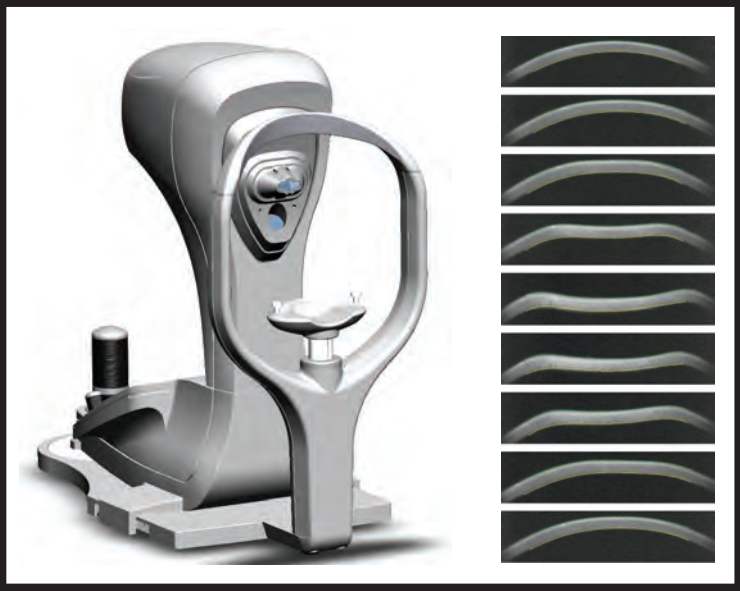
ISSN 0034-7280
Versão impressa

Revista Brasileira de Oftalmologia

PUBLICAÇÃO OFICIAL:
SOCIEDADE BRASILEIRA DE OFTALMOLOGIA
SOCIEDADE BRASILEIRA DE CATARATA E IMPLANTES INTRAOCULARES
SOCIEDADE BRASILEIRA DE CIRURGIA REFRATIVA

Publicação bimestral

vol. 72 - nº 2 - Março/Abril 2013



RBO

DESDE 1942

ISSN 0034-7280
(Versão impressa)

ISSN 1982-8551
(Versão eletrônica)

Revista Brasileira de Oftalmologia

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Publicação bimestral

Rev Bras Oftalmol, v. 72, n. 2, p. 79-150, Mar./Abr. 2013

Redação:
Rua São Salvador, 107
Laranjeiras
CEP 22231–170
Rio de Janeiro – RJ
Tel: (0xx21) 3235–9220
Fax: (0xx21) 2205–2240
Tiragem: 5.000 exemplares
Edição:Bimestral
Secretaria: Marcelo Diniz
Editoração Eletrônica:
Sociedade Brasileira de Oftalmologia
Responsável:
Marco Antonio Pinto
DG 25341RJ
Publicidade:
Sociedade Brasileira de Oftalmologia
Responsável: João Diniz
joaodiniz@sboportal.org.br
Contato publicitário:
Westinghouse Carvalho
Tel: (11)3726–6941 /
99274–0724
westincarvalho@yahoo.com.br
Revisão:
Eliana de Souza
FENAJ–RP 15638/71/05
Normalização:
Edna Terezinha Rother
Assinatura Anual:
R$420,00 ou US$280,00
Impressão:
Gráfica Stamppa

Associada a
ABEC - Associação Brasileira de Editores Científicos

Revista Brasileira de Oftalmologia

Rua São Salvador, 107 - Laranjeiras - CEP 22231-170 - Rio de Janeiro - RJ
Tels: (0xx21) 3235-9220 - Fax: (0xx21) 2205-2240 - e-mail: **sbo@sboportal.org.br - www.sboportal.org.br**

Revista Brasileira de Oftalmologia, ISSN 0034-7280, é uma publicação bimestral da Sociedade Brasileira de Oftalmologia

Diretoria da SBO 2013-2014

SOCIEDADES FILIADAS À SOCIEDADE BRASILEIRA DE OFTALMOLOGIA

ISSN 0034-7280
(Versão impressa)
ISSN 1982-8551
(Versão eletrônica)

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SOCIEDADE BRASILEIRA DE CATARATA E IMPLANTES INTRAOCULARES
SOCIEDADE BRASILEIRA DE CIRURGIA REFRATIVA

Fundada em 01 de junho de 1942
CODEN: RBOFA9

Indexada nas bases de dados:

THOMSON REUTERS WEB OF SCIENCE
SciELO Scientific Electronic Library OnLine
Free Medical Journals www.freemedicaljournals.com
SCOPUS
LILACS Literatura Latino-americana em Ciências da Saúde

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Publicação bimestral
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Choosing the subject of a scientific study for publication

A escolha adequada do tema de um estudo científico para publicação

Encouraged mostly 1-) by the visibility of the scientific journals in the nonprofessional and professional environment resulted from indexation of good quality journals based on electronic data and search tools, allowing the reader (clients or colleagues) to find related publications on the internet, and 2-) by the introduction of Graduate Programs (stricto sensu - master and doctor degrees) of the main universities, and also by the need of young ophthalmologists to distinguish themselves with academic titles, many doctors may become motivated to write scientific papers aiming at publications [1,2].

In the academic environment, we often say that 90% of a scientific study arise from "inspiration" and only 10% arise from "transpiration". In other words, energy invested in the preparation of the strategy of the study is enormous and much more significant than its production. The certainly most important step in the preparation of a scientific study is choosing the subject.

Scientific research starts from a doubt, something that, in the opinion of the researchers, could be different and maybe more effective. The next step would be looking up in the literature all the information published about the subject, by means of bibliographic research based on electronic data. It would be like asking to the rest of the world what it is known about a certain subject. The objective of the bibliographic review is to discover if someone, in any part of the world, had had this same doubt and if he had tried to solve it [3].

Review of the literature, by selecting and reading the main articles related to the subject, allows us to understand details of a content that would not be available in text books in an updated way. This study is the most effective and practical way of getting updated. In case the initial doubt had already been clarified (published), the expertise acquired about the subject will allow to discover a "gap" in knowledge, which could yet be studied in an unprecedented way. For example, If the original doubt is about the possibility of an aspheric intraocular lens (when improving the visual perception of contrast) influence in diagnostic exams that use the sensibility to contrast and if this doubt had already been responded to the blue-yellow visual field exam, a possible "gap" would be question if the findings were also valid for other types of exams (FDT, for instance) or other types of aspheric lenses [4,5].

In the case of epidemiologic research, the "gap" in knowledge could be, for example, study variables already studied, though in an area with different demographic features. In other words, epidemiologic features and patient needs with indication of cornea graft are not generally the same in southeast and northeast. This information could be useful for the preparation of guidelines in public health [6,7].

Best studies are those prepared to respond to only one specific doubt, and many times ideas for additional studies are also suggested. As a result, medical knowledge progresses.

Since the doubt is defined and novelty is confirmed, the next step is to check if the institution where the study will be conducted has all the materials and humane requisites to carry out research. It is, for instance, an excellent study to evaluate the efficacy of laser for doing the capsulorhexis in intumescent cataracts[8,9]. But, first it would be necessary to have the laser available for research. Scarcity of material resources is the principal limitation for carrying out scientific papers in Brazil.

Research do not need to be unprecedented, but have to render some contribution to the existing knowledge. So, we can publish a study with conclusions formerly described. Also, this study should be much more extensive than the original one and the objective would be to confirm the former information. Editors are not willing to publish (and readers are not willing to read) studies that simply repeat what it was done numerous times before.

Authors should consider the importance of the chosen subject as well, because the information resulted from the study has to contribute to the improvement of medical practice in general, increased by what is known about the subject. An article, which describes the epidemiological profile of patients seen at a certain hospital, would hardly be accepted for publication, since this information would only be useful for administrators or that hospital or area. Studies that carry relevant information are those allowing to extrapolate their findings, by transmitting information to a great number of readers.

Publishers are constantly charged by readers and periodically evaluated by bibliometric indexes. Yet, pressure

in this sense, is much greater than diplomatic needs with authors who had had denied submissions [10].

Scientific journals tend to progressively improve their quality and impact. Articles well written, with adequate methodology and mainly relevant information to the existing knowledge, are ardently desired by best journals. Constant improvement of journals is necessary along with competent researchers. Besides university Graduate Programs, there are independent and very well prepared research groups. We believe that all the researchers should encourage the leaders of national ophthalmology to carry out activities related to training in scientific research.

So, the Brazilian Ophthalmology Journal will try to systematically show on its editorials information that help promoting the researchers. Our task is to improve quality of our publications by enriching our authors.

Newton kara-junior
Postgraduate professor, Faculdade de Medicina,
Universidade de São Paulo, São Paulo, SP, Brazil.

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Therapeutic refractive surgery: why we should differentiate?

Cirurgia refrativa terapêutica: por que diferenciar?

In the early '80s, the advent of elective surgeries in order to reduce dependence of vision correction (eyeglasses or contact lenses) determined profound changes in Ophthalmology. Although refractive procedures were initially controversial, they quickly gained popularity among physicians and potential candidates. This determined a demand for developments in knowledge. With that, there was a great stimulus for research in basic and clinical chairs, which increased the understanding of various aspects of physiology, pathology, and diagnosis in corneal and ocular optics. As a result of this rapid evolution, Refractive Surgery achieved recognition by the international scientific community to be considered as a true subspecialty of Ophthalmology.

The need for evolution has always been related to the fact that these procedures involve patients without ocular disease apart from refractive errors (myopia, hyperopia and astigmatism). With this, the technologies related to pharmacological and surgical treatments and had still an ongoing development. Noteworthy is the advent of different types of lasers, such as excimer and femtosecond lasers.[1] Unquestionably, this evolution has provided a dynamic and constant increase in the safety and efficacy of these procedures. In this scenario, the "gold standard" is highly mutable, which requires for the specialist or ophthalmologist interested in this area, constant updating and investment.

The knowledge and technological development related to Refractive Surgery have also been applied in different ophthalmic conditions, highlighting cataract.[2-4] Either the diagnosis, as an indication, planning and performing cataract surgery had great influence and benefits of scientific progress driven by new subspecialty. Given this undeniable revolution, there is a worldwide trend of scientific societies related Cataract and Refractive to work together and to unify, as happened in Brazil with SBCII (Brazilian Society of Cataract and Intraocular Implants) and SBCR (Brazilian Society of Refractive Surgery). In addition, the diagnosis and treatment of various conditions and diseases of the cornea also had positive influence of this accumulated knowledge, highlighting keratoconus.[5-6] However, the fundamental differences of truly therapeutic and elective refractive surgeries should be recognized and considered.

