DCP = deep capillary plexus.
**: Paired t-test.*

Discussion

Mydriatics are commonly used to dilate pupils for fundus examination for a lot of retinal circumstances and prior to ocular surgeries. Also, they were used prior to different imaging modalities including fundus fluorescein angiography, indocyanine green angiography and OCTA. Commonly used mydriatics are phenylephrine (a sympathomimetic), tropicamide and cyclopentolate (parasympatholytics). Phenylephrine induces vasoconstriction by its α1 adrenergic effect in peripheral capillaries including the conjunctival vessels and anterior ciliary arteries [**10**]. Tropicamide and cyclopentolate had no effect on peripheral vessels although they have muscarinic receptors on them. But, the main effects of these drugs on peripheral vessels were the decreased parasympathetic tone and the increased sympathetic tone.

Mizuno et al. reported that the instillation of topical drugs can pass through the conjunctival pouch, through the periocular region and reach the retrobulbar region. In this region, the agent achieves an effective dose around the central retinal artery and short posterior ciliary arteries [**11**]. Moreover, after topical usage, the drug could diffuse into the globe and a direct effect could be observed through the retinal capillary [**11,12**]. In the macular region, the microvessels had a shortage of smooth muscle and they were managed by pericytes that were induced by adrenergic receptors [**13-15**].

OCTA allows clinicians to quantitatively measure different parameters including FAZ area, AI, FD-300 and vessel densities of macular capillary plexuses in various retinal disorders [**5-8**]. These parameters offer information about the prognosis of retinal diseases and can also be used in the follow-up process. Mydriasis is frequently an important step to provide a good retinal image. In this present study, we aimed to find out the effects of phenylephrine and cyclopentolate on the FAZ area and vessel density of macular capillary plexus measurements using density, non-flow and FAZ evaluation software of the OCTA.

In our study, FAZ evaluation software parameters including FAZ perimeter, acircularity index of FAZ, FAZ area and FD-300 did not change in both eyes of both groups ($p>0.05$). The FD-300 values in phenylephrine and cyclopentolate groups were 53.44±7.00% and 52.64±5.59% and changed to 52.97±7.41% and 51.44±3.73% respectively, after drop instillation in dilated eyes ($p=0.842$ and $p=0.884$). The mydriatics did not affect the FD-300 parameter. On the other hand, density values of SCP and DCP in foveal zone via density evaluation software of OCTA in both groups were significantly decreased ($p=0.041$ and $p=0.032$ in group 1 and $p=0.035$ and $p=0.028$ in group 2 respectively). Whole image density, parafoveal zone density and perifoveal zone density did not change significantly in both phenylephrine and cyclopentolate groups in dilated eyes ($p>0.05$ for all).

Foveal density-300 is a vessel density variable of the FAZ evaluation software of OCTA. The instrument discovers the boundaries of avascular zone and draws a new ring around this zone at a space of 300 μ (**Fig. 2**) [**16**]. The instrument always calculates the vessel density in between these rings. However, in the vessel density evaluation software of OCTA, the rings are fixed at a diameter of 1, 3, and 6 mm in two different plexuses including SCP and DCP (**Fig. 1**) and the central 1 mm area includes lower vessel density values when compared with the FD-300 values. In the light of these findings, we speculated that the mydriatics did not affect the FD-300 values via the FAZ evaluation software of the OCTA in full retinal segmentation and we hypothesized that vessel density in foveal region should be evaluated via FAZ evaluation software of the OCTA.

Vessel density parameters did not show any significant changes in non-dilated eyes in both plexuses of both groups ($p>0.05$ for all). Topical usage of ophthalmic drugs could induce alteration in contralateral eye or might lead to systemic side effects [**17-19**]. Systemic effects of ocular drugs could be seen after the absorption through the cornea and conjunctiva or via the nasal mucosa. Also, eye drops could accumulate in the anterior chamber and could be disseminated to systemic circulation via the iridocorneal angle [**20**]. However, in our study we did not observe any significant alteration in the vessel density value of foveal region in contralateral eyes.

Cheng et al. evaluated the influence of topical mydriatic eye drops (0.5% tropicamide/ 0.5% phenylephrine mixture and 0.5% tropicamide alone) on the macular and peripapillary circulation via OCTA in eight healthy subjects [**21**]. They reported that vessel density of the peripapillary area was reduced, however, there was no significant reduction in the macular areas. The limitations of their study are the very small sample size and the fact that they evaluated the macula with the flow evaluation software of the device without dividing plexuses as SCP and DCP. Density evaluation software of the device allow clinicians to asses both SCP and DCP in different zones separately.

Our study has contributed as a recent invention to literature, highlighting the fact that the topical usage of phenylephrine and cyclopentolate did not affect the foveal density-300 values of macular region via FAZ assessment tool of OCTA in full retinal vasculature segmentation in dropped eyes and undropped contralateral eyes. The strength of the present study is its prospective design. Another strength is that measurements were made automatically using FAZ, density and non-flow evaluation software of the device. Previous studies demonstrated high reproducibility and reliability of these calculations [**22-25**]. We also explored the crossover effects of mydriatics that is another strength of our study.

Conclusion

Mydriasis with phenylephrine and/ or cyclopentolate did not affect the foveal density-300 values while analyzing the perfusion of macula. Vessel density in foveal region should be evaluated via FAZ assessment tool of the OCTA.

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Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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GENERAL ARTICLE

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The role of Visual Evoked Potential (VEP) in monitoring the progression and in guiding the treatment of glaucoma patients with poor compliance

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Abstract

Objectives: The objectives of the present study were to analyze the possibility of using pattern VEPs (VEP of pattern type) in glaucoma patients and their role in the follow-up and coordination/ management of anti-glaucoma treatment.

Patients and Methods: This is a prospective study on 54 eyes of 30 consecutive glaucoma patients, whose compliance capacity did not allow automatic perimetry and OCT scan to be carried out.

The patients were divided into two groups: group A – the study group and group B – the control group.

All patients underwent FO exam and pachymetry, plus VEP exam for group A patients.

Patients were analyzed at the initial visit and at 1 month, 3, 6, 12 months.

Statistical analysis was made using t-test, ANOVA, Fisher test and Pearson correlation coefficient.

Results: These participants presented a positive correlation between C/ D ratio and the latency of the P100 wave at 1 degree and a negative correlation between C/ D ratio and the amplitude of the P100 wave both at 1 degree (60 arc minutes) and at 0.25 degrees (15 arc minutes). During the study, the values of the latent P100 changed statistically at 6 months and at 1 year.

Using all the data, the authors of the study considered it necessary to modify the treatment for 2 patients out of 13 in group B and for 9 patients out of 16 in group A ($p = 0,02892$).

Conclusions: VEP supplies additional/ further data that significantly help guiding the treatment and monitoring the progression, therefore, it should be part of the routine examination for these patients.

Further studies are necessary to deepen our understanding of the visual evoked potentials utility.

Keywords: visual evoked potential, glaucoma, amplitude, latency

Introduction

Glaucoma is the most important cause of permanent vision loss and, once diagnosed, glaucoma patients need to be frequently and continuously monitored through their lives, and their treatment should be adjusted considering the permanent changing parameter, in order to preserve a satisfying visual function.

Visual evoked potentials are represented by the measurement of an electric impulse at the occipital level following a light stimulation. As the cortical projection area of the fovea and macula in generalis much larger than that of the peripheral retina, VEP mainly has in view signs with central origin and peripheral defects that may not be rendered evident by VEP analysis. Of the VEP analyses available in retinal abnormalities, a special interest was shown to PRVEP (Pattern Reversal Visual Evoked Potential), which represents an initial negative peak at about 70 ms (N70), then a positive peak (P100) at about 100 ms, followed by another negative peak at about 155 ms (N155). These can be used by stimulation on 15 arcminutes (0.25 degrees) or by stimulation on 60 arcminutes (1 degree). VEPs proved to be effective in detecting and monitoring glaucomatous progress [**1-4**].

To our knowledge, no results of the VEPs measurements have been able to replace automatic perimetry and/ or optical coherence tomography examination (OCT) of the optic nerve, even if there were studies that promisingly correlated with the perimetry modifications or OCT scan of the optic nerve.

In spite of all advances of perimetry and OCT, there are still patients for whom those examinations cannot be carried out with satisfying precision due to compliance difficulties, i.e. elderly patients exhibiting concentration issues as well as patients of any age with attention deficit or with motor of psychic dysfunctions.

Aim of the study

The aim of the study was to analyze the possibilities of using pattern type VEPs in glaucoma patients and their role in the follow up and management of glaucoma treatment.

Patients and Methods

This is a prospective study on 30 consecutive glaucoma patients, whose compliance made impossible to perform all glaucoma specific investigations, and specifically, patients in whom automatic perimetry and OCT scan of the optic nerve could not be performed in order to determine the progression of the glaucoma. The University Emergency Hospital Ethics Committee approval was obtained and an Informed Consent about the study procedures and visits schedule was signed by all participants.

These patients were divided into two groups:

- The study group included 16 patients for whom visual acuity exam, Goldman applanation tonometry, biomicroscopic exam of fundus oculi (FO) with 90 diopter lens and Visual evoked potentials of pattern type (flash and PRVEP = pattern reversal visual evoked potential), were carried out;
- The control group included 16 patients for whom visual acuity examination, Goldman applanation tonometry, FO, biomicroscopic exam with the 90-diopter lens, were carried out.

Inclusion criteria:

- Patients over 18 years of age diagnosed with primary glaucoma with open angle, with or without treatment.
- Patients in whom reduced compliance did not allow automatic perimetry and OCT scan.
- Patients in whom visual acuity could be measured.
- Patients from whom informed consent could be obtained.
- Patients with iridocorneal open angle at indirect gonioscopic exam (Goldmann lens): III or IV grade angle on at least two quadrants, were included.

Exclusion criteria:

- Patients with significant transparency modifications of the transparent media.

- Patients with refraction error with the sphere over +/ - 5 diopters or astigmatism greater than +/ - 2 diopters.
- Patients with concomitant vascular retinal disease.
- Patients with edema of the optic nerve; either stasis edema or associated to an ischemic neuropathy.
- Patients with a history of intraocular injections with corticosteroids.
- Patients with a history of intraocular injections with vascular endothelial growth factor (VEGF) inhibitors on the respective eye.
- Amblyopia.
- Patients who have presented cerebral vascular strokes or transitory ischemic strokes.
- Patients with inflammatory lesions of neuritis type, irrespective of their location.
- Patients who underwent eye surgery in the past 6 months, exception: 3 months previous non-complicated surgery for cataract.
- Patients with significant macular abnormalities.

Study group A (**Table 1**) was represented by 16 patients (27 eyes). Investigations were represented by visual acuity, applanation tonometry, gonioscopy, fundus examination with the 90-diopter lens, retinophotography – if possible – and the pattern visual evoked potentials (PRVEP and flash) with stimulation on 1 degree (60 arc seconds) or on 0.25 degrees (15 arc seconds).