Elective can be defined as what you choose. Therefore, elective Refractive Surgery would be an option (alternative) to other efficient forms of vision correction, such as glasses or contact lenses. In these cases, glasses or contact lenses typically allow optical correction satisfactory and relatively adequate. Surgeons must perform tests to determine the feasibility and safety of surgery for each case and enable appropriate surgical planning. However, the decision to perform such a procedure should be exclusive of the patient, who must be informed of the risks, benefits and limitations for a conscious decision.

On the other hand, in the case of therapeutic procedures, correction by glasses or contact lenses is relatively unsatisfactory for the patient, which may occur in varying degrees of limitation of visual acuity (quantity) and visual quality. For example, the visual acuity could be less than 20/400 in a case of advanced keratoconus, or even 20/20 in a case of irregular astigmatism that causes severe impairment of visual quality of the patient and the consequent impact on their quality of life. In these cases, there are high levels of higher order aberrations, and keratoplasty (corneal transplantation) could possibly be considered. In fact, it would be the only alternative before the advent of technology that enables us to perform refractive procedures therapeutic presenting unquestionably as a less invasive alternative for visual rehabilitation.

Several procedures originally described as refractive may also be indicated for therapeutic purposes. The implant of ring segments for intra-corneal keratoconus was originally described for refractive treatments. Moreover, treatment for promoting stromal covalent bonds in collagen (crosslinking) emerged in research center Refractive Surgery, purely as a therapeutic procedure to stabilize the progression of ectasia.[7] However, other procedures may be performed either as therapeutic ou refractive. For example, a patient with anterior stromal opacity associated with irregular astigmatism due to dystrophy or scarring after keratitis may benefit from surface ablation therapy. In this case, besides the application of the excimer laser on PTK mode (Phototherapeutic keratectomy), the customized ablation mode PRK (Photorefractive keratectomy) based on total or corneal wavefront followed by application on mitomycin C is used quite similarly to elective advanced surface ablation treatments (laser vision correction). However, the goals of advanced surface ablation in both situations are very different, as the outcome measures and success.

In therapeutic procedures, the goal is to provide good corrected vision with sphere-cylindrical refraction (glasses) for the patient. Thus the measure of success is related with improvement of visual acuity. In these cases, the refractive goal is secondary. In refractive surgery, the goal is to reduce ametropia to provide adequate uncorrected vision and less dependence on glasses or contact lenses. Thus, the uncorrected visual acuity is the primary variable that represents

the effectiveness and the benefit from surgery. However, the comparison of visual acuity with correction before and after surgery has always been related to the safety of any eye surgery.

While refractive surgery is essentially optional, there are special situations in which its indication has a greater need. For example, a patient with anisometropia and intolerance to contact lenses may not have satisfactory correction with glasses, and in these cases we can even consider surgery as therapeutic. Additionally, other situations may be related to activities that the patient has, such as athletes and military.

A case with therapeutic indication may, with the evolution of the initial treatment, become refractive. For example, a patient with keratoconus is operated with implantation of corneal ring segments with marked improvement of visual acuity with glasses to correct high myopia. In this scenario, the phakic intraocular lens implantation may be considered for the treatment of low-order aberrations - as in Bioptics Therapeutic approach (R. Ambrósio Jr, Ocular Surgery News, December, 2011). The need and indication of such refractive treatments should be considered according to each case .

Another aspect of capital importance is related to the confusion between cosmetic surgery and elective refractive surgery. In general, all cosmetic surgeries are optional. However, refractive surgical correction does not, in any way, have an esthetic nature. The procedure is functional because ametropia reduces the ability of the patient to function on simple daily tasks.[8] In fact, the use of glasses can have aesthetic appeal and a great relationship with the image of the person. For example, a patient with LASIK refractive surgery the next plan and acuity without correction was 20/20, so no need to fix to improve visual acuity, is asking for prescription glasses to wear at work, since he, like psychoanalyst, sit with your image better with the glasses.

Therefore, it is essential to distinguish refractive surgery with the goal of refractive corrections and therapeutic surgery. While elective refractive surgery aims to reduce dependence on vision correction (spectacles or contact lenses), the therapeutic aims for restoring vision, with a refractive secondary objective. The term elective could also be used to designate a non-urgent or other emergency procedure. Thereby, all surgery that can be planned without urgency is properly designated as an elective. In this context the therapy is essentially an elective surgery, with exception to special cases in which there is an associated risk of progression with sequels. However, the fundamental differentiation between the refractive surgery for therapeutic purposes is related to the preoperative status in which corrected visual acuity is not suitable with glasses or contact lenses due to high levels of higher order aberrations. The implications of the distinction should be considered for clinical and medico-legal standpoints.

Renato Ambrósio Jr.
Professor Associado da Pós Graduação em Oftalmologia,
Universidade Federal de São Paulo, São Paulo (SP), Brazil;
Professor Associado da Pós Graduação em Oftalmologia,
Pontifícia Universidade Católica do Rio de Janeiro, Rio de Janeiro (RJ),Brazil;
Presidente da Sociedade Brasileira de Cirurgia Refrativa (2012-2014).

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Reflections on mycotic keratitis based on findings from histopathologically examined specimens

Reflexões sobre a ceratite fúngica por meio dos achados de exames histopatológicos

Fernando Queiroz Monte[1], Niedja Marques Stadtherr[2]

ABSTRACT

Purpose: *The study of fungal invasion and pathogenicity in corneal tissue observed through the histopathological examination of specimens obtained through penetrating keratoplasty ('PKP') of samples obtained from an Eye Bank ('EB'), with the aim of applying findings in diagnosis and treatment of the condition* ***Methods****: Retrospective non-comparative case studies on samples collected between January 2006 and June 2011 based on identification data comprised of scant historical information sent by surgeons and material obtained through PKP, consisting of 38 samples from 35 patients. Processing involved special stains for fungi in order to detect the presence thereof, with one to three colourations being performed in accordance with diagnostic difficulty in relation to each sample.* ***Results****: Patients were predominantly male (20 compared to 15 females), and the most represented age group was 60+ years of age (1/3 of the patients). Mycotic keratitis was detected in 6.4% (n= 597) of cases referred to the EB and in 1.65% (n= 2310) of transplants using corneal material provided by the EB over the last five years. According to historical information provided by surgeons, 39.5% (n= 38) of cases were due to perforation of the cornea. A statistical table was prepared using transplant data. 11 specimens (n= 38) were due to an anterior corneal graft. Yeasts were present in 63% (n= 38), and 50% (n= 38) of corneal tissue had mild or non-existing inflammation. 13% (n= 38) had whole Descemet layers, while 45% (n= 38) presented fungi on the corneal surface.* ***Conclusion****: Corneal grasping and confocal microscopy may be performed successfully after treatment has been initiated, although in corneal ulcers samples should ideally be collected with a spatula for laboratory testing in vivo. The high prevalence of yeasts in the samples we looked at may be due to morphologic changes in corneal tissue of fungal origin. Intraocular penetration of the fungi is facilitated by changes to the Descemet layer, and assisted by the fungi's own properties. Therefore systemic treatment is justified from the outset.*

Keywords: *Keratitis/diagnosis, Keratitis/pathology; Eye infections, fungal/diagnosis*

RESUMO

Objetivo: Estudo de botões corneanos por meio do exame histopatológico para verificar as alterações ocorridas nos tecidos corneanos numa infecção fúngica e tirar desses achados orientações para o diagnóstico e o tratamento. **Métodos:** Trabalho retrospectivo, realizado num Banco de Olhos (BOO) entre janeiro de 2006 e junho de 2011, usando dados de prontuários a partir das informações enviadas pelos cirurgiões e sendo examinado material recebido de ceratoplastia penetrante com o exame de 38 peças de 35 pacientes, sendo processadas e feitas de uma a três colorações de acordo com as dificuldades diagnósticas. **Resultados:** Os pacientes eram na maioria homens, 57% (n=35), a faixa etária acima de 60 anos a mais numerosa com 1/3 dos pacientes. Os casos de ceratite fúngica correspondiam à média de 6,4% (n=597) do material recebido no BOO e 1,65% (n=2310) dos transplantes ocorrido com o material fornecido nos últimos 5 anos. Pelas informações dos cirurgiões 39,5% (n=38) dos casos deviam-se a perfuração corneana. Usando as datas dos transplantes foi feita uma Tábua de Observação. Em 11 (n=38) casos, a córnea procedia de transplante anterior. As formas leveduriformes nos tecidos corneanos eram de 63% (n=38). Em 50% (n=38) dos casos o infiltrado inflamatório era pequeno ou inexistente. A camada de Descemet estava íntegra em 13% (n=38), enquanto eram encontrados fungos na superfície corneana de 45% (n=38) dos casos. **Conclusão:** A coleta do material poderá ser feita com sucesso mesmo depois de instalado o tratamento, entretanto, nas úlceras de córnea deve ser feito preferentemente a coleta de material com espátula para exame laboratorial e a microscopia confocal *in vivo*. A predominância das leveduras poderá ser devido a alterações morfológicas do fungo sofridas no tecido corneano. A penetração intraocular é facilitada por alterações da Camada de Descemet e pela própria capacidade do fungo de penetrar nos tecidos justificando o tratamento sistêmico desde o início.

Descritores: Ceratite/diagnóstico; Ceratite/patologia; Infecções oculares fúngicas/diagnóstico

[1]Eye Bank, Health Department, State of Ceará – Fortaleza (CE), Brazil.
[2]Ophthalmology Department, General Army Hospital – Fortaleza (CE), Brasil
Work conducted at the Eye Bank, Health Department, State of Ceará
General Hospital of Fortaleza - Fortaleza (CE), Brazil. Winner, the Master Category, of the 40th Varilux Prize for Ophthalmology

The authors declare no conflicts of interest
Received for publication: 9/4/2012 - Accepted for publication: 29/5/2012

Introduction

The study of fungal keratitis used to be of little interest to research centres because the disease is more common in warm climates, in countries with little investment in research. The condition also used to affect rural populations, which have been decreasing in recent centuries due to urbanisation after the industrial revolution. However, the condition was described in a temperate country, where cases are rare. Fungal keratitis was first described in 1879 by Leber in a 54-year-old farmer who was working with a shredder (Dreschmaschine) when he suffered a mild corneal trauma by oat chaff (haferspelze)[1]. In 1907, Zade presented the case of a 44-year-old female peasant and, upon consulting the literature, found 22 cases of fungal keratitis. In an Annex to the text he presented a drawing of the organism found in the laboratory, showing the appearance of Aspergillus[2].

In the second half of the 20th century the number of cases increased, mostly due to the widespread use of antibiotics and topical corticosteroids and the increased number of transplants and immunosuppressed patients. This led to a relative resurgence of interest in the disease, as it started to affect urban populations.

Few published articles studied the histopathology of the cornea during fungal infections. The most comprehensive article to which we had access was Naumann et al.[3], which presented the cases of patients in the Southern United States, African and South American countries and examined by the Armed Forces of Ocular Pathology Laboratory. Previously, Zimmerman had presented images of the corneal tissue of 7 patients using the same sample[4].

There is a practical explanation for the lack of interest in the histopathology of fungal keratitis, apart from the ones presented above: the fact that histopathology does not reveal the aetiological diagnosis, which is more directly relevant for treatment according to the predominant thinking in medicine. However, as we had access to a satisfactory amount of cases, we decided to take advantage of our findings to reflect on the disease and to present suggestions aimed at minimising its harmful effects. We were moved by curiosity about what happens to the corneal tissue during this infection. The examined cases had no results of microbiological tests and little associated information, which allowed us to focus on the slides and try to learn lessons that could be of practical interest.

Methods

The study was conducted in the Eye Bank of the Health Department of the State of Ceará, Brazil, which tracks emergencies by demanding that the corneas of recipients be submitted to the Eye Bank to undergo histopathological examination. The cases that were not urgent could be examined if the surgeon required some information about them.

The samples came only with the standard form with summary data about the case and no additional information. There was no detailed medical history, except for the clinical signs that could justify the examination, but without any chronological data describing the progression of the disease.

The samples were forwarded to the Laboratory of Pathology of the General Hospital of Fortaleza, where the Eye Bank is based. Macroscopic examination of the corneal buttons was done by an Eye Bank pathologist, who described the specimen and then sliced the material to examine all layers of the cornea. The samples were embedded in paraffin and then cut into 5-ì thick slices. All the material was stained with haematoxylin-eosin (H&E). In cases where there remained doubts about the diagnosis of fungal keratitis, PAS (Periodic Acid of Schiff reaction), silver methenamine, Gomori's stain, and Masson's stain were used. In most cases there was no difficulty in establishing the diagnosis with routine staining (H&E), and the few doubts that remained were solved with the other stains. H&E was used alone in 30 cases (79%); H&E and silver methenamine were used in 3 cases (7.9%); H&E, silver methenamine and PAS were used in 4 (10.5%) cases; and H&E, silver methenamine and Masson's stain were used in 1 (2.6%) case.

The study began in January 2006 and ended in June 2011. 597 cases were assessed retrospectively, out of 2310 transplants done in the period. In total, 38 specimens had a histopathological diagnosis of fungal keratitis.

The medical records of patients were reviewed, extracting information provided by the surgeon about the transplant upon their request for a donor cornea.

With regard to the histopathological examination, the following data were considered: Staining, fungus morphology, general appearance of the cornea, location of the infection, appearance of Descemet's membrane, and description of the corneal inflammatory infiltrate. The data were plotted for presentation of the results.

Results

The sample included 20 males and 15 females; there were three cases of relapse, which occurred in two men and one woman.

The youngest patient was 20 years old and the oldest was 81. Of these, 3 (8,5%) patients were aged 20-29 years; 8 (23%) were 30-39 years; 6 (17%) were 40-49 years; 5 (14%) were 50-59 years; and 11 (31.5%) were over 60 years — the age group with the largest number of cases.

General sample data included the annual distribution of corneal buttons obtained through transplantation in 35 patients, where 38 cases of fungal keratitis were diagnosed in the five and a half years during which the samples were submitted to the Eye Bank. Table 1 shows the number of cases of fungal keratitis as a proportion to the number of corneas submitted to the Eye Bank per year; the table also includes the number of transplants done in the period with corneas provided by the Eye Bank and the annual rate of fungal keratitis.

The information provided by the surgeons to justify the priority of their patients for transplantation is shown in Table 2.

In a large number of cases of fungal keratitis we were able to monitor the progress of the case chronologically by reviewing the medical record and the notes by the Eye Bank. In cases where a transplant was done after the initial operation where the fungal keratitis was diagnosed, it was possible to determine that the keratitis was cured. When the patient underwent a second operation and there was no evidence of relapse, the case was considered as cured; however, cases whose samples were not submitted were not counted as cured. As the number of operations seemed significant, we decided to examine it through an Observation Chart.

The table above shows that case 1 underwent two transplants without a histological diagnosis of fungal keratitis (yellow and orange) before it was diagnosed (red). In cases 2 and 10, fungal keratitis was found in two transplants, and no samples were submitted afterward (red). Cases 3, 5 and 7 had a diagnosis of keratitis, but the infection was not found in the

Table 1

Cases of fungal keratitis diagnosed by histopathological examination from January 2006 to June 2011 as a proportion to the number of samples examined per year, and the annual rate with regard to the total number of transplants

Year	Cases	Samples Examined	(%)	Transplants/ Year	Rate
2006	3	74	4	253	11,9/1000
2007	2	77	2,60	382	5,2/1000
2008	5	76	6,60	444	11,3/1000
2009	17	201	8,50	443	38,4/1000
2010	6	121	4,95	465	12,9/1000
2011	5	48	10,40	323	15,5/1000
Total	38	597	6,40%	2310	16,5/1000

Table 2

Information included in the requests for donor corneas submitted to the Eye Bank among patients diagnosed with fungal keratitis

Information	N	(%)
Perforated ulcer	15	39,50
Keratitis with intense hyperaemia	15	39,50
Previous surgery	11	29
Keratitis without hyperaemia	10	26,30
Keratitis with moderate hyperaemia	8	21
Bacterial keratitis	7	18,40
Ulcer resistant to treatment	4	10,50
Fungal keratitis	2	5,30
Other	4	10,50

Table 3

Type of surgery before and after a corneal transplant in which it the fungal keratitis was diagnosed

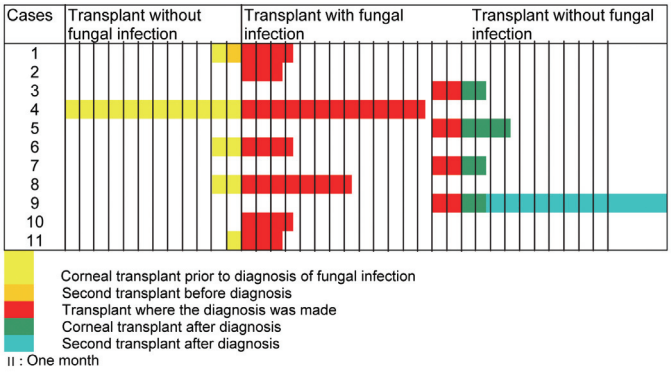
Procedure	Number of procedures	Number of patients
Anterior transplant	11	7
Posterior transplant	5	3
Cataract+Transplant	6	3
Cataract	1	1
Corneal suture	1	1
Pterygium	1	1
None	22	22
Total	47	38

Table 4

State of Descemet's membrane in corneal buttons removed from the receiver in a transplant where the fungal keratitis was diagnosed

State of Descemet's Membrane	N	%
Normal	5	13
Ruptured	7	19
Ruptured with detachment	5	13
Detachment	6	16
Spores	13	34
Guttata	2	5
Total	38	100

Observation chart for the cohort of cases of fungal keratitis undergoing corneal transplant



following transplant (green). In case 4, the time until diagnosis between the first and second transplant was long, and the infection was late (yellow followed by red), but the relapse was treated in less time. Still, in the chart it seems like the infection was treated for a long time, as the long period during which the patient received no treatment was included into the "transplant" column, so that we didn't have to extend the chart, even though the recurrence was treated immediately. In cases 6, 8 and 11, the infection was noted in the second transplant but not in the first (yellow and red). In case 9 the infection was noted in the first transplant but not in the following two (two shades of green).

In the Observation Chart the data is not homogenous, therefore the dates of surgery were maintained without calculating the average interval between them. Due to the absence of chronological data about the onset of treatment, we could not determine the mean and standard deviation, as the data is largely about cases with markedly different progression.

As we had a relatively large number of operations before and after a transplant with a histological diagnosis, we assessed the reasons for the procedure, which are shown in Table 3.

In 24 (63%) cases only yeast forms were found, in 12 (32%) cases both yeast and hyphae were found, and in 2 (5%) cases only hyphae were found.

To determine the degree of vulnerability of the eyeball to a disseminated infection, we assessed Descemet's membrane, which is considered one of the barriers against intraocular penetration of the parasite after rupture of the previous barrier – the epithelium and Bowman's membrane. Table 4 shows that in only 13% of cases Descemet's membrane was normal, and in 34% the fungus crossed the membrane, which is a cause of concern.

We also assessed the presence of an inflammatory infiltrate

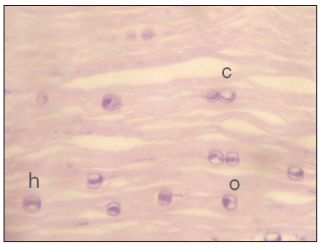


Figure 1A

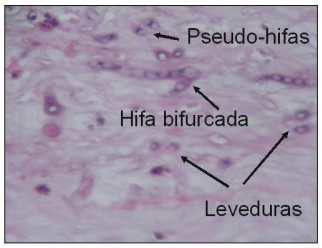


Figure 1B

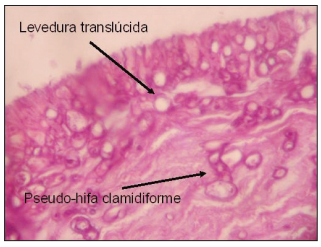


Figure 1C

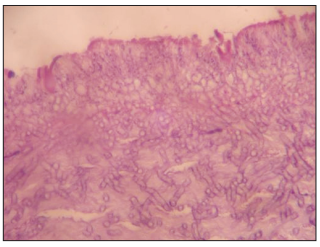


Figure 1D

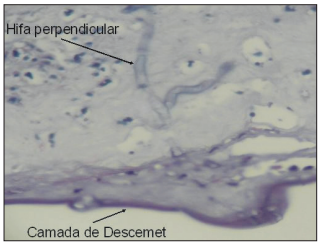


Figure 2A

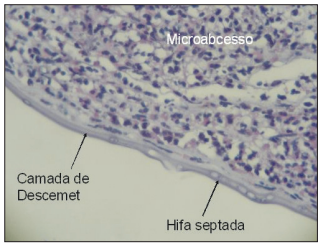


Figure 2B

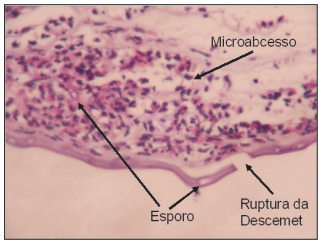


Figure 2C

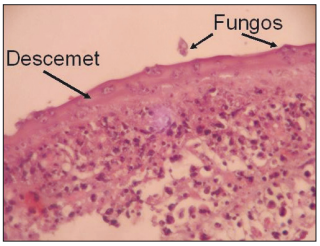


Figure 2D

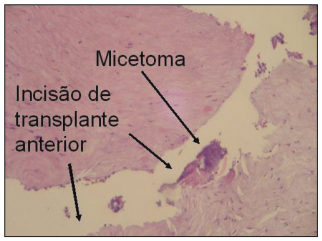


Figure 3A

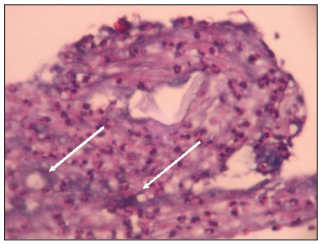


Figure 3B

and found that in half of the cases there was practically no hyperaemia, in 15 (39.5%) cases there was moderate hyperaemia, and in 4 cases there was intense hyperaemia (10.5%).