Table 1. Study group A results at the initial visit

Name	Sex	Age	VA	IOP	Gonio	Pachy-	c/d ratio	Pat lat 1gr	Pattern amp 1gr	Patlat 15	Pattern 15 amp	Fla-ampl	Fla lat
AE	F	83	0.9	18	3	518	0.5	113.3	11.6	143	14.9	3.76	108
AE	F	83	0.8	20	3	520	0.9	148.5	3.98	120.9	2.6	5.3	103.3
BM	F	65	0.5	21	4	549	0.3	108	9.07	129.2	12.3	7.02	148.4
BM	F	65	1	22	4	536	0.5	109.2	12	125	9.05	4.87	134.3
BN	M	58	1	16	2	530	0.7	115.1	7.88	126.2	8.75	8.21	113.7
BN	M	58	1	18	2	528	0.6	116	7.71	120.9	9.89	5.48	112.7
BG	F	72	1	16	3	538	0.5	128.6	7.33	142.7	9.2	16.8	129.6
BT	F	59	1	15	3	542	0.5	122.7	11.1	140.3	9.19	19.1	133.4
CB	M	81	0.9	20	4	550	0.7	113.9	6.14	129.7	4.39	4	99.6
CB	M	91	0.8	20	4	555	0.7	120.4	6.34	131.5	2.91	1.62	98.6
DI	F	76	0.9	18	4	532	0.4	110.4	8.34	128	17.4	11.7	111.8
DI	F	76	0.9	21	4	530	0.5	109.8	11.4	123.3	18.8	9.58	107.1
DA	F	75	0.6	23	2	574	0.8	132.1	5	118	1.73	14.1	157.7
DA	F	75	0.6	19	3	580	0.8	145	2.73	112.7	2.82	1.53	118.1
EA	M	67	1	23	3	520	0.75	118.6	12.5	134.4	18.4	0.46	133.4
EA	M	67	1	19	3	518	0.7	116.8	14.5	123.9	21.3	7.96	132.4
FI	F	83	0.8	22	3	538	0.75	102.7	11.2	125	11.2	8.47	84.5
FI	F	83	1	24	2	550	0.3	104.5	12.1	122.7	13.2	10.5	85.5
GFG	F	66	0.3	35	3	550	0.6	128	0.29	76.9	1.21	3.82	107.1
GFG	F	66	0.5	19	3	525	0.85	116.8	2.33	76.3	1.41	0.63	112.7
GE	M	81	0.9	21	3	533	0.5	116.8	5.04	132.1	11	3.45	131.5
GE	M	81	0.9	22	3	532	0.8	113.3	5.17	127.4	12.3	1.8	134.3
GF	F	76	0.4	35	2	550	0.6	128	0.29	76.9	1.21	3.82	107.1
GF	F	76	0.5	19	3	525	0.85	116.8	2.33	76.3	1.41	0,63	112.7
IA	F	58	0.9	28	3	560	0.65	113.3	12.3	135.6	8.49	10.2	116.5
IM	M	82	0.9	20	3	541	0.6	109.8	12.6	118.6	11.7	12.5	113.7
LF	M	81	1	14	4	520	0.4	115.7	10.9	128	26.3	13.8	123.1

Group B, the control group, was represented by 14 patients (27 eyes). Investigations were similar except for PRVEP and flash. During the study, one patient missed part of the study visits and was removed from the group; thus, only 13 patients (25 eyes) remained in this group (**Table 2**).

Table 2. Control group B results at the initial visit

Name	Sex	Age	VA	IOP	Gonio	Pachy	C/ D ratio
LM	M	83	0,9	20	grade 3	524	0,65
LM	M	83	0,9	19	grade 3	526	0,7
NE	F	73	0,9	18	grade 3	524	0,7
NE	F	73	0,9	19	grade 3	526	0,7
OI	M	80	0,4	26	grade 4	530	0,8
OI	M	80	1	21	grade 4	528	0,4
PA	F	64	0,3	20	grade 4	528	0,7
PA	F	64	0,5	22	grade 4	530	0,8
PG	F	81	0,9	19	grade 3	535	0,7
PG	F	81	0,9	20	grade 3	537	0,7
PI	M	65	0,7	12	grade 3	543	0,9
PI	M	65	0,8	12	grade 3	538	0,85
PS	F	83	0,8	19	grade 3	530	0,9
PS	F	83	0,8	20	grade 3	524	0,65
PT	F	58	1	23	grade 3	545	0.5
PT	F	58	0.8	22	grade 4	522	0.8
RA	M	65	0,9	21	grade 3	556	0,2
RA	M	65	0,9	20	grade 3	560	0,2
RD	F	76	0.8	20	grade 2	555	0.4
RD	F	76	1	19	grade 3	549	0.4
RML	M	81	1	17	grade 2-3	527	0.7
RML	M	81	1	17	grade 2-3	533	0.85
SC	M	59	1	18	grade 2	512	0,4
TE	F	72	1	15	grade 3	530	0,35
TE	F	72	1	15	grade 3	526	0,35

The patients were followed up for 5 visits – the first, then at 1, 3, 6 months and 1 year. Slit lamp exam, visual acuity exam, fundus exam and IOP measurement were carried out at each visit.

Results

A direct correlation between VEP latency at 1 degree and C/ D ratio of the optic disk evaluated by FO exam was observed at the initial visit (V0) for group A (**Fig. 1**).

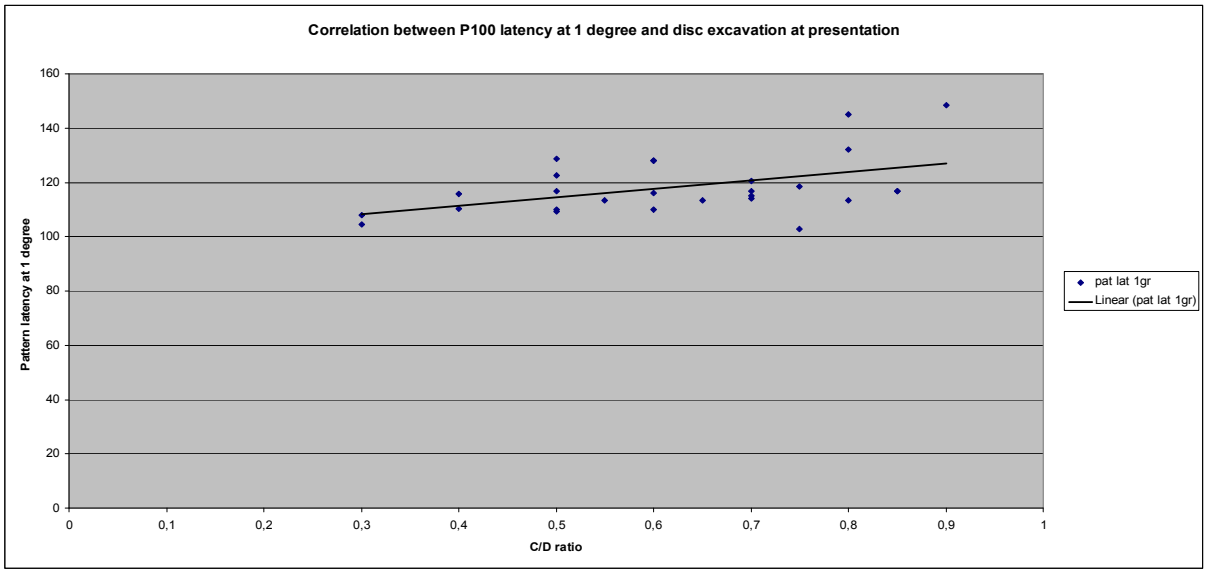

Fig. 1 Correlation between P100 latency at 1 degree (60 arc minutes) and disc excavation at presentation

The Pearson index for this correlation was 0,469893, which indicated a positive correlation of medium value. Regarding the correlation between P100 amplitude at 1 degree and the size of the excavation, a negative correlation (Pearson index = - 0,421838318) not as strong as latency correlation was observed (**Fig. 2**).

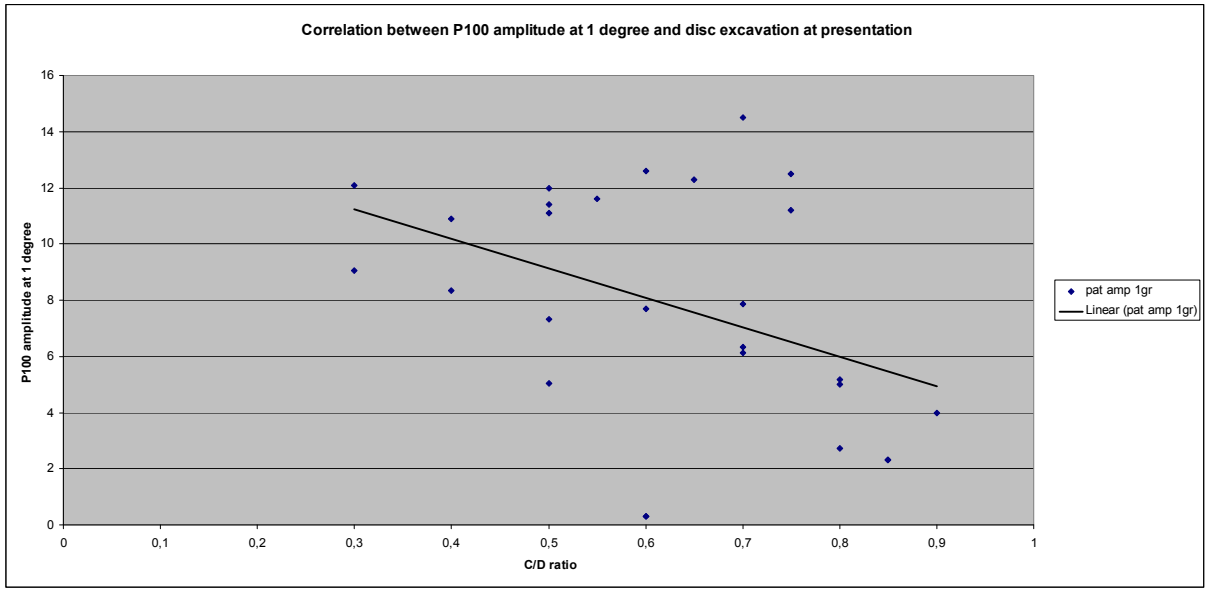

Fig. 2 Correlation between P100 amplitude at 1 degree (60 arc minutes) and disc excavation at presentation

No significant correlation between P100 latency at 0.25 degrees (Pearson index = 0,283411325) and C/ D ratio was obtained, but we have noticed a significant negative correlation between excavation and the P100 amplitude at 0,25 degrees (Pearson index = - 0,516267568) (**Fig. 3**).