Many of the corneal buttons had fungi on the corneal surface, on the de-epithelised area or within ulcers. In total, 17 (45%) samples had superficial infections and 21 (55%) had deep infections.

As shown in Figures 1A, 1B and 1C, fungal organisms can have different shapes. Figures 1C and 1D show the parasite on the surface of the cornea both as yeast and mycelia, which consist of hyphae.

Figure 1 - A) Yeast of different appearance: (c) crescent-shaped nucleus, (o) triangular-shaped nucleus; (h) dumbbell-shaped nucleus. Note the absence of inflammatory reaction (HE x 200); B) Hyphae, pseudohyphae and septate hyphae, as well as crescent-shaped yeast. Note the absence of inflammatory reaction (HE x 200); C) Yeast on the de-epithelised surface and, deeper, translucent yeast with a thick capsule and a Chlamydia-shaped pseudohypha consisting of one larger and four smaller yeast cells (HE x 200); D) Mycelium on the ulcerated surface of the cornea, consisting of non-septate hyphae (HE x 120).

Deeper, beyond the hyphae that are parallel to the surface, perpendicular hyphae can be seen, as shown in Figure 2A. Table 5 shows that in 34% of cases the Descemet's membrane had been infected either with spores, hyphae, or yeast (Figure 2B). As shown in Table 7, several changes were found in Descemet's membrane: Figure 2C shows spores close to a rupture zone, and Figure 2D shows the various stages of penetration of the fungus into Descemet's membrane.

Figure 2 - A) A hypha parallel to the corneal surface, which is common, and a perpendicular hypha in the deepest part of the stroma. Descemet's membrane has spores in its structure, with folds and increased thickness (HE x 200); B) Septate hypha within Descemet's membrane, underlying a microabscess in the innermost part of the corneal stroma (HE x 120); C) Microabscess in the innermost part of the corneal stroma, where a spore can be seen. Descemet's membrane is ruptured, and even though penetration could be easier through this breach, the fungus has penetrated the membrane's structure, showing its slow progression coupled with a great capacity of penetration. (HE x 120); D) Fungal spores, of which one has partially penetrated into the anterior chamber and the other is fully within the chamber (HE x 200).

A less common presentation is the formation of a mycetoma, which is present at the incision site of a previous transplant, indicating a recurrence (Figure 3A). Confirming that the parasite has entered the anterior chamber of the eyeball, hypopyon with the presence of parasites can be seen in Figure 3B.

Figure 3 - A) A mycetoma, which is a cluster of fungal cells, is situated within the keratoplasty incision done before the presentation of the fungal infection (HE x 80); B) Hypopyon, with arrows indicating yeast (HE x 200).

Discussion

Studies on the aetiology of keratitis follow along two lines: they either focus on prevention or on aetiology in order to

implement treatment. By studying the flora of the conjunctiva, the preventive and epidemiological aspects of the disease are highlighted, which is important now that the frequency of opportunistic infections is increasing. Due to this, the focus is more directed to bacteriology[5-12], and the presence of saprophytic fungi in the conjunctiva is stressed[13-16]. Some articles focus on fungal keratitis[17,18].

Histopathological studies on fungal keratitis are rare. Still, the condition has already been studied in Brazil[19], although with corneal buttons obtained immediately after transplantation, as is usually the case. This paper could confirm or express a more critical view on our sample, but unfortunately tissue changes were not explored. Therefore, it only served to confirm the previous diagnosis by examining the specimens collected from ulcers.

Having received a larger number of cases of fungal keratitis than expected, from samples submitted to the Eye Bank for control of emergencies and with almost no information presented by surgeons, we sought to do our research within a restricted universe, especially given the staggering number of cases in 2009, which raised of the possibility of a problem of public health. From the findings, we tried to determine which preventive measures could be adopted and/or suggested to clinical ophthalmologists and anterior segment surgeons.

Nearly all articles report the results of laboratory tests identifying the species of fungus. Being deprived of this useful resource, we had to assess tissue responses to make a rough identification of the genus. Species identification was impossible because the pieces had been fixed with neutral formaldehyde, therefore there was no material suitable for tissue culture.

Our study has no value regarding the aetiological diagnosis, but it points to clinical procedures to be adopted in the treatment of keratitis and during the postoperative period of cataract surgery and corneal transplant. As we had scarce information, we had to do our research almost like the people in the cave examining the world outside in Plato's allegory (427-348 BC) in Book VII of the Republic. To support our research, we used histopathology to confirm the diagnosis and to determine what could be offered in terms of aetiology, epidemiology, treatment and prevention of relapse.

A fact that reveals an aspect of the change that has been detected in recent years, related to the risk factors for fungal keratitis, is the predominance of opportunistic infections, and no longer of trauma with plant materials. One reason for this is that the age group most often affected is over 60 years, even though this can also be related to cataract surgery, as seen in our results.

From the epidemiological point of view, it is important to determine whether our findings represent prevalence or incidence rates. As shown in Table 1, the samples received by the Eye Bank indicate an incidence, due to the demonstration of the fungal infection. However, they can also represent a point prevalence[20]. The incidence rate was lower in 2009 than in 2011, while the point prevalence in 2009 was more than 2.5 times higher than in 2011, which would serve as an alert for health authorities. We can not speak in absolute terms because many of the cases were diagnosed clinically and treated until full recovery. We can use, in an inverted sense, the quote attributed to Diogenes (404-323 BC) by the Greek philosopher Diogenes Laertius. Upon visiting a temple, Diogenes was shown a large amount of ex-votos as a proof of benevolence of the gods towards the faithful who sought their help. The philosopher then asked: How many sought the gods and did not receive what they asked? In our sample, we saw the failures without having access to cases with satisfactory results.

The cases we studied were those which did not respond to treatment, did not undergo microbiological studies and had a clinical picture compatible with bacterial keratitis, as was explicitly stated by 7 surgeons. Only two cases were treated for fungal keratitis, without adequate response to treatment (Table 2).

The small number of preoperative diagnoses of fungal keratitis should be considered with caution. On the one hand, in half the cases the disease progressed slowly, as shown in the results section. Surgeons reported intense hyperaemia, but little inflammatory infiltrate was found in many histopathological specimens. This shows a disagreement between the justification provided by surgeons and the histopathological findings, which leads to the following epistemological question: what needs to be investigated in a prospective study?

We cannot say there was an error, due to the lack of data. Even in the 10 cases (26.3%) where there was severe ulceration with little or no hyperaemia, we can not claim incompetence or ignorance by the surgeons as we do not have the medical record showing the disease's progression or symptoms. On the other hand, the impressive number of cases of enucleation for diagnostic confirmation cited by Naumann et al. showed not only the ineffectiveness of the existing therapeutic choices, but also a change in the management of the disease over time[3]. After that study there was a change of attitude among surgeons, who, counting on more accurate tests, started to perform enucleation only in suspected cases of intraocular tumour. Evisceration started to be used in cases of eye infection. In our context, eviscerated material is not routinely sent to histopathology; therefore, cases where recurrence was not demonstrated could not be considered as cured, as they may have had endophthalmitis and undergone evisceration.

Even universities may lack the laboratory tests for keratitis, despite favourable operating factors, as mentioned by Tanure et al.; and there are still cases where the fungus is only positively identified by histopathological examination of corneal buttons. Definitive identification through culture of corneal tissue may take several days or weeks[21].

In Brazil there is an absolute predominance of infections by filamentous fungi, with some studies reaching figures above 70%[11,13,14,18], although there is no consensus about which species are more frequent. Salera et al. found 60% of infections by Fusarium and 30% by Aspergillus, both filamentous fungi[17]; Santos et al. also found a predominance of filamentous fungi, but the most common were Penicillium and Cladosporium[16]; Carvalho et al. found that filamentous fungi were relatively more common, with 32% by Fusarium, 17% by Aspergillus and 10% by Penicillium[18]; Dalfré et al. found 44% by Fusarium and 23% by Geotricum[14].

With regard to other countries, in the United States Aspergillus was the most frequently isolated fungus; in Saudi Arabia, the most common were Aspergillus and Trycophytum, both filamentous[22]; in Japan, Fusarium and Aspergillus[23]; in India, Fusarium and Aspergillus were also the most frequent[24]; and the same was found in China, where filamentous fungi were found in 90% of cases[25].

Table 3 shows the high number of cases related to previous surgery. In our sample, 20 operations out of 47 (42.5%) led to fungal infection of the cornea. Similar results were found in Saudi Arabia. Jastaneiah et al. found that 38.7% of cases had surgery prior to the diagnosis of fungal keratitis[22].

As can be seen in Figures 1C and 1D, the organisms remain on the surface of the cornea. Therefore, we decided to quantify

the possibility of diagnosing the presence of the fungus in cases where treatment had been instituted and found a significant number of cases (45%) where the parasite remained on the surface even though there was deep penetration in the cornea. Garg et al., which also did a study based on histopathology, found similar results[24]. We support the mistaken statement by Naumann et al. that the organisms were found throughout the thickness of the cornea, but in almost all cases there were no fungi on the surface or in the corneal ulcer[3], as those authors worked with samples from enucleation.