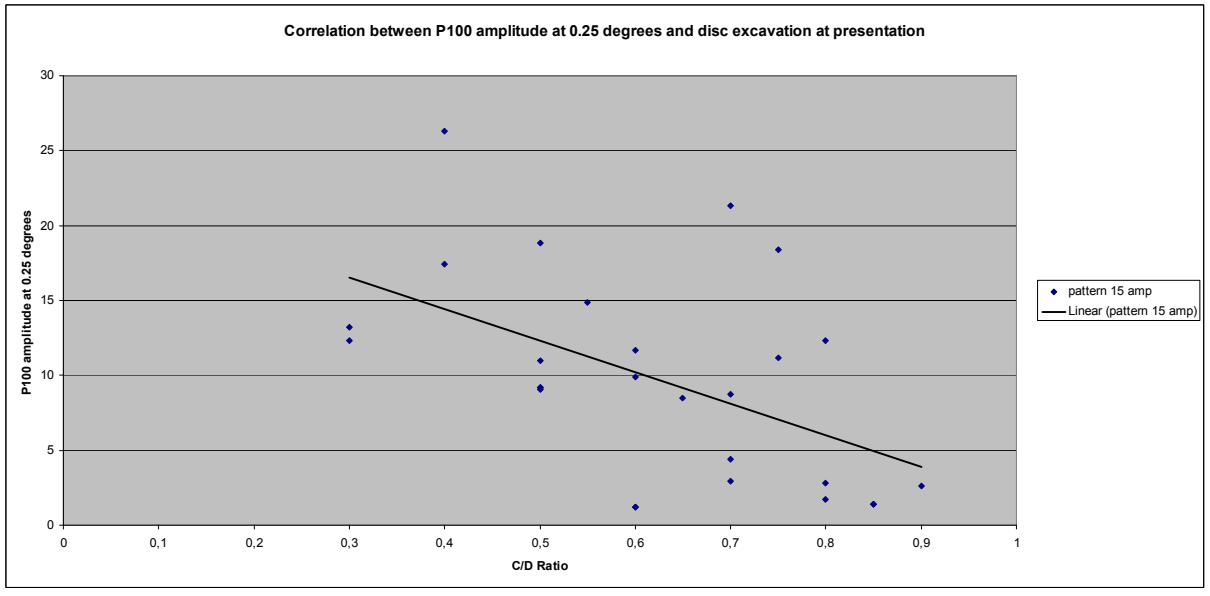

Fig. 3 Correlation between P100 amplitude at 0.25 degrees and disc excavation at presentation

These strong correlations between C/ D ratio and amplitude might be explained by the group composition, which had a relatively larger proportion of advanced glaucoma as compared to global glaucoma population.

At subsequent visits, C/ D ratio in group A remained identical, except for 3 patients: the excavation of LE in patient B.M. increased on LE from 0,5 to 0,6; in patient F.I. left eye C/ D ratio increased from 0,3 to 0,5 and in patient G.F. increased both on RE (from 0,4 to 0,5) and on LE (from 0,5 to 0,6). On the other hand, VEP modifications were significant for most patients, even without changes in fundus exam (**Table 3**).

Table 3. P100 latency evolution between visits in group A

Initial	1 month	3 months	6 months	1 year
113,3	112,8	114,8	113,9	115,3
148,5	149,3	148,7	151,2	150,1
108	108,6	108,2	107,6	107,8
109,2	109,5	109,7	109,3	110,6
115,1	115,4	115,2	116,4	118,1
116	114,5	114,7	112,9	113,6
128,6	132,4	135,7	130,3	133,6
122,7	120,8	124,8	126,7	125,1
113,9	114,7	118,4	120,6	118,7
120,4	120,8	120,7	128,4	129,2
110,4	114,2	107,3	111,6	112,4
109,8	111,4	113,5	111,7	115,7
132,1	135,7	136,6	138,9	137,5
145	149,8	146,2	146,4	145,9
118,6	121,5	126,8	130,2	130,5
116,8	116,4	123,7	127,9	125,7
102,7	111	114,8	115,6	114,6
104,5	101	102,8	103,5	102,9
128	133,1	131,9	135,8	136,3
116,8	118,2	119,5	120,6	123,7
116,8	115,7	117,4	119,9	121
113,3	116,4	119,4	122,3	125,7
128	128,8	130,6	132,4	133,5
116,8	117,4	119,5	122,3	121,8
113,3	114,1	113,6	117,4	116,9
109,8	114,2	116,5	120,3	119,4
115,7	116,4	115,2	115,9	117,1

Thus, at the initial visit, the medium value of the P100 latency at 1 degree was 118.3 (+/ - 4,3211 for 95% CI; +/ - 5,8313 for 99% CI). At the final visit, the medium value was 123,063 (+/ - 4,4584 for 95% CI; +/ - 6,0167 for 99% CI). Between the first and final visit there was a statistically significant difference (p 0,0001) for P100 latency at 1 degree (**Table 4**).

Table 4. Analysis of statistical significance of P100 latency between initial visit and final visit

Data Summary					
	A	B	Total		
n	27	27	54		
$\sum X$	3194.100000	3322.700000	6516.800000		
$\sum X^2$	380950.79	412189.5299	793140.3199		
SS	3086.76	3288.223	6683.2415		
mean	118.3	123.063	120.6815		
Results					
Mean a – Mean b	t	df		one-tailed	<.0001
-4.763	-6.11	26	P	two-tailed	<.0001

At the 6 months visit, the medium value of P100 latency at 1 degree was 122,5926 (+/ - 5,8313 for 99% CI, +/ - 6,1829 for 99% CI), which has been significant (p<0,0001). At the 3 months visit, the medium value of the P100 latency at 1 degree was 120,9704 (+/ - 4,4532 for 95% CI, +/ - 6,0096 for 99% CI), not statistically significant (p = 0,377565) (**Table 5**).

Table 5. Analysis of statistical significance of P100 latency between initial visit and at 3 months visit

Data Summary					
	A	B	Total		
n	27	27	54		
∑ X	3194.100000	3266.200000	6460.300000		
∑ X^2	380950.79	398393.9599	779344.75		
SS	3086.76	3280.5363	6465.5631		
mean	118.3	123.063	120.6815		
Results					
Mean a – Mean b	t	df		one-tailed	0.1887825
-2.6704	-0.89	52	P	two-tailed	0.377565

At the 1-month visit, the medium value of P100 latency at 1 degree was 119,7815 (+/ - 4.5701 for 95% CI, +/ - 6,1674 for 99% CI), also not statistically significant (p = 0.626195).

In group B, the modification of C/ D ratio was noticed in 3 patients. In patient T.E., it changed both for RE (from 0,35 to 0,5) and for LE (from 0,35 to 0,4). In patient P.A., the C/ D ratio increased on RE from 0,75 to 0,8. In patient R.A. it increased on RE from 0,2 to 0,4.

During the study, it was necessary to modify the anti-glaucomatous treatment for 2 patients out of 13 in group B. For group A, change of treatment has been necessary for 9 patients out of 16 (Fischer test p = 0.02829688993848931). Therefore, supplementary data helped adjust the treatment for more patients in group A as compared to group B, and the difference was significant from a statistical point of view.

Discussions

Examination in glaucoma includes certain mandatory exams, such as applanation tonometry, fundus exam and automatic perimetry. Besides these, there are other types of examinations that can be supplementary or complementary. The choice of tests to be used should be considered according to how much information they are able to provide and according to how easily they can be carried out for the respective patient.

In order to determine how informative such a test is, we have to consider its prediction power, its sensitivity and specificity, as well as its relevance and variability. Other types of information may refer to costs and time necessary to carry it out.

PRVEP was a useful tool in glaucoma diagnosis and progression monitoring when compared to the visual field (MD = mean defect and PD = pattern deviation), with different results between studies. Thus, Mokbel TH and Ghanem AA and, respectively, Cothary et al. obtained a negative correlation between MD and the P100 latency, while Grippo et al. did not obtain a clear correlation between MD and the P100 latency. To our knowledge, no correlation between PRVEP and RNFL or various sectors of RNFL has been analyzed in these patients.

There are studies that analyzed the way the patients perceived these investigations. In addition, Gardiner et al. [**5**] followed up 7 tests that the patients had to place in order between 1 (the most comfortable) and 7 (the least comfortable). In this study, the patients indicated Goldmann applanation tonometry on the first place (median/ average place 2.5), followed by HRT (median place 3.3), double frequency perimetry and VEP (median place 4), then automatic perimetry (median place 4.8) and SWAP automatic perimetry (median place 5.3). Bjerre et al. also showed that the patients preferred VEP in comparison with automatic perimetry SITA [**6**].

Unlike other studies, the present prospective study included patients whose

compliance capacity did not allow automatic perimetry and OCT exam to be carried out. The study analyzed if, under these circumstances, VEP examination could be performed within the routine management of these patients.

Conclusions

- To our knowledge, no results of VEP measurements, able to replace automatic perimetry and/ or OCT exam of the optic nerve, have been determined so far, even if there have been studies in which OCT modifications correlated to the perimetry modifications or those of the OCT scan of the optic nerve;
- There are glaucoma patients who, due to varied reasons, are not compliant enough to be able to carry out these tests.
- These patients are usually older persons, as age also represents one of the three significant risk factors for the development of glaucoma; these patients will frequently develop more advanced glaucoma than normal glaucomatous population.
- Even as early as the first visit, these patients presented a positive correlation between the C/ D ratio and the P100 latency at 1 degree and a negative correlation between C/ D ratio and the P100 amplitude both at 1 degree (60 arcminutes) and at 0.25 degrees (15 arcminutes);
- For these patients, the C/ D ratio variation in this study was not significant, but the P100 latency has varied significantly at 6 months and 1 year compared to the initial visit. For 1 month and 3 months visits, the difference was not significant compared to the initial visit;
- The data thus obtained led to the modification of treatment in 2 patients out of 13 for group B and in 9 patients out of 16 in group A (Fisher test, p = 0.02892698993848931);
- The authors of the study consider that VEP provides supplementary data that significantly helps guide treatment and monitor progression.
- For these patients, we recommend the PRVEP evaluation at a 6 months interval;
- We intend to follow up these patients for a longer period and add new patients, in order to deepen our understanding of the visual evoked potentials utility.

Acknowledgements

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CASE REPORT

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A multimodal study and management of retinitis punctata albescens

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Abstract

Purpose: To study disease progression and visual function in a patient with retinitis punctata albescens (RPA).

Method: Observational case report. The retinaldehyde-binding protein 1 gene (RLBP1) was analyzed by direct genomic sequencing. A complete ophthalmologic examination was performed.

Results: Mutations in the RLBP1 gene were identified in the patient. The patient's fundus (OF) showed numerous white dots with diffuse retinal mottling. Her visual function deteriorated progressively during the follow-up. Optical coherence tomography (OCT) demonstrated bilateral cystic macular edema that worsened if the patient stopped dorzolamide topical therapy.

Conclusions: The multimodal study is useful in the characterization of retinal dystrophies, in association with neurophysiological tests. Degenerative changes of the outer retina were detected by OCT.

Keywords: retinitis punctata albescens, electroretinogram, visual field, optical coherence tomography

Abbreviations: RPA = Retinitis punctata albescens, RP = retinitis pigmentosa, IOP = Intraocular Pressure, BCVA = Best Corrected Visual Acuity, OD = right eye, OS = left eye, OU = both eyes, BMC = biomicroscopy, AF = autofluorescence, OF = ocular fundus, ERG = electroretinogram, OCT = optical coherence tomography, VF = visual field, VEP = visual evoked potentials, CME = cystic macular edema, MD = mean deviation, RLBP1 = retinaldehyde-binding protein 1

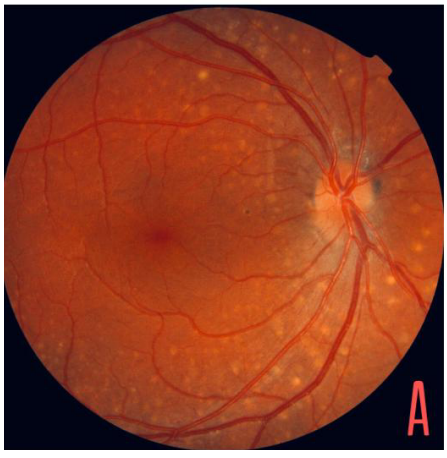
Introduction

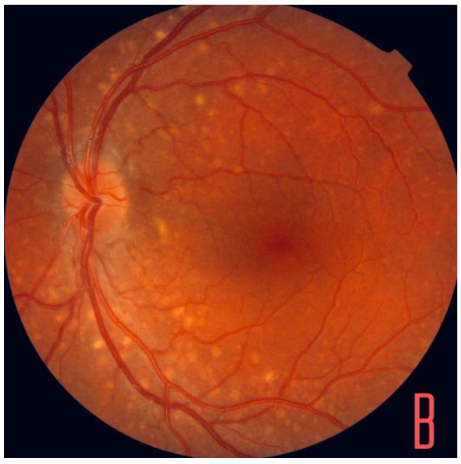
Retinitis punctata albescens (RPA) is a progressive retinal rod-cone dystrophy, primarily of autosomal recessive inheritance, considered an atypical or incomplete variant of retinitis pigmentosa (RP) [**1**]. It is characterized by the funduscopic finding of rounded white-yellowish deposits in the retina, especially at the level of the equator. It is associated with nyctalopia, decreased visual acuity (BCVA), campimetric alterations, and reduction or

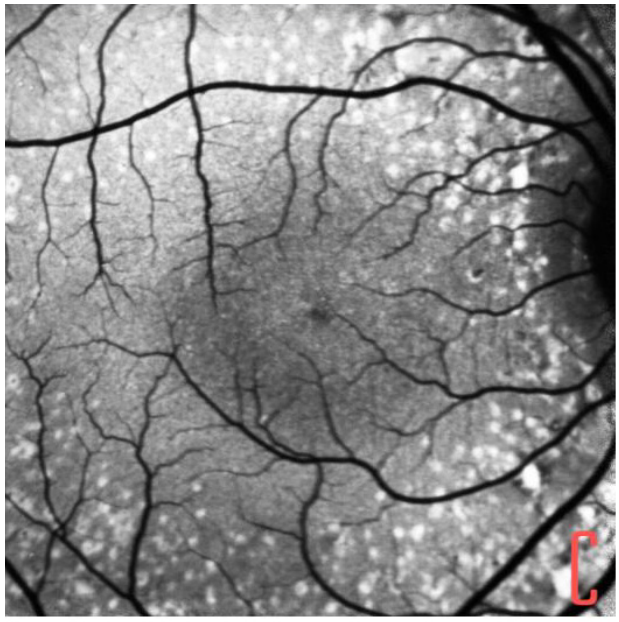
absence of response to stimuli in the electroretinogram (ERG), as well as RP [**2,3**].

Case report

We presented a 10-year-old woman who had nyctalopia as the main symptomatology. She presented no personal or family history of interest, except hyperopia of +9 diopters. In the ophthalmological examination, the BCVA was 20/ 20 in the right eye (OD) and 20/ 25 in the left eye (OS). Biomiscroscopy (BMC) and intraocular pressure (IOP) were normal. In OF, yellowish rounded subretinal lesions were observed in both eyes (OU), following the distribution of the temporal vascular arches, respecting both macules (**Fig. 1 A,B**). The OCT did not show alterations at the macular level. In autofluorescence (AF), hyperfluorescent lesions corresponding to subretinal lesions were observed, without other pathological findings (**Fig. 1 C,D**).







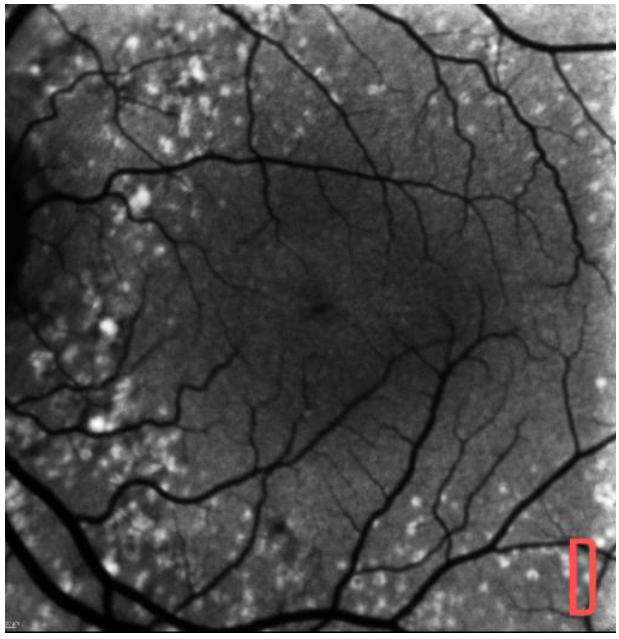


Fig. 1 A,B Color retinographies: Presence of numerous white-yellowish rounded lesions of subretinal appearance that respect the macular area. **C,D** Autofluorescence: Hyperreflectivity corresponding to subretinal lesions

Due to these findings, complementary neurophysiological tests such as visual evoked potentials (VEP) and electroretinogram (ERG), and visual field (VF) 30-2, were requested. The VEPs showed a regular morphology with wave

latency peaks and amplitudes within normal limits, while the ERG revealed some irregular morphology potentials, collecting the latencies of a waves and conserved and increased the b waves in OU, both in photopic and in scotopic conditions.

The VF 30-2 showed peripheral arciform defects and general reduction of sensitivity in OU, with a mean deviation (MD) of -5.93 dB (p <1%) in OD and -7.46 dB (p <0,5%) in OS, and with a standard deviation above the average of 1.91 dB in OD and 1.82 dB in OS. The genetic test was positive for the mutation in the gene that codes for retinaldehyde-binding protein 1 (RLBP1), so the diagnosis of retinitis punctata albescens was confirmed.

In subsequent reviews, the patient presented several episodes of cystic macular edema (CME) of less than 500µ, which have been partially controlled by treatment with topical dorzolamide every 12 hours, occasionally using different oral acetazolamide guidelines. Due to the worsening of the CME after the suspension of the topical treatment, the application of topical dorzolamide has been maintained chronically. In the last examination, the BCVA was 20/ 30 in OU, the lesions described in the OF did not present changes and small intraretinal cysts could be seen in the macular OCT (**Fig. 2**).

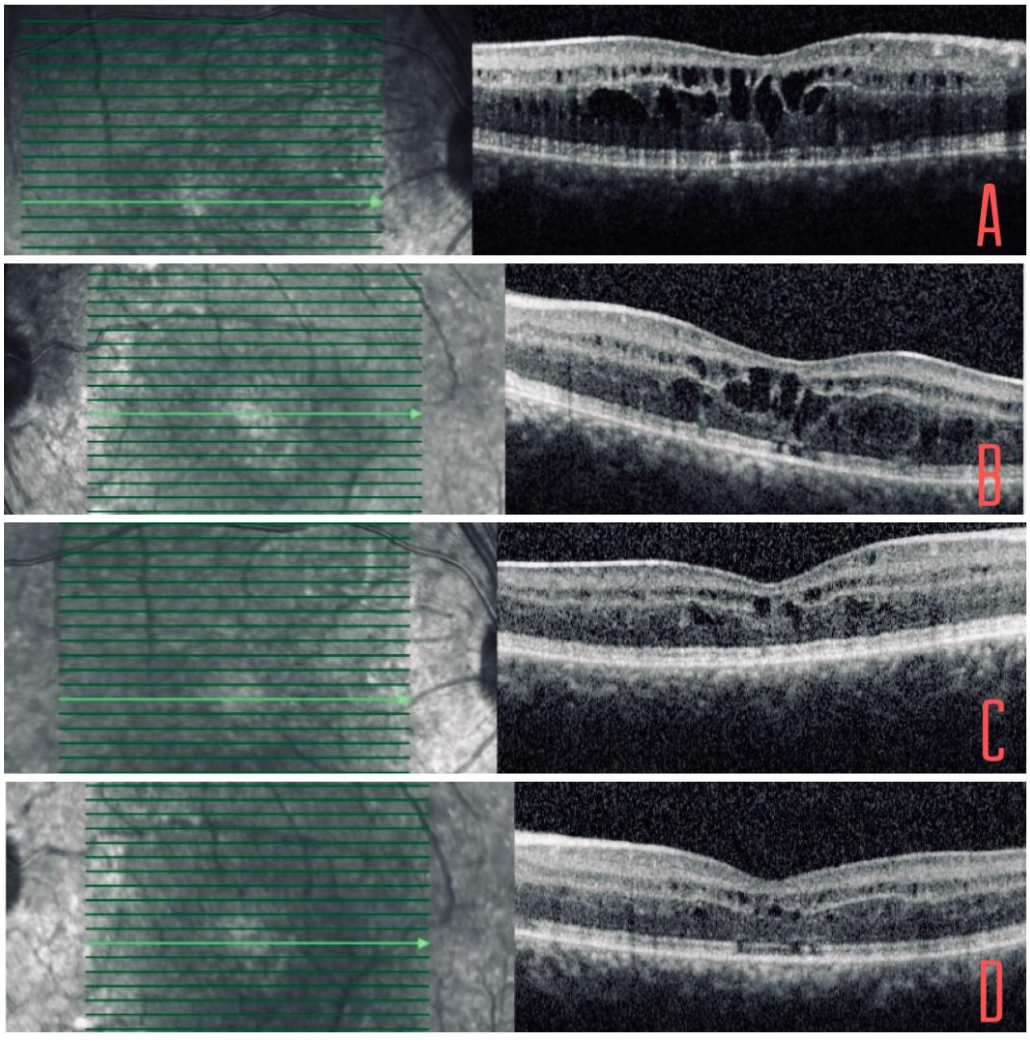


Fig. 2 A,B Macular OCT at the onset of cystic macular edema in which foveal profile involvement and irregularities in external layers can be seen. **C,D** Current macular OCT with control of cystic macular edema due to chronic treatment with topical dorzolamide

Discussion

RPA is a rare form of RP. This rod-cone dystrophy has an incidence of 1/ 800,000 cases worldwide [**3**].

Various forms of transmission have been described, the autosomal recessive inheritance being the best known, generally due to mutations in the RLPB1 gene, although other associated genes have been described, as well as mutations in this gene, relations with other retinal dystrophies, such as Bothnia retinal dystrophy (BD), Newfoundland rod-cone dystrophy (NFRCD), and fundus albipunctatus (FA), so it can be stated that there is heterogeneity of phenotypic expression, according to the structure of the compromised protein [**4-6**].

The RLPB1 gene codes for the so-called cellular retinaldehyde-binding protein 1 (CRALBP), whose function is to bind to 11-cis-retinol that will be transformed into 11-cis-retinal to form visual pigments in both cones and rods, have as main manifestation the reduction of vision, starting with nyctalopia [**7,8**].

As observed in the case described, the same clinical manifestations as in a pigmentary retinopathy are present in the disease, with the OF in salt and pepper and characteristically the appearance of well-defined and rounded white-yellowish lesions, whose origin is at the level of the pigmentary epithelium [**2,9**].

Because the function of the photoreceptors is affected by the pathophysiological process, neurophysiological tests confirm the deterioration and, in advanced stages, the abolition of the responses of both cones and rods may be present [**1**].

The visual prognosis depends on the degree of macular atrophy generated during the course of the pathology, which is usually progressive [**2**].

Conclusion

In conclusion, the case presented is a rare association between the RPA and the CME, in which, besides the dystrophy itself, we faced the challenge of the management of persistent CME within the pathology, probably caused by the incompetence of the RPE, which worsened the patient's visual prognosis.