Our sample presented a different result from other studies, based on purely morphological findings of fungi with a predominance of yeast forms. Two issues have to be considered. (1) The growing number of cases of fungal keratitis due to the high prevalence of antibiotic use, especially broad-spectrum agents, and the indiscriminate use of steroids in diseases of the anterior segment and during the postoperative period, as well as aspects related to the urbanisation of populations; (2) The biological behaviour of the fungus within tissues as described by McGee et al.[26]. According to these authors, morphological changes occurred due to an adaptation of saprophytic fungi to parasitism as they invade host tissues. Pathogens may present different types of dimorphism generally expressed by the transition from the filamentous form to yeast as they invade tissues.

This is supported by the fact that other studies on fungal keratitis usually perform laboratory tests on samples taken from the corneal surface, while we worked with material from inside the tissues. Figure 2, from Carvalho et al.[18], is very different from the ones we presented because the material was collected with a spatula from the corneal surface for direct examination and culture.

Our findings are also supported by the work of Höfling-Lima et al., who found that yeasts were more frequent in patients who had previously had eye surgery or who were locally or systemically immunosuppressed. This is related to the use of topical or systemic drugs, debilitating diseases and the presence of systemic mycoses. Ocular surgical procedures prior to ocular infection were significantly more associated with infection by yeasts. Topical antibiotics were used both in both yeast and filamentous fungal infections[27]. The large number of corneal buttons we examined came from patients with fungal infection who had undergone surgery, therefore these patients had used antibiotics and anti-inflammatory agents.

Based on these findings, we suggest the study of cases that do not respond to treatment for filamentous fungal keratitis to see if they would respond to the recommended treatment for yeast keratitis, based on the possible morphological changes of the fungus. In cases where the drug has so little specificity, it could be better to target the active parasite form, rather than its superficial one. This represents a different conceptual approach — to treat the morphological change, and not the aetiological manifestation. Even with the morphological changes of the fungus and the prevalence of filamentous forms, we still argue for the need to perform microbiological examination before treatment and to wait for the results in order to decide whether the therapeutic strategy has to be changed.

Clinical signs, which are more subjective, can be associated with the more objective histopathological findings, comparing the information provided by surgeons with the findings of histopathology. The information that about 40% of cases had an inflammatory process with intense hyperaemia contrasts with the histopathological examination, which only found intense infiltrate in less than a third of cases. In half the cases there was of little or no inflammatory reaction. The number of cases cited as having moderate hyperaemia was almost half of those with moderate infiltrate in histological sections. These data may provide the level of reliability of the subjective information in relation to the reality inside tissues. It also shows the difficulty in finding the correct diagnosis when an aetiological diagnosis is not determined, especially in the case of fungal keratitis.

Figure 2C shows a ruptured Descemet's membrane and spores inside it. Table 4 gives an idea of the risk of intraocular penetration by the parasite, showing a high incidence of changes to of Descemet's membrane favouring the passage of the fungus. However, this would explain the presence of corneal oedema. Fungal keratitis can produce de-epithelisation or ulcers, which facilitates the passage of the fungus from the surface into the stroma. Penetration through the stroma can occur by thermotaxis or chemotaxis. Fungal proteases can also contribute to the destruction of the extracellular matrix, as reported by Hua et al.[28].

The importance given to Descemet's membrane as a barrier to intraocular penetration by the fungus can be seriously questioned, as suggested by the image shown here. It is not possible to assess the degree of protection it provides, as the fungus can be seen penetrating the membrane instead of taking advantage of the rupture point. According to the authors mentioned above, there are strains that, when inoculated experimentally, invade the cornea in 24 hours, whereas others advance rapidly over the first three days, then are slowed down until the fifth day; there are also strains that do not have penetrating hyphae. The authors also point out that conidial adhesion, germination of spores and hyphae with extensions facilitate the invasion. The presence of fungal spores in Descemet's membrane shows its great ability to invade the eye and justifies the use of systemic drugs from the beginning of treatment.

Although a literature review showed that endophthalmitis presents in patients with general health vulnerabilities[29], Godoy et al.[30]show a case of endophthalmitis following penetrating keratoplasty. Knowing the penetrating capacity of the organisms and the changes in Descemet's membrane facilitating intraocular invasion, and having no feedback on cases undergoing transplantation, we conclude that there may have been cases of fungal endophthalmitis in our sample without our knowledge. It is also important to note that Fusarium and Aspergillus can quickly reach the intraocular space, as reported by Uno[23].

Our results also show that 2/3 of infections were caused by yeasts. We do not have a mechanical explanation for this, although we can argue that as the fungus penetrates it changes from filamentous to yeast, as suggested by McGee et al. [26]. However, Figure 2A shows hyphae perpendicular to the surface in the innermost part of the inner third of the corneal stroma. Hyphae are almost always parallel to the corneal surface; perpendicular hyphae were found in experimental studies in rabbits subjected to intense corticosteroid use[31].

Figure 3A shows a mycetoma in the incision site for a previous transplant; this confirms the hypothesis by Garg et al. of contamination of the incision tunnel for cataract surgery with sutureless, self-adhesive material[32].

Xie et al. recommend penetrating keratoplasty for fungal ulcers of difficult treatment[25], which is reasonable, as we confirmed cure in four patients after the second transplant; however, in two others cases there was no confirmed cure,

although they have not been submitted to other transplants. Also, there was relapse in three cases, which are not evident in the Observation Chart because we used the same colour for cases of relapse. The success of those authors is due to the combination of topical and systemic antifungal agents for up to 2 months after transplantation, associated with cyclosporine and perhaps corticosteroids when the patient had significant inflammation before the transplant.

From what was discussed here we recommend that the aetiological diagnosis should be investigated in cases of keratitis, including tests for fungi. If this is not done, a sample can be collected from the ulcer, due to the significant probability of discovering the diagnosis even after the onset of treatment. As test results take a long time, and taking into account the urgency of the situation, in vivo confocal microscopy can be used to guide treatment earlier[25-33].

Conclusion

In this paper we presented the reality of a sample, which in many aspects does not correspond to the common findings for this fungal keratitis. We presented our findings, starting from inferences that led to our deductions, therefore we conclude by simply suggesting experimental research that can clarify some of our findings.

The predominance of yeast forms, contradicting the findings of both national and international studies, can be attributed to the fact that other studies found the aetiological agent through microbiology, and the samples we received came from corneal buttons obtained through perforating keratoplasty. A field of research is thus opened up, aiming to determine whether a filamentous fungus tends to change into yeast once the hyphae penetrate tissues and whether they would respond to drugs targeting yeast.

A cause of concern is the ability of the infection to penetrate the intraocular tissues, which is facilitated by corneal oedema and changes in Descemet's membrane, requiring systemic medication from the onset of treatment.

Finally, we recommend that the aetiological diagnosis should be investigated of cases of keratitis, including through confocal microscopy.

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Corresponding author:
Fernando Queiroz Monte
Rua Dr. José Lourenço, 2180/ Apto. 501
60115-282 Fortaleza (CE), Brazil.
Telephone: +5585 3246 6790
E-mail: fernandoqueirozmonte@hotmail.com

Corneal topographic changes after 20-gauge pars plana vitrectomy associated with scleral buckling for the treatment of rhegmatogenous retinal detachment

Alterações topográficas da córnea após vitrectomia via pars plana 20-gauge associada à introflexão escleral para o tratamento do descolamento de retina regmatogênico

Alexandre Achille Grandinetti[1], Janaína Dias[2], Ana Carolina Trautwein[3], Natasha Iskorostenski[3], Luciane Moreira[4], Ana Tereza Ramos Moreira[4]

ABSTRACT

Purpose:*To evaluate the changes in corneal topography after 20-gauge pars plana vitrectomy associated with scleral buckling for the repair of rhegmatogenous retinal detachment.* ***Methods:*** *Twenty-five eyes of 25 patients with rhegmatogenous retinal detachment were included in this study. 20-gauge pars plana vitrectomy associated with scleral buckling was performed in all patients. The corneal topography of each was measured before surgery and one week, one month, and three months after surgery by computer-assisted videokeratoscopy.****Results:*** *A statistically significant central corneal steepening (average, 0,9 D , p<0,001) was noted one week after surgery. The total corneal astigmatism had a significant increase in the first postoperative month (p=0,007). All these topographic changes persisted for the first month but returned to preoperative values three months after the surgery.* ***Conclusion:****Pars plana vitrectomy with scleral buckling was found to induce transient changes in corneal topography.*

Keywords:*Retina; Cornea; Retinal detachment; Scleral buckling; Vitrectomy*
ClinicalTrials.gov Identifier: NCTO1446367

RESUMO

Objetivo: Avaliar as alterações topográficas da córnea após a realização de vitrectomia via pars plana 20-gauge associada à introflexão escleral para o tratamento do descolamento de retina regmatogênico.**Métodos:** Vinte e cinco pacientes com descolamento de retina regmatogênico foram incluídos neste estudo. Vitrectomia via pars plana 20-gauge associada à introflexão escleral foi realizada em todos os pacientes. O exame de topografia de córnea computadorizada de cada paciente foi realizado antes da cirurgia e ao sétimo dia, trigésimo dia e três meses após a cirurgia. **Resultados:** Um aumento da curvatura corneana estatisticamente significativo foi encontrado no sétimo dia após a cirurgia (média 0,9 D, p<0,001). O astigmatismo corneano total teve um aumento significativo no primeiro mês pós-operatório (p=0,007).Todas as alterações topográficas persistiram no primeiro mês pós-operatório, mas retornaram aos valores pré-operatórios três meses após a cirurgia.**Conclusão:** A vitrectomia via pars plana associada à introflexão escleral pode induzir alterações transitórias na topografia corneana.

Descritores: Retina; Córnea; Descolamento retiniano; Recurvamento da esclera; Vitrectomia
Identificador ClinicalTrials.gov : NCTO1446367

[1]Retina and pterígeos Vitreo, Hospital de Clínicas da Universidade Federal do Paraná (UFPR) – Curitiba (PR), Brazil;
[2]Hospital Universitário Evangélico de Curitiba – Curitiba (PR), Brazil;
[3]Universidade Federal do Paraná (UFPR) – Curitiba (PR), Brazil;
[4]Professor of Ophthalmology, Universidade Federal do Paraná (UFPR) – Curitiba (PR), Brazil.
10th Euretina Meeting, 2-5 september 2010, Paris, France – Universidade Federal do Paraná (UFPR) – Curitiba (PR), Brazil

The authors declare no conflicts of interest

Received for publication: 21/11/2011 - Accepted for publication: 7/3/2012

Introduction

The treatment of rhegmatogenous retinal detachments and it complications continue to be one of the most important indications for vitreoretinal surgery, being a well-known cause of ocular refractive changes. The use of an encircling band creates an indentation of the eye that increases the anteroposterior axial length and can change the corneal shape[1,2]. A myopic shift or lowering hypermetropia and irregular corneal astigmatism owing to the explants can be found[3]. More recently, with the advent of small gauge transconjunctival vitrectomy, the effects of the vitrectomy surgery on the cornea have been compared when using different techniques[4]. Some studies have evaluated corneal changes after pars plana vitrectomy and scleral buckling surgery, and although some studies found statistically significant corneal shape changes[5,6], others found no significant changes[7].

Current techniques of rhegmatogenous retinal detachment repair allow most detachments to be repaired successfully. However, even after successful retinal reattachment, postoperative vision may be unsatisfactory for the patient in some cases due to severe myopia or astigmatism that might persist after surgery[8].

The cornea's refracting surface is responsible for about two thirds of the refractive power of the eye and plays an important role in focusing images on the retina. This function can be defined in terms of corneal shape, regularity, clarity and the refractive index[5], all of which might be susceptible to intraoperative compromise after vitreoretinal surgery.

In this study, we investigated the possible corneal changes after 20-gauge pars plana vitrectomy (PPV) associated with scleral buckling for the treatment of rhegmatogenous retinal detachment using computer-assisted videokeratography.

Methods

Twenty-five patients with rhegmatogenous retinal detachment who underwent 20-gaugePPV combined with scleral buckling were prospectively included in this study. Approval from the appropriate ethics committee was obtained, and informed consent was acquired from all patients before surgery.

Patients with a history of corneal changes prior to surgery (rigid contact lens use, refractive surgery, cataract surgery, corneal trauma, corneal transplant, keratoconus, corneal ulcers) and other causes of retinal detachment (proliferative diabetic retinopathy, tractional, traumatic, associated with tumors of the choroid, and inflammation, among others) were excluded from the study. All surgeries were planned and performed by the same surgeon successfully (AAG).

All patients underwent a 20-gauge PPV combined with scleral buckling, which consisted on the placement of a infusion cannula 4 mm from the corneal limbus in the inferior temporal quadrant between the insertions of the rectus muscles, and two sclerotomies 4mm from the corneal limbus in the upper quadrants, always located at the top of the line of the rectus muscles insertion. Total vitrectomy was performed, demarcation of the tears with endodiatermy, drainage of subretinal fluid followed by endolaser photocoagulation around the retinal tears. Scleral buckling technique was performed using a silicone band number 42 (Labtician S2971; Labtician Ophthalmic Inc, Canada), which was sutured in the 4 quadrants at a distance of 11 mm from the corneal limbus, using Mersilene 5.0 sutures to hold the band in the middle of the quadrant. After the surgery was performed, the vitreous cavity substitute was chosen according to the discretion of the surgeon (perfluoropropane gas or silicone oil) and the sclerotomies and conjunctiva were closed using 7.0 vicryl sutures.

Twenty-five eyes of these 25 patients were analyzed using computerized videokeratography (EyeSys 2000; Corneal Analysis System v4.0). Corneal topography was measured before surgery, as well as one week, one month and three months after surgery. At least three videokeratographs were recorded from each patient, and the data were obtained from the best quality keratograph. The analysis of the corneal videokeratographs was based on the Holladay Diagnostic Summary (HDS) software package. The HDS gives four color-coded maps and 15 corneal parameters. The maps include two refractive power maps on standard and auto scales, a profile difference map for determining the corneal shape, and a distortion map that provides information about the visual performance and optical quality of the cornea. The parameters from the HDS provide information of the central 3mm of the cornea. It should be noted that optical distortions outside this 3.0mm pupil zone are shown to have little effect on the visual performance except when the pupil is dilated.

In this study, steep refractive power, flat refractive power, and total astigmatism parameters from the HDS were used to investigate the changes in corneal topography. The steep refractive power (K2) is the strongest refractive power in the central cornea, whereas the flat refractive power (K1) is the weakest refractive power. The difference between these two parameters is defined as the total astigmatism of the cornea.

Results

Of the twenty-five patients included in this study, 15 (60%) were male and 10 (40%) were female. The left eye was affected in 14 patients (56%) and the right eye in 11 patients (44%).

The mean age ofthe patients admitted to surgeries was 54.52 years, the youngest being 28-year-old and the oldest 68-year-old.

The assessment of the macula in the preoperative period was defined as attached in 6 cases (24%) and detached in 19 cases (76%).

The vitreous substitute most commonly used was perfluoropropane gas (C3F8), in 19 patients (72%), and silicone oil in 7 cases (28%).

After surgery, an average of a 0,9 diopter (D) increase in central corneal steepening, was detected in the first week. The difference was statistically significant when compared with preoperative values ($p < 0.001$). Figures 1 A and B illustrate the postoperative change in a patient with marked steepening of the central cornea in the first week. This central steepening started to decrease gradually throughout the first month after surgery and came close to preoperative values at three months. The flat refractive power (K1) increased on an average of 0,6 D in the first week after surgery. The difference was statistically significant when compared with preoperative values ($p < 0.05$). There was no residual central corneal flattening at the three-month visit compared with preoperative values. All these changes are listed in table 1.

Total corneal astigmatism before surgery was found to be mean 0,78 D. It reached its highest level in the first postoperative week (mean, 1,14 D). This difference was statistically significant ($p < 0,005$). The corneal astigmatism slightly decreased and was a mean of 1,06 D by the first postoperative month. The induced corneal astigmatism was a mean of 0,89 D at the three month visit, and no statistically significant difference was seen by that time when compared to the preoperative values. The changes in total corneal astigmatism are listed in table 2.

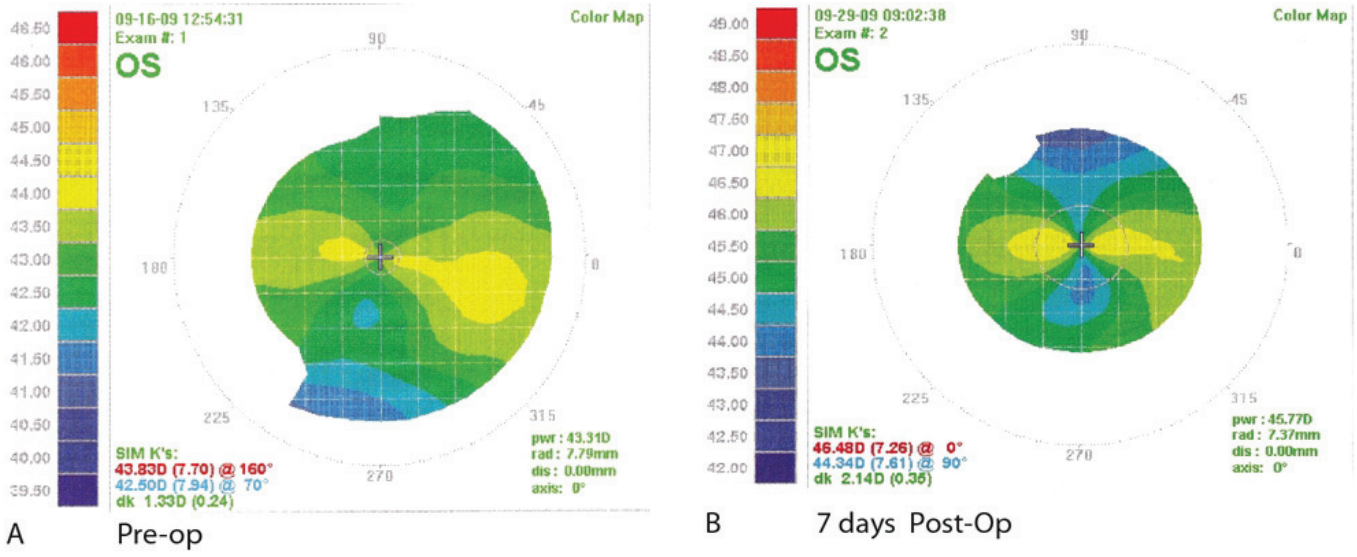

Figure 1: A) Corneal videokeratography of a patient before PPV with scleral buckling; B) note the central corneal steepening seven days after surgery

Table 1

Changes in corneal steepening and flattening after surgery

	Before surgery	1st week	1st month	3rd month
Central steepening				
Mean	42.4	43.3	43.3	42.5
±SD	1.7	2.0	2.1	1.7
p		<0.001[a]	<0.001[a]	0.504[a]
Central flattening				
Mean	41.6	42.2	42.2	41.6
±SD	1.5	1.8	1.9	1.7
p-value		<0.05[a]	<0.05[a]	0.747[a]

[a] Compared with preoperative values / All values are in diopters

Table 2

Changes in corneal total astigmatism after surgery

	Before surgery	1st week	1st month	3rd month
Total astigmatism				
Mean	0.78	1.14	1.06	0.89
±SD	0.72	0.78	0.61	0.61
p-value		<0.05[a]	<0.05[a]	0.441[a]

[a] Compared with preoperative values / All values are in diopters

Discussion

It is well known that changes in the corneal shape and refractive status induced by scleral buckling may occur soon after surgery. These changes include postoperative corneal astigmatism, particularly steepening and flattening of the cornea, and a myopic shift[4].

We analyzed the central corneal topographic changes that occur after vitrectomy surgery with scleral buckling, for the treatment of rhegmatogenous retinal detachment with the use of videokeratography.

In the current study, we found a significant central corneal steepening in the first week postoperatively, which persisted during the first 30 days after surgery and regressed to preoperative values three months after surgery. Hayashi et al.[9], who have used videokeratography after scleral buckling surgery, reported increased postoperative central corneal steepening and peripheral corneal flattening. Weinberger et al.[3], also found central corneal steepening after scleral buckling that lasted for as long as 3 months. It is assumed that, the scleral buckle indents the eye circumferentially and causes corneal steepening and corneal flattening postoperatively.

The corneal contour isknown to be altered after PPV and scleral buckling. Domniz et al.[5], measured the corneal topography in eyes undergoing PPV by means of videokeratography and reported that the corneal surface cylinder, average corneal power, regularity index , surface asymmetry index and irregular astigmatism index were increased at two days and one week after surgery and returned to its baseline onemonth after surgery. Similarly, Avitabile et al.[4] described a transient increase of keratometric astigmatism 1 week after PPV when comparing 20-gauge and 25-gauge techniques , and that it returned to the preoperative levelone month after surgery on the 25-gauge group and 2 months after surgery on the 20-gauge group. The differences between the two groups were thought to happen due to different durations for complete scleral healing, loosening of the sutures and the use of scleral cautery on the 20-gauge group.