Formerly, the diagnosis was based on clinical and neurophysiological tests. At present, a more complete study can be carried out to characterize the damage of the retinal outer layers, as well as the possible additional complications.

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Disclosures

The authors declare that they have no links of interest in relation to this article.

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CASE REPORT

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CRMP-5-IgG Antibody: role in the bilateral uveitis with swollen disc

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Abstract

Autoimmunity against collapsin response-mediator protein-5 (anti-CRMP-5) has been associated with ocular inflammation in paraneoplastic syndrome.

We present a 59-year-old Caucasian man with optic neuritis and vitreous cells in both eyes (OU), at different stages. Despite the fact that the patient did not have any systemic disease, we suspected a paraneoplastic syndrome and requested CRMP-5-IgG and a mediastinoscopy. After performing the tests, a small cell lung carcinoma was diagnosed.

Autoantibody CRMP-5-IgG positivity and optic neuritis combined with vitreous inflammation was defined as a paraneoplastic entity, avoiding vitreous biopsy and allowing us to suspect malignancy before systemic symptoms appeared.

Keywords: paraneoplastic conditions, optic neuritis, CRMP-5 IgG, small cell lung carcinoma

Introduction

Uveitis is a vision threatening disease that represents a diagnostic and therapeutic challenge for ophthalmologists [**1**]. Noninfectious uveitis' effect on years of vision loss and its economic repercussions are particularly important [**2**]. Posterior uveitis can be classified by its etiology and that includes infectious causes (tuberculosis, syphilis) and non-infectious causes (sympathetic ophthalmia, masquerade neoplastic, Behçet disease, sarcoidosis or Voght-Koyanagi-Harada disease).

Paraneoplastic syndromes result from immune-mediated reactions produced by antibodies that cause cross-reactions between components of the tumor and other components of our body. They can be associated with many malignancies but the most common is small-cell lung cancer (SCLC) (9% of the patients) and usually precedes the tumor diagnosis [**3**].

Ophthalmic paraneoplastic syndromes impair about 0.01% to 1% of the patients with malignancies [**4**] with manifestations purely affecting the eye - retina or choroid involvement - or also involving central and peripheral nervous system. The ophthalmologist may have an important role in the work-up, because paraneoplastic syndrome can be the first sign of a non-diagnosed cancer. Bussat et al. have recently reviewed the predominant antibodies in paraneoplastic syndromes affecting the eye, identifying 9 of them: Anti-Ri, Anti-Ma, Anti-Hu, Anti-Yo (PCA1), Anti-TR (PCA2), CV-2 (CRPM5), Amphiphysin, Recoverin and Anti-surface antigen Ab VGCC [**5**].

SCLC generates from neuroendocrine-cell precursors and distinguishes itself by its fast growth and its chemotherapy and radiotherapy's high response rates, whereas resistance to treatment is very low. In the Western world, the ratio of population with SCLC has reduced to 10-15% of the total of lung cancer cases. Most of those patients suffering from SCLC share a history of tobacco use, this being one of the main risk factors known (ESMO). A wide diversity of paraneoplastic syndromes has been related to SCLC. In fact, this cancer type has a high mutational burden, which is associated with the presence of multiple neoantigens that can modulate the immune system.

We present the case of a patient with posterior uveitis and bilateral papillitis manifesting as a paraneoplastic syndrome, with a positive CRMP-5 antibody, comparing it with the ones in published literature.

Case report

A 59-year-old man consulted our service due to a bilateral and painless visual loss. He started presenting blurred vision on his left eye (LE) the prior week, which became bilateral in 48 hours. He was a smoker of 52 packets/ year and he also reported high blood pressure, which was controlled with torasemide 5mg/ day and amlodipine 10mg/ day. He denied any other relevant medical history past.

Ophthalmic examination revealed a reduced visual acuity (VA), 20/ 125 in his right eye (RE) and hand movement in his left eye (LE). The slit lamp examination revealed a non-swollen anterior pole, but in the fundus examination we found a moderate vitreous cellularity (1+) on his RE and a dense vitreous cellularity (2+) on his LE. Moreover, we found a bilateral swollen optic disc (**Fig. 1A**), an arteriolar narrowing and vascular tortuosity without sheathing retinal veins. Fluorescein angiography examination revealed a hyper fluorescence and leakage in the optic nerve without any vasculitis signs (**Fig. 1B**). A CT-scan was normal and the chest X-ray revealed enlargement of both hila. With a suspicion of posterior uveitis with bilateral papillitis we initiated 1-gram Methylprednisolone x 5 days.

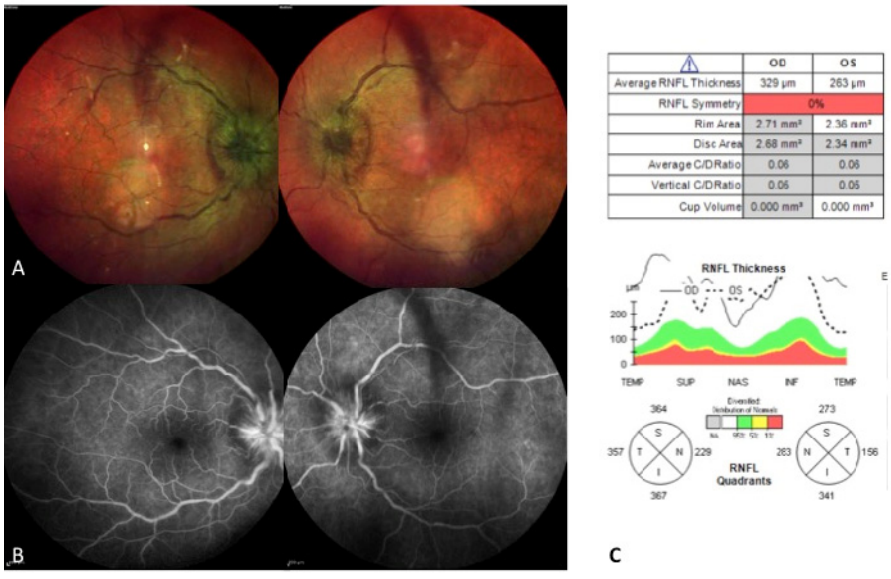

Fig. 1 The swollen disc at diagnosis. A bilateral leakage with no signs of vasculitis is shown in the fluorescein angiography

A total-body CT-scan only revealed enlargement of para tracheal bilateral nodes, and the cerebral MRI was normal. The purified protein derivative (PPD) skin test, Interferon-γ release assay, HLAB27, HLA B51 and Angiotensin-converting enzyme (ACE) were negative, with the rest of the biochemistry being unremarkable. Two different biopsies made by echo-endoscopy revealed necrotic areas without granulomas or evidence of malignancy. A new ophthalmologic examination showed a total resolution of the vitritis, without evidence of retinitis or choroiditis, with diminution of the swollen optic disc (**Fig. 2A**) and a fast recovery of his VA becoming 20/ 20 in OU during the first weeks, although an enlargement of the blind spot, and some peripheral scotoma in his visual field persisted (**Fig. 2C**).

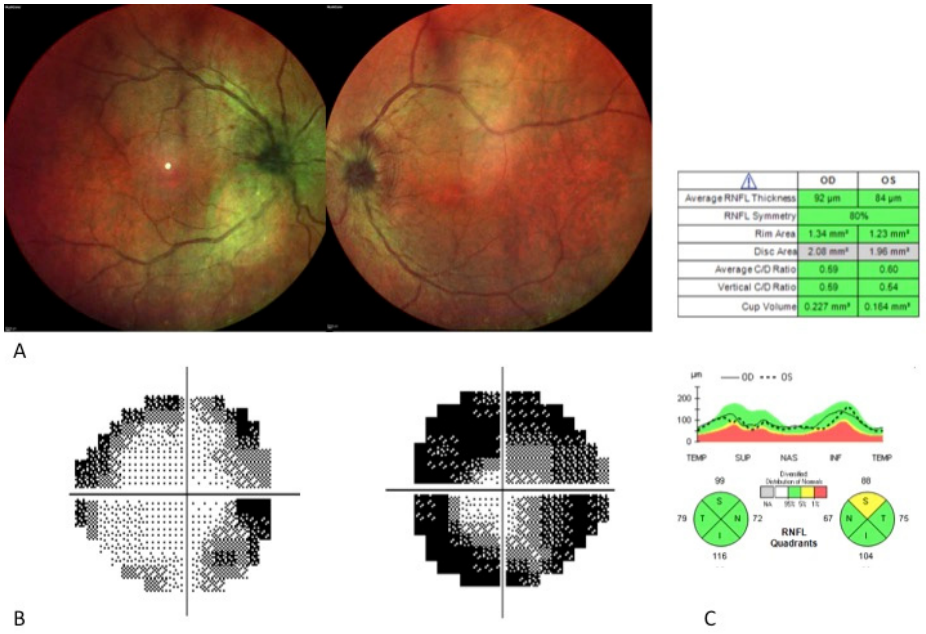

Fig. 2 Improvement of the bilateral swollen disc after corticosteroid treatment

A CT-scan was repeated and multiple node enlargements in mediastinum and bilateral hilum were still identifiable, so we decided to perform a mediastinoscopy, which revealed a SCLC. Serologic evaluation of paraneoplastic autoantibody profile was positive to CRMP-5-IgG positive.

The patient was referred to the oncology department with a diagnosis of SCLC with limited involvement of the thorax. Initially, a concomitant treatment with cisplatin and etoposide together with radiotherapy was considered. However, due to the fact that all the affected territories could not be included in a single radiation field, an induction chemotherapy was started. After three cycles of treatment, a partial response was achieved, hence concomitant radiotherapy was at that point feasible. After three cycles of chemo radiation, a complete response was achieved.

Discussion

Acute or subacute visual loss with papillitis and vitritis is a challenging clinical problem for ophthalmologists and other clinicians. Paraneoplastic syndromes have always intrigued neurologists because of their role in the identification of the malignancy of a neurologic syndrome and in the molecular biology, which characterizes the antigens recognized by paraneoplastic antibodies, as well as in the identification of neuronal restricted proteins that are major for a successful operation of the nervous system.

CRMP-5 is the 62kDa member of a family of nervous system-restricted proteins that mediate signaling by the axon repulsive guidance cue collapsing-1 (Sema3A) [**6**]. Autopsy findings in CRMP-5 positive patients proved a prevailing infiltration of CD8+ T cell and corresponding areas of nerve fiber and myelin loss, microglial activation with perivascular lymphocytic cuffing (90% CD8+ T cells) in mesial temporal structures, cerebellum, brainstem and spinal cord, and loss of myelinated axons in peripheral nerves, spinal rootlets and spinal sensory ganglia [**7**]. Malik et al. first reported CRMP-5 in 1992 and Honnorat et al. called it CV-1 in 1996 [**8**]. Yu et al. studied 121 CRMP-5 positive patients among 68.000 who were suspected of paraneoplastic syndrome. The most frequent diagnosis was chorea (11%) and cranial neuropathy (17%, including 10% loss of olfaction/ taste, 7% optic neuropathy). Other signs were peripheral neuropathy (47%), autonomic neuropathy (31%), cerebellar ataxia (26%), subacute dementia (25%), and neuromuscular junction disorders (12%). Lung carcinoma (mostly limited small-cell) was found in 77% of the patients; thymoma was found in 6% [**9**]. The main studies relating optic neuritis and CRMP-5-IgG, and paraneoplastic syndrome are summarized in **Table 1**.

Table 1. Reports of other paraneoplastic syndromes

Table 1	Age Sex	Tumor	Presentation	Visual field (VF)	Fundoscopy	Fluorescein angiography	Evolution
Cross et al. 16 cases [7]	52-74 (W)	11 SCLC 1 Breast C 1 MGUS 1 Mesenchyme	15 Subacute and painless 1 progressive myelopathy	Blind spots enlargement Arcuate, altitudinal defects Paracentral scotoma Peripheral constriction General depression	Bilateral swelling (15/ 16) Cells in posterior vitreous (9/ 16) Cells in anterior chamber (1/ 16)	Nerve head hyperfluorescence Leakage (Peripheral retinal inflammation)	6 Died (> 5 years) 8 alive (12 months) 2 no follow-up
Toribio-garcia et al. [10]	64 (M)		Subacute painless Bilateral RE 0,4 LE: Hands movement	---	Vitritis	---	Resolution visual abnormalities. Not reported
Murakami Y et al. [11]	55 (W)	Lung adeno-carcinoma	Subacute, Bilateral 20/ 400	Central scotoma Enlarged blind spot	Bilateral Swelling No inflammatory cells	Hyperfluorescence Leakage	
Cassewell et al. [12]	52 M	SCLC	Painless loss of vision progressing over 4 months in OU	Constricted bilaterally with central scotomata	6/ 60 RE, 3/ 60 LE pale and swollen (**Fig. 1a**) and clinically diffuse odd retinal sheen	Optic disc diffuse leakage OCT revealed bilateral macular atrophy, with disruption of IS/ OS junction	Chemotherapy completed. Remission
Cassewell et al. [12]	58 (M)	SMLC	6/ 60 RE and counting fingers LE	RE VF markedly constricted; LE VF constricted and with a dense central scotoma	OU moderate vitritis. Swollen and pale optic discs	Diffuse optic disc's capillaries leakage and marked peripheral vessels leakage	The patient died soon afterwards
Saito M et al. [13]	67 (M)	SMLC	Central vision loss RE progressin over a month VA was 0.8 RE and 1.2 LE		++ anterior vitreous cells OU. Swollen optic disc surrounded by serous retinal detachment (SRD), dilated tortuous veins OU, and subretinal opaque exudation at the fovea RE	Hyperfluorescence with late leakage from the optic disc and retinal venous wall staining OU Hyperfluorescence at the fovea OCT showed SRD adjacent to the optic disc OU and dome-shaped hyperreflective lesion extending from the inner nuclear layer to the photoreceptor layer (foveal exudation)	
Margolin E et al. [14]	62 (M)	SCLC	Slow progressive visual loss 20/ 70 in the RE and finger counting in the LE	A mean deviation of 15 dB in the RE and 15.8 dB in the LE without localizable features	++ vitritis and bilateral papillitis	Mild late optic disc leakage in OU	
Morita M et al. [15]	60 (M)	SCLC	Photophobia, vision decreased and paresthesia of limbs	Reduced VA (RE 20/100, LE 20/ 22)	Few abnormal findings in the fundoscopy	No other abnormal optic nerves findings by fundoscopy and fluorescent fundus angiography	Died 7 months after diagnosis

Our case was relevant because in the diagnosis of posterior uveitis with bilateral papillitis, the CRMP-5 antibody should have been performed and malignancy should have been ruled out in order to obtain a definitive diagnosis as soon as possible. Despite the great efforts to improve the outcome of the patients with SCLC, the treatment has not changed in the past 30 years. Platinum salts and radiotherapy remain the standard of treatment in both, advanced and limited disease of the chest. The stage of the disease is the main prognostic factor, but in general, this cancer type has poor prognosis, showing an overall survival at two years of around 20% in limited-disease and < 5% in extensive-disease.

Ethical approval

This report has been approved by Valencia University research ethics committee and adheres to the tenents of the Declaration of Helsinki.

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Conflicts of interest and source of funding

None.

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None.

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CASE REPORT

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Use of Vivostat PRF® in Acanthamoeba keratitis

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Abstract

We present a case of a 27-year-old contact lens male user who was diagnosed with Acanthamoeba keratitis. Given the inefficiency of medical treatment and high risk of corneal perforation, we decided to use Vivostat PRF®, with satisfactory results. To our knowledge, this is the first described case in medical literature in which Vivostat PRF® is used as part of Acanthamoeba keratitis treatment.
Keywords: Acanthamoeba, keratitis, Vivostat PRF®

Introduction

Acanthamoeba is a protozoon that is ubiquitous in air, dust particles, water and upper respiratory tract. Its life cycle is based on a cystic state, which is very resistant and can turn into a trophozoite state when correct ambient conditions are given, which is capable of breaking through and destroying tissues [**1,2**].

Symptoms of patients with Acanthamoeba keratitis include blurry vision and pain, which may be not proportional to the severity of clinical signs. Initial alterations observed are superficial punctate keratopathy, epithelial pseudodendrites and perineural infiltrates. On a second stage, patients develop a corneal ulcer with an annular infiltrate and a marked inflammatory reaction in anterior chamber with hypopyon. Limbitis is also characteristic in affected patients [**1,2**].

Acanthamoeba keratitis is more frequent in contact lens users [**2**].

It is especially important to assure a correct diagnosis of Acanthamoeba keratitis in an early phase given that the prognosis is more favorable if early diagnosis and treatment are established. In fact, it is convenient to begin treatment with diamides and biguanides with the slightest doubt, even before laboratory's diagnosis confirmation [**1,2**].

Case report

A 27-year-old soft contact lens Caucasian male user with no medical history of interest, referred intense pain, photophobia, tearing and ocular redness in his left eye over the past four weeks. He had been previously treated with topical erythromycin, ciprofloxacin, tobramycin and dexamethasone with no symptomatic improvement. He admitted to have given contact lens an inappropriate use, as he wore them for over 12 hours each day, he showered with them on and even swam in rivers and swimming pools while wearing them.

His visual acuity was 1.0 and 0.1 in his right and left eye respectively according to Snellen's scale. Intraocular pressure and pupillary light reaction were normal in both eyes. Anterior segment biomicroscopy of his left eye showed conjunctival hyperaemia, diffuse corneal

decompensation and a paracentral annular infiltration with radial perineuritis (**Fig. 1A,B**). Fundus examination revealed no significant findings. Right eye examination showed no alterations.

Acanthamoeba keratitis was suspected, corneal scraping was carried out and PCR, Gram analysis and sample cultures were requested. Empirical treatment with topical 0.1% Brolene®, 0.02% chlorhexidine, vancomycin, ceftazidime and atropine were started. A favorable initial response was observed as ten days after starting this treatment visual acuity in his left eye had improved to 0.6. Topical fluorometholone was then added.

PCR results were positive for Acanthamoeba, Klebsiella, Serratia and S. Aureus.

Treatment was not modified due to the patient's positive response.

The follow-up was at eight weeks after he showed a significant clinical improvement. Conjunctival hyperaemia, stromal haze and anterior chamber reaction had noticeably decreased and visual acuity was 0.8 (**Fig. 1C,D**). Treatment was therefore slowly tapered down over the following weeks. Weekly follow-up check-ups were carried out.

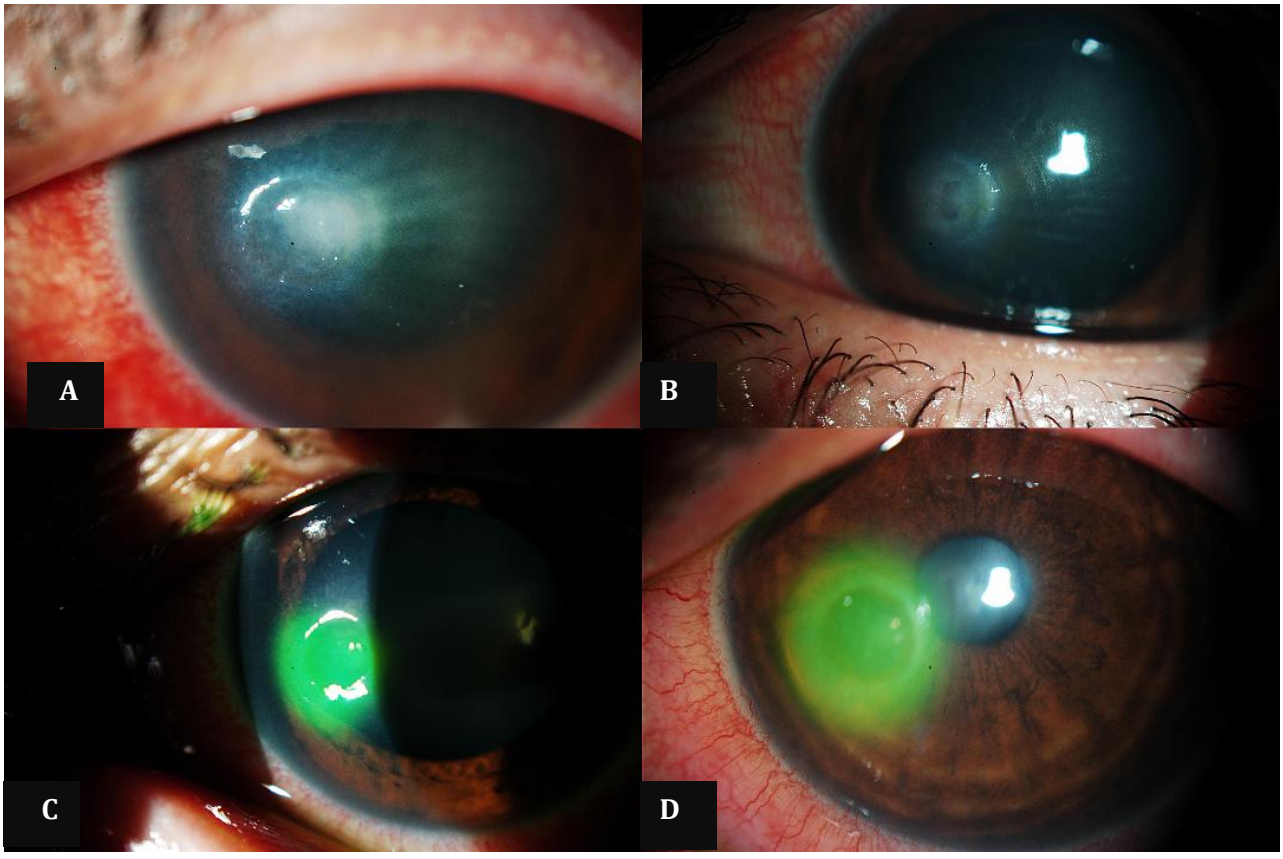
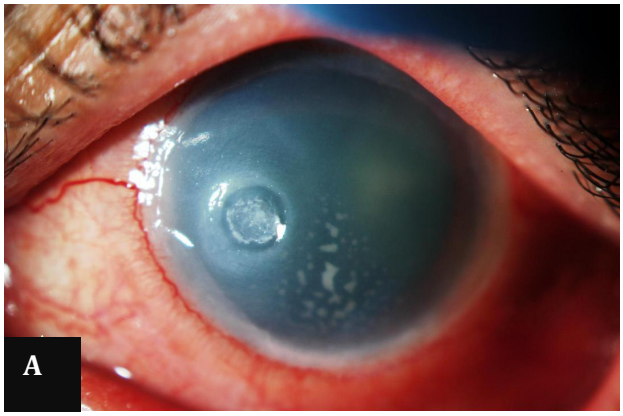


Fig. 1 A,B Conjunctival hyperaemia and annular infiltration with radial perineuritis; **C,D** Eight weeks after diagnosis; improvement in corneal transparency and no radial perineuritis

Another follow-up review took place five months after he showed a drastic clinical deterioration. Anterior segment biomicroscopy revealed diffuse corneal transparency loss with endothelial deposits affecting inferior hemicornea, ulcer thinning, intense anterior chamber reaction and cataract formation (**Fig. 2**). Corneal scraping was repeated to rule out overinfection and autologous serum, topical linezolid and oral valaciclovir were empirically added to the initial treatment. Cultures then showed Pseudomona aeruginosa growth.