Our findings are consistent with previous reports. However, the amount of astigmatic changes in this study was 0.36 D at one week postoperatively, which is much smaller than a range of 1.5 to 3.0 D, at two to seven days after surgery reported previously. In our study, all patients were submitted to 20-gauge PPV combined with scleral buckling so that we had effects from both techniques inducing steepening of the cornea on different meridians, which could explain such results. Tear film dynamics affecting corneal topography may also be relevant to the differences between our results and those of previous studies[8].

We concluded that 20-gauge PPV associated with scleral buckling for the treatment of rhegmatogenous retinal detachment induces transient changes in the corneal topography causing corneal astigmatism, and that videokeratography is helpful for documenting such corneal changes after vitreoretinal surgery.

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Corresponding author:
Alexandre Achille Grandinetti, MD
Av. Vicente Machado, nº 1171 – Curitiba (PR) – Brazil
Postal Code 80420-011
Phone/Fax: (55) 41 3323-1120
E-mail: alexandregrandinetti@gmail.com

Dynamic ultra high speed Scheimpflug imaging for assessing corneal biomechanical properties

Avaliação Dinâmica com fotografia de Scheimpflug de alta velocidade para avaliar as propriedades biomecânicas da córnea

Renato Ambrósio Jr[1,2,3], Isaac Ramos[1,2], Allan Luz[2,3], Fernando Correa Faria[1,2], Andreas Steinmueller[4], Matthias Krug[4], Michael W. Belin[5], Cynthia Jane Roberts[6]

ABSTRACT

Objective: *To describe a novel technique for clinical characterization of corneal biomechanics using non-invasive dynamic imaging.* ***Methods:*** *Corneal deformation response during non contact tonometry (NCT) is monitored by ultra-high-speed (UHS) photography. The Oculus Corvis ST (Scheimpflug Technology; Wetzlar, Germany) has a UHS Scheimpflug camera, taking over 4,300 frames per second and of a single 8mm horizontal slit, for monitoring corneal deformation response to NCT. The metered collimated air pulse or puff has a symmetrical configuration and fixed maximal internal pump pressure of 25 kPa. The bidirectional movement of the cornea in response to the air puff is monitored.* ***Results:*** *Measurement time is 30ms, with 140 frames acquired. Advanced algorithms for edge detection of the front and back corneal contours are applied for every frame. IOP is calculated based on the first applanation moment. Deformation amplitude (DA) is determined as the highest displacement of the apex in the highest concavity (HC) moment. Applanation length (AL) and corneal velocity (CVel) are recorded during ingoing and outgoing phases.* ***Conclusion****: Corneal deformation can be monitored during non contact tonometry. The parameters generated provide clinical in vivo characterization of corneal biomechanical properties in two dimensions, which is relevant for different applications in Ophthalmology.*

Keywords: *Biomechanics; Cornea/physiology; Corneal topography/methods; Tonometry, ocular/methods*

RESUMO

Objetivo: Descrever uma nova técnica para caracterização clínica das propriedades biomecânicas da córnea, usando sistema de imagem dinâmica não invasivo. **Métodos:** A resposta de deformação da córnea é monitorada durante tonometria de não contato com fotografia de Scheimpflug de altíssima velocidade. O Oculus Corvis ST (Scheimpflug Technology; Wetzlar, Germany) apresenta uma câmera UHS Scheimpflug que adquire mais que 4.300 fotos por segundo com cobertura de 8mm horizontais para monitorar a resposta de deformação durante a tonometria de não contato por sopro de ar. O pulso de ar é muito bem controlado, apresentando uma configuração simétrica em sua pressão, com máxima pressão da bomba fixa de 25 kPa. O movimento bidirecional da córnea em resposta ao jato de ar é monitorado. **Resultados:** A medida dura 30ms, com 140 fotos adquiridas. Algorítmos avançados identificam os limites anterior e posterior da córnea em cada imagem. A pressão intraocular (PIO) é calculada com base no primeiro momento de aplanação. A amplitude de deformação é determinada pelo maior deslocamento do ápice, durante o momento de maior concavidade. A extensão da aplanação e velocidade da córnea são medidos nas fases de entrada e saída. **Conclusão**: A deformação da córnea durante a tonometria de sopro por pulso de ar pode ser monitorada em detalhe com sistema de fotografia de altíssima velocidade. Os parâmetros gerados possibilitam caracterização clínica das propriedades biomecâmicas da córnea em duas dimensões. Tais achados têm relavância para diversas áreas da Oftalmologia.

Descritores: Biomecânica; Córnea/fisiologia; Topografia da córnea/métodos; Tanometria ocular/métodos

[1]Instituto de Olhos Renato Ambrósio – Rio de Janeiro (RJ), Brazil;
[2]Rio de Janeiro Corneal Tomography and Biomechanics Study Group – Rio de Janeiro (RJ), Brazil;
[3]Department of Ophthalmology, il;
[4]Oculus GmbH - Wetzlar, Germany;
[5]Ophthalmology, University of Arizona – Tucson, AZ, USA;
[6]Ophthalmology, Department of Biomedical Engineering, The Ohio State University – Columbus, OH, USA.

Financial Disclosure(s): Mr. Steinmueller, Mr. Krug are employee of Oculus; Dr. Ambrósio, Dr. Belin and Dr. Roberts are consultants for Oculus

Received for publication: 11/4/2012 - Accepted for publication: 3/12/2012

Introduction

From central keratometry to corneal topography (front surface curvature maps), then into 3-D corneal tomography systems, there was a tremendous evolution on the diagnostic methods for characterizing corneal shape[1,2]. Biological properties, such as wound healing response and biomechanics, are essential for determining and maintaining corneal transparency, as well as geometrical and optical properties[3]. Corneal biomechanical behavior is well known to influence the development of ectatic diseases[4], and the results of surgery[5]. Also, corneal properties influence intraocular pressure measurements[6], and also may be an independent risk factor for glaucomatous neuropathy[7-9].

The assessment of corneal biomechanical properties has been limited to laboratory in vitro studies[4,10], and to virtual mathematical corneal finite element models[6 11,12]. The Ocular Response Analyzer (ORA, Reichert Inc., Depew, NY), a modified non-contact tonometer (NCT) designed to provide a more accurate measurement of IOP through the understanding of compensation for corneal properties, was the first clinical tool for assessing in vivo biomechanical properties of the cornea[13]. Other nondestructive methodologies have been described, including radial shearing speckle pattern interferometry[14,15], Brillouin optical microscopy[16], OCT (ocular coherence tomography)[17], and other forms of dynamic corneal imaging[18,19].

We present the Corvis ST (Scheimpflug Technology), a new NCT system integrated with an ultra-high-speed (UHS) Scheimpflug camera that was recently introduced by Oculus (Wetzlar, Germany).

Methods

The instrument has an ergonomic design (Figure 1), with adjustable head console and chin rest. The patient is comfortably positioned with proper placement of the chin and forehead. The patient is asked to focus at the central red LED (Light Emitting Diodes). A frontal view camera is mounted with a keratometer-type projection system for focusing and aligning the corneal apex. The exam is programmed for automatic release when alignment is achieved with the first Purkinje reflex of the cornea. Manual release is also possible.

The UHS Scheimpflug camera takes over 4,300 frames per second to monitor corneal response to a metered collimated air puff with fixed profile that has symmetrical configuration and fixed maximal internal pump pressure of 25 kPa (Figure 2). The UHS Scheimpflug camera has blue light LED (455 nm, UV free) and covers 8.5mm horizontally of a single slit. Recording measurement time is 30ms, which allows for acquiring 140 digital frames. Each image has 576 measuring points.

This imaging system allows dynamic inspection of the actual deformation process during NCT. Advanced algorithms for edge detection of the corneal contours are applied for every frame (Figure 3). The recording starts with the cornea at the natural convex shape. The air puff forces the cornea inwards (ingoing phase) through applanation (first or ingoing applanation) into a concavity phase until it achieves the highest concavity (HC). There is an oscillation period before the outgoing or returning phase. The cornea undergoes a second applanation before achieving its natural shape when there is a possible oscillation.

The timing and corresponding pressure of the air puff at the first and second applanations and at the HC moments are identified. Intraocular pressure (IOP) is calculated based on the timing of the first applanation event. This initial IOP measurement is dependant of corneal resistance. The deformation amplitude (DA) is detected as the highest displacement of the apex in the HC moment image. The radius of curvature at highest concavity is recorded. Applanation lengths

Figure 1: Oculus Corvis ST (Wetzlar, Germany)

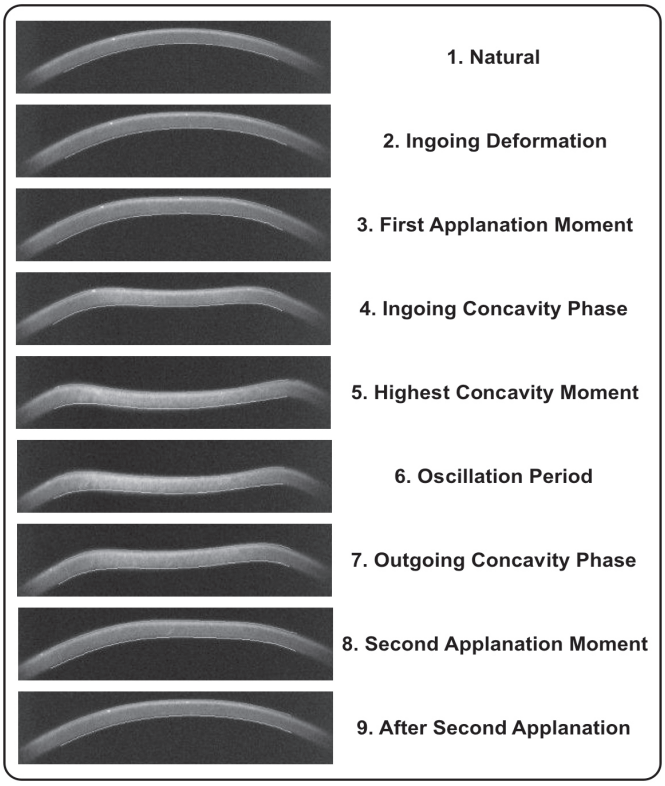

Figure 2: Graphic presentation of the air pressure (internal) and the corneal apex signal with detected applanation moments