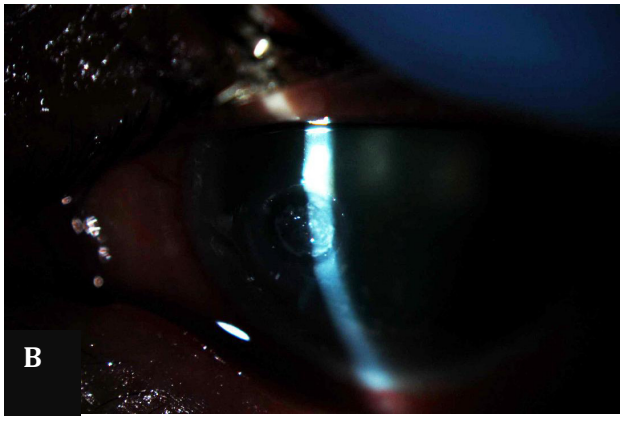


Fig. 2 Five months into treatment; loss of corneal transparency, ulcer thinning and endothelial precipitates

Over the following two weeks, corneal thinning increased, therefore underlying the existence of a significant perforation risk. Having no corneal donor, the amniotic membrane was used to cover the corneal defect, with unsatisfactory results. Two weeks later we decided to add Vivostat PRF® in order to increase the corneal resistance to perforation and to favor its regeneration (**Fig. 3A**).

6 weeks into Vivostat PRF® treatment, corneal ulceration was healed leaving behind a dense residual leukoma and inflammatory activity ceased (**Fig. 3B**). Our patient is currently waiting for combined keratoplasty and cataract surgery.

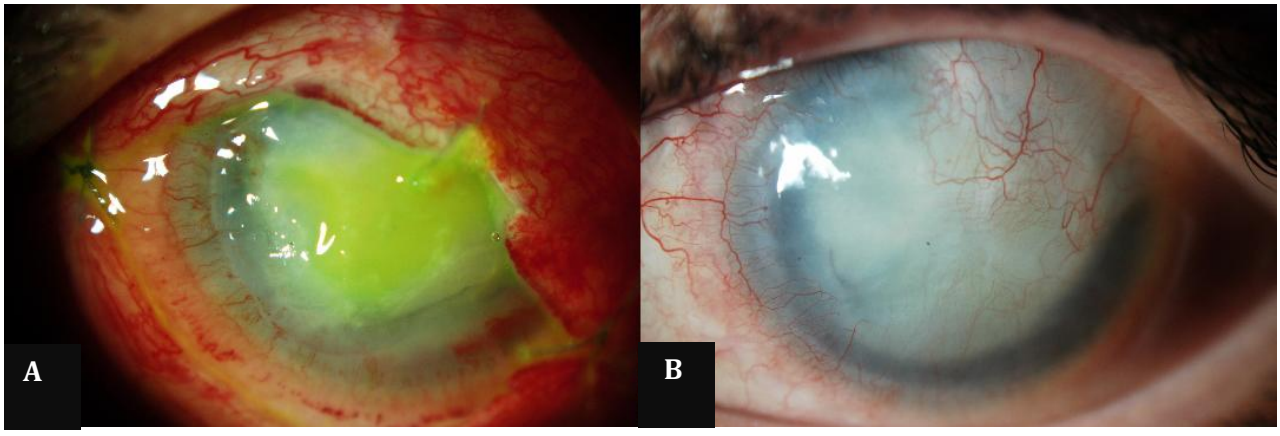


Fig. 3A Vivostat PRF® over the cornea with absorbable sutures; **B** Six weeks after Vivostat PRF®; noticeable inflammatory activity decrease, corneal leukoma and neovascularization and white cataract

Discussion

Although there is no protocolized treatment for Acanthamoeba keratitis, in most cases topical treatment with 0.1% diamidines, 0.02% biguanides and low dose corticoids is initially used [**3**].

Vivostat PRF® is a fibrin sealant platelet-rich membrane, which aids tissue regeneration and is obtained from the patient's own blood after carrying out high-speed centrifugation. The membrane is then sutured over the area-to-treat and fibrin polymerization immediately takes place over the defect covered by the membrane [**4-6**]. In our case, we sutured the fibrin compound to the cornea using absorbable

sutures (**Fig. 3**).

Vivostat PRF® has been used in different medical specialties such as traumatology, cardiology, maxillofacial surgery, digestive tract surgery, urology, plastic surgery, otorhinolaryngology and neurology during surgical interventions in order to aid tissue regeneration [**6-9**]. To our knowledge, this is the first described case in medical literature in which Vivostat PRF® is used in Acanthamoeba keratitis treatment.

In our case, adding Vivostat PRF® to the classic treatment of Acanthamoeba keratitis was the key to increase corneal resistance and ease its regeneration process.

Conflict of interest

Authors declare no conflict of interest.

Sources of funding

There are no funders to report for this submission.

Ethical Clearance for study

A written consent was gathered from the patient in order to obtain and publish these images.

Ethical Statement

Our study did not require an ethical board approval because it did not contain human or animal trials.

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CASE REPORT

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Ocular cicatricial pemphigoid

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Abstract

Ocular cicatricial pemphigoid (OCP) is an autoimmune ocular disease that causes severe dry eye syndrome, conjunctival scarring with inferior fornix shortening and entropion along with trichiasis. Corneal keratinization and corneal ulcers may lead to permanent vision loss. The therapeutic approach of OCP is a challenging one. Thus, the treatment consists of a systemic therapy that includes immunosuppressive as well as corticosteroid medication. Also, surgical procedures for modifications of eyelid position, symblepharon and cataract may aggravate the evolution of the disease.

Dry eye syndrome, which is known to be a multifactorial disorder of the ocular surface secondary to qualitative or quantitative alteration of the tear film, is a severe and frequent complication of OCP.

In this article, we presented 3 patients diagnosed with OCP, who developed severe dry eye syndrome, entropion, corneal erosions and ultimately, permanent vision loss.

Keywords: OCP, dry eye syndrome, entropion, symblepharon

Introduction

Ocular cicatricial pemphigoid (OCP) is a form of mucous membrane pemphigoid (MMP) characterized by chronic, relapsing bilateral conjunctivitis. Patients affected by this autoimmune disease will ultimately experience conjunctival cicatrization or scarring and, in case of not responding to treatment, or being left untreated, they will develop corneal opacification and permanent vision loss. MMP affects the skin as well as the mucous membranes of the mouth, nose, esophagus, genitals and anus, leading to erosions, blisters, and strictures. Ocular cicatricial pemphigoid represents about 60-70% of the MMP manifestations.

Ocular cicatricial pemphigoid predominantly affects females twice more than males [**1**], and the age of onset is around 60 years or older. There is no racial predilection. Ocular cicatricial pemphigoid is considered a rare disease and its incidence is estimated to be about 1 per 10,000 to 50,000 [**2**].

Patients with ocular cicatricial pemphigoid experience bilateral chronic conjunctivitis [**3**] with remissions and exacerbations. OCP is often misdiagnosed and delayed due to the insidious onset and nonspecific signs and symptoms in the early stages of the disease [**4**]. In the beginning, patients experience ocular redness, tearing, burning, light sensitivity and foreign body sensation. These presentations are similar to dry

eye syndrome and to many other inflammatory conditions of the anterior segment of the eye. There is minimal to no discharge present. As the disease progresses, the signs become pathognomonic for ocular cicatricial pemphigoid, most notably with the development of a symblepharon.

In the early stages of the disease, the conjunctiva exhibits the following signs: diffuse hyperemia, papillary reaction, dry eye syndrome and keratoconjunctivitis sicca due to destruction of goblet cells.

Ocular cicatricial pemphigoid affects the cornea and early manifestations include punctate epithelial erosions, exposure keratitis, epithelial defects, peripheral infiltrates, ulcers and neovascularization. The worsening of the condition results in limbal stem cell failure, which leads to keratinization and conjunctivalization. Corneal opacification is possible in the late stages of the disease. The eyelids are also affected during the process and the first signs of that include blepharitis, trichiasis and entropion, due to subepithelial scarring and keratinization of the eyelid margin [**5**].

Cases report

Case 1

The patient is a 74-year-old female. She was diagnosed with diabetes mellitus. She presented an acute bullous skin eruption after some oral medication 30 years before, of which she had no records. She reported that the eye symptoms, including ocular pain and visual disturbances, began after that episode.

The patient has been in our care for 10 years. Her first visit diagnosis was symblepharon and dry eye syndrome in both eyes with corneal keratinization in the left eye. During the years, she had several acute episodes of corneal ulcer in the right eye (RE), which needed hospitalization, while the left eye (LE) was quiet. The LE had a visual acuity (VA) of light perception and presented an opaque cornea and ankyloblepharon, for which she was treated only with artificial tears.

The period of time between 2017 and 2018 presented a particular ocular evolution.

Thus, the RE presented several recurrent episodes of corneal erosions, severe corneal neovascularization and severe dry eye symptoms. The treatment consisted in 3 subconjunctival injections of Bevacizumab-Avastin 0,05 ml (1,25 mg), artificial tears and monthly soft contact lens. Meanwhile, she developed cataract in this eye and the visual acuity became “count fingers”. She was told that cataract surgery had poor prognosis. However, she still underwent cataract surgery with posterior chamber IOL implantation. The surgery took place in September 2018. On the other hand, the LE maintained the same biomicroscopic aspect, with no further symptoms or complications.

Nonetheless, in December 2018, 3 months after having the cataract surgery, the RE developed corneal ulcer with aggressive evolution to descemetocele. Local antibiotics, mydriatic and steroids were administrated. No perforation of the cornea happened, instead it healed with a central scar after three weeks.

In the next period, March-April 2019, the RE developed several inflammatory episodes with ocular pain, blurred vision and enlargement of the corneal neovessels. The therapeutic plan included 3 peribulbar injections of 4 mg dexamethasone, one per week. No relief of the pain was observed.

In May 2019, the patient complained of recurrent and short (30 minutes) episodes of acute loss of vision. She was hospitalized because the RE cornea had a new ulcer and was so hazy that the pupil and posterior pole could not be examined. Treatment consisted of antibiotics and dexamethasone in peribulbar injections every 2 days. After one week, some part of the retina could be examined and several retinal hemorrhages were observed. We concluded that it was a retinal venous branch occlusion, but we could not exclude diabetic retinopathy. Neurological and cardiological examinations along with cerebral MRI showed no signs of stroke or arrhythmias. The patient was discharged and the local treatment she continued at home consisted of artificial tears and soft contact lens in both eyes, while the general treatment included Aspenter. VA at that time was “counting fingers at 30 cm” in the RE and light perception in the LE.

Case 2

The second patient is a 72-year-old female. She was diagnosed with arterial hypertension. Both eyes presented intense dry eye symptoms for the last two years with no relief from artificial tears.

The first visit in our clinic was in May 2018. VA in both eyes was 20/ 20 without correction. Both eyes presented inferior symblepharon, entropion with corneal erosions, and a severe dry eye syndrome. Schirmer 1 test was 0 mm/ 5 min and the tear break up time was 2 sec. No corneal vascularization was observed (**Fig. 1-3**).

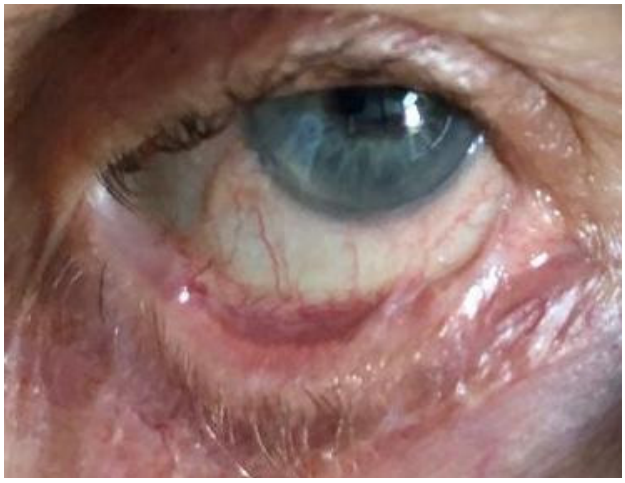

Fig. 1 Right eye symblepharon formation

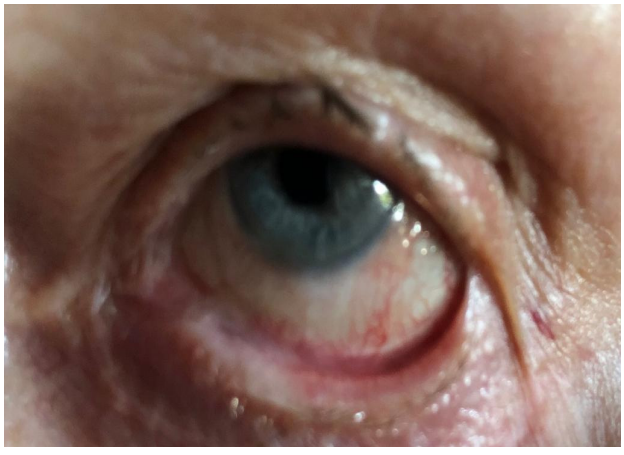

Fig. 2 Left eye symblepharon formation

We started bilateral treatment with local antibiotics, lipid artificial tears during day time and gel during night time, associated with topical steroids for 2 weeks. Because symptoms persisted, she was prescribed topical 1 mg/ ml cyclosporine (Ikervis), 1 drop per day in both eyes. Soon after introducing Ikervis in the therapeutic plan, the patient reported symptoms of ocular pain, hyperemia and blurred vision. Thus, the cyclosporine was discontinued after 3 weeks because the patient did not tolerate it. She continued the local treatment with lipid artificial tears, and in May 2019 she underwent surgery for entropion in both inferior eyelids. A conjunctival biopsy was sampled and examined by direct immunofluorescence, which was positive for IgA, leading to the diagnosis of Ocular cicatricial pemphigoid. The collaboration with a dermatologist led to the patient being immediately treated with immunosuppressive therapy, respectively azathioprine. Systemic oral corticoid treatment was also administered. After 3 months, the patient developed elevated transaminases and the immunosuppressive therapy was interrupted. At present, her treatment consists of lipid artificial tears along with oral corticoid therapy.

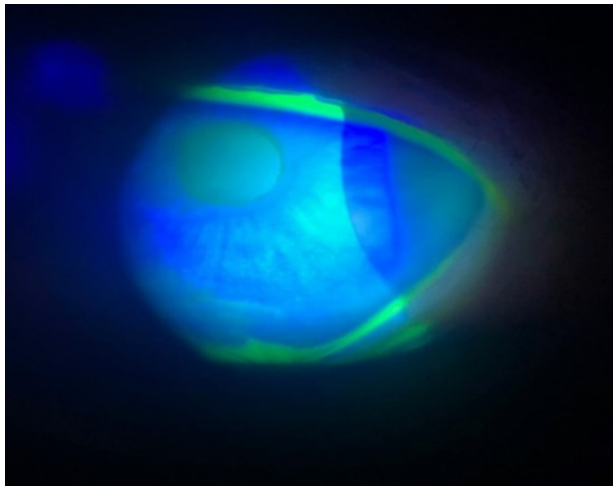

Fig. 3 Slit lamp: Corneal punctate epithelial erosions in the right eye

Case 3

The third patient is 74-year-old male suffering from arterial hypertension. For the last 10 years, both eyes presented dry eye syndrome, corneal neovascularization, symblepharon, misdirection of the cilia and multiple episodes of corneal ulcers, the ulcers being predominant in the right eye. It must be noted that the misdirection of the cilia was present only on the superior right eyelid and the cilia were very soft and did not hurt the corneal epithelium. VA of RE decreased over the years mainly because of the cataract evolution, while VA of LE maintained at

"count fingers at 1 meter" due to corneal opacification and neovascularization.

Patient asked intensively for cataract surgery in the RE, despite being strongly recommended not to, considering his pemphigus disease. He had cataract surgery with posterior chamber IOL implantation in March 2016, when his VA was 0,3. After surgery, VA was 0,6 for six months and then began to decrease due to cystoid macular oedema. The patient had 6 intraocular injections with Avastin (1,25 mg), and 4 with Triamcinolone the next year, but VA decreased significantly to "count fingers at 3 meters". At present, his treatment consists of lipid artificial tears.

Discussion

Ocular cicatricial pemphigoid (OCP) is a systemic disease affecting the eye. The cause of ocular cicatricial pemphigoid is an autoimmune type II hypersensitivity response [**2**]. This autoimmune response occurs when a patient has a genetic predisposition and is exposed to an environmental trigger. Conjunctival biopsy with direct immunofluorescence is the most reliable method and the gold standard to confirm the ocular cicatricial pemphigoid diagnosis.

Ocular complications of ocular cicatricial pemphigoid (OCP) include the following: corneal epithelial defects, corneal stromal ulcers, corneal perforation, endophthalmitis, glaucoma. The differential diagnosis includes all medical conditions that cause an asymmetric bilateral chronic conjunctivitis with conjunctival cicatrization. These include Stevens-Johnson syndrome, toxic epidermal necrolysis, trachoma, graft-versus-host disease, dry eye syndrome, history of adenoviral conjunctivitis, chemical burn, medicamentosa (from topical glaucoma medications and anti-viral medications for herpetic eye disease), atopic keratoconjunctivitis, radiation exposure, systemic lupus erythematosus, and Sjogren syndrome. A distinguishing clinical feature of OCP is a progressive symblepharon [**6**]. Symblepharon from the above etiologies may form and then remain stable. However, a few conditions in which progressive cicatrization occur include neoplasia, lichen planus, and paraneoplastic pemphigus [**6,7**].

In the three cases of this study the diagnosis of OCP is sustained by the progressive symblepharon. In case 1 it could have been Steven-Johnson syndrome (30 years ago) but the cicatrization of the conjunctiva progressed aggressively during time. Only case 2 had conjunctival biopsy. Generally, of those with MMP, the ones with ocular involvement have a worse prognosis than the ones affected with skin and/ or oral mucosa involvement alone. Systemic therapy can stop the progression of ocular cicatricial pemphigoid in about 90% of the patients, and the rate of recurrence is about 20% to 30%, but this is variable.

All three cases had only ocular lesions, and case 1 and case 3, with long standing disease, developed corneal opacification and neovascularization.

OCP is a general disease, therefore, no topical medication can be curative. In selected patients, subconjunctival steroid injections or subconjunctival injections of mitomycin C may be used temporarily to slow disease progression, while systemic therapy takes effect.

Adjuvant treatment with topical lubricants should be used in patients with dry eye symptoms. The use of topical cyclosporine and tacrolimus ointment has also been described to aid in the control of surface inflammation.

Our patients received topical therapy for dry eye and corneal ulcerations. We did not use general therapy with immunosuppressants because we considered that ocular complications such as corneal ulcers and corneal neovascularization were caused by dry eye syndrome.

Systemic corticosteroids can control the activity of the disease; however, they are not as effective as other immunosuppressive drugs, and the doses required have been shown to be very toxic.

Dapsone is the first-line treatment for mild to moderate disease. Dapsone is a sulfonamide antibiotic that also has anti-inflammatory and immunomodulatory action. It must be avoided in patients with G6PD deficiency due to the risk of hemolytic anemia. Moderate to severe disease or lack of response to Dapsone or other first-line alternatives after 2 to 3 months will likely require a systemic corticosteroid pulse over 6 to 8 weeks with concurrent immunosuppressant therapy with azathioprine, mycophenolate

mofetil, methotrexate, or cyclosporine. Cyclophosphamide should be considered in severe and rapidly progressing disease states, especially when previous therapies have been unsuccessful.

Biologics such as etanercept or rituximab and intravenous immunoglobulin therapy are reserved for patients who have a poor response to conventional therapy.

The need for cataract surgery is common in patients with OCP. Cataract surgery performed on patients with OCP is followed by increased conjunctival inflammation, rapid progression of keratopathy, and conjunctival scarring if the disease is not medically controlled.

Two of our patients (case 1 and case 3) underwent cataract surgery and both had a favorable course for six months postoperatively and ocular complications occurred after that period. None of them presented progression of symblepharon years before and after the surgery, but active disease could not be ruled out.

Corneal transplantation on a dry eye with impaired lid function and limbal stem cell deficiency has a very poor prognosis; therefore, corneal grafting in patients with advanced OCP should be avoided. This procedure should only be performed in case of corneal perforation. In patients with advanced corneal damage from OCP keratoprosthesis may be the only feasible alternative for visual rehabilitation.

Entropion surgery is usually avoided in patients with OCP because of the interference with the conjunctiva. Several cases of lower lid entropion have been treated successfully with a retractor plication technique. The procedure is repeatable in case of undercorrection. Moreover, the conjunctiva remains intact during the surgery, which can avoid the exacerbation of conjunctival inflammation.

In case 2, the entropion surgery consisted of resection of a lamellae of lower palpebral skin (parallel with the entire eyelid margin and 9 mm width) in order to avoid hurting the conjunctiva. In this case, the treatment with methotrexate would be considered because of the progressive symblepharon, while the symptoms of dry eye syndrome are well controlled with artificial tears.

Conclusions

Ocular cicatricial pemphigoid is a general autoimmune disease with ocular manifestations that could lead to blindness. Ocular complications are dry eye, corneal ulcers, corneal neovascularization and entropion. Even if the disease is inactive due to natural evolution or to treatment effect, the ocular sequelae threatens the visual function and the patient must be supervised all his/ her life.

The pathognomonic sign of OCP is progressive symblepharon.

The disease must be treated by a multidisciplinary approach. Thus, the treatment must be systemic and needs to be concluded by a medical team composed of ophthalmologists, rheumatologists, dermatologists.

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