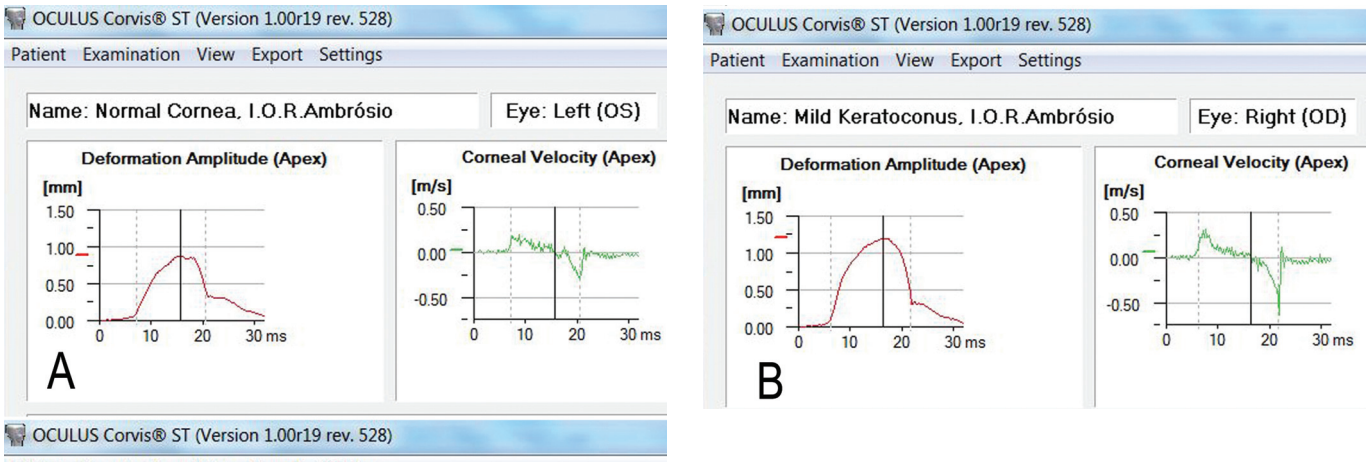

Figure 3: Selected Scheimpflug image frames of a normal cornea during the measurement

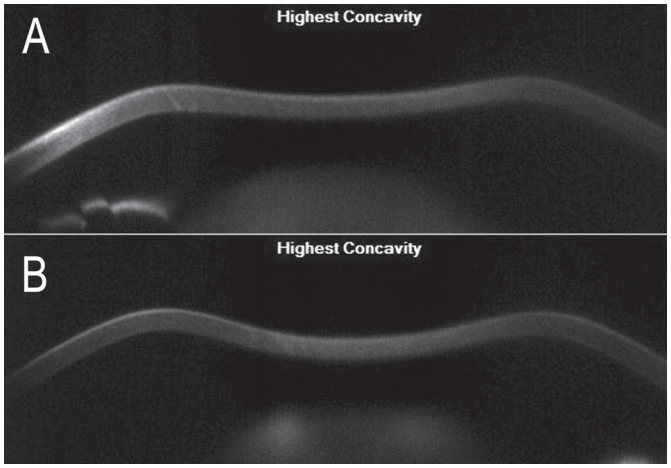

Figure 4: Graphic display report of a normal thin (A) and mild keratoconic cornea; (B) with the deformation amplitude and corneal velocity plots versus time

(AL) and corneal velocities (CVel) are recorded during ingoing and outgoing phases. Corneal thickness is also calculated through the horizontal Scheimpflug image. The lowest value is displayed.

Results

Figures 3 and 4 summarize the Corvis ST findings in a normal thin cornea (Figures 3A and 4A), compared to one with mild keratoconus (Figures 3B and 4B). Both corneas have relatively similar central corneal thickness of 500µm and similar IOP of 14mmHg . The deformation of the ectatic cornea is more pronounced, having higher DA and corneal velocities. The applanation lengths in the ectatic cornea are smaller.

Such parameters have been found useful for the diagnosis of ectasia[2], as well as for assessing CXL results (Roberts, unpublished data 2011). In the FDA trial of corneal collagen crosslinking conducted at The Ohio State University, subjects were evaluated biomechanically using the Corvis ST before and after the procedure. 11 keratoconic subjects randomly selected for the treatment group, were compared with 8 keratoconic subjects randomly selected to be in the sham group. At one month post-procedure, a significant difference ($p < 0.0014$) was found in the radius of curvature at highest concavity in those subjects who received treatment, consistent with increased stiffness. Subjects in the sham group showed no difference ($p = 0.6981$) at one month. Greater negative magnitude in the radius of curvature after corneal collagen crosslinking or a flatter curvature at maximum deformation was observed.

Discussion

We have described a new technique for the non-invasive imaging of the dynamic response of the cornea to an air puff during NCT, using UHS Scheimpflug imaging. The inspection of the corneal slit during the deformation allows for objective and subjective analysis. The different corneal responses to the same deformation stimuli obtained with the normal thin and mild keratoconic cornea indicate that there are significant differences in biomechanical properties despite these corneas having similar thickness. The relative contribution of intraocular pressure in the measurement is relatively eliminated in the example, as both eyes have similar IOP. In addition, the ability to evaluate the deformation response has the potential for demonstrating clinical evidence for biomechanically evaluating the effect of collagen crosslinking procedure.[20]

The retrieved data and deformation obtained by the Corvis ST provide information related to the biomechanical properties of the tissue, including elasticity and viscoelasticity. Very importantly, the deformation data may allow for more precise intraocular pressure measurements, which is also a significant influent of the deformation response. Therefore, the ultimate goal to understand the biomechanical properties of the corneal tissue and to measure IOP will have to be achieved together.

The generated parameters can be integrated using linear and/or more advanced artificial intelligence algorithms for improving the accuracy of detecting disease and the impact of surgery. These parameters can be also used in combination with corneal tomography and ocular biometry data.

The integration of ultra-high-speed Scheimpflug imaging with NCT has an enormous potential as a research and clinical tool to retrieve in vivo biomechanical properties of the cornea. These measurements could be considered in finite element models that would improve diagnosis and prognosis of corneal diseases and improve safety and efficacy of corneal surgery.

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Corresponding Author:
Renato Ambrósio Jr, MD, PhD
Rua Conde de Bonfim, nº 211/712 - Tijuca
CEP 20520-050 – Rio de Janeiro (RJ), Brazil
email:dr.renatoambrosio@gmail.com

Refractive results of cataract surgery using optical biometry and Haigis formula in eyes with refractive keratotomy

Resultado refracional da cirurgia de catarata utilizando biômetro óptico e fórmula Haigis em olhos com ceratotomia refrativa

Juan Carlos Sánchez Caballero[1]; Virgilio Centurion[2]

ABSTRACT

Objective: *To analyze refractive results in postoperative cataract surgery in eyes previously submitted to keratotomy using Haigis formula and data provided by IOL Master® optical biometer.* ***Methods:*** *The measurements for IOL calculation were obtained through optical biometry by partial coherence interferometry (IOL Master® - Zeiss, 5.4 and 5.5 version) that provides us with the axial length, the central keratometry of 2.5mm, white-to-white diameter and anterior chamber anatomical depth. The formula chosen was Haigis. The surgical technique applied was with the scleral incision at 1.5 mm from the limbus, with scleral-corneal tunnel of 2.2 mm wide, phacoemulsification using INFINITI Ozil® - Alcon and implantation of hydrophobic acrylic aspheric intraocular lens - SN60WF® - Alcon.* ***Results:*** *We studied 20 eyes submitted to keratotomy in the past and currently with cataract with indication for cataract surgerywith intraocular lens implantation using phacoemulsification. Postoperative spherical equivalent was plano in 40% of the eyes and lower than -1.00 in 85% of the eyes.* ***Conclusion:*** *The optical biometry by partial coherence interferometry associated with Haigis formula is a valid alternative in IOL calculation for eyes submitted to keratotomy. The refractive results are highly predictable and reproducible.*

Keywords: *Intraocular lens;Anterior chamber; keratotomy, radial; Biometry/instrumentation; Axial length, eye/pathology*

RESUMO

Objetivo: Analisar os resultados refracionais no pós-operatório de cirurgia de catarata em olhos previamente submetidos à ceratotomia, utilizando a fórmula Haigis e os dados fornecidos pelo biômetro óptico IOL Master®. **Métodos**: As medidas para o cálculo da LIO foram obtidas por meio da biometria óptica por interferometria de coerência parcial (IOL Master® - Zeiss, versão 5.4 e 5.5) que nos fornece o comprimento axial, a ceratometria central de 2.5mm, o diâmetro branco-a-branco e a profundidade anatômica da câmara anterior. A fórmula escolhida foi a Haigis. A técnica cirúrgica aplicada foi com incisão escleral a 1.5mm do limbo, com túnel esclero-corneal de 2.2mm de largura, facoemulsificação com equipamento INFINITI Ozil® – Alcon e implante de lente intraocular acrílica hidrofóbica asférica – SN60WF® – Alcon. **Resultados**: Foram estudados 20 olhos submetidos à ceratotomia no passado e atualmente portadores de catarata com indicação de facectomia com implante de lente intraocular por meio da facoemulsificação. O equivalente esférico pós-operatório foi plano em 40% dos olhos e menor que -1.00 em 85% dos olhos. **Conclusão**: A biometria óptica por interferometria de coerência parcial associada à fórmula Haigis se apresenta como uma alternativa válida no cálculo da LIO em olhos submetidos à ceratotomia. Os resultados refrativos são altamente previsíveis e reproduzíveis.

Descritores: Lentes intraoculares; Câmara anterior; Ceratotomia radial; Biometria/instrumentação; Comprimento axial do olho

[1]Oftalmologista do Instituto de Moléstias Oculares (IMO) – São Paulo (SP), Brasil;
[2]Oftalmologista do Instituto de Moléstias Oculares (IMO) – São Paulo (SP), Brasil.

Trabalho realizado no Instituto de Moléstias Oculares (IMO) – São Paulo (SP), Brasil

The authors declare no conflicts of interest

Received for publication: 28/6/2012 - Accepted for publication: 27/1/2012

Introduction

Individuals submitted to keratotomy for correction of myopia and / or astigmatism in the 80's, an average age of 30, now reaching 60 years, are looking for cataract surgery or for surgical correction of other refractive errors such as secondary progressive hyperopia.These patients have behavioral characteristics that is known as "refractive profile", that is, they are individuals who have had correction of refractive errors and now, at the moment of selecting a new surgery they have an expectation equal to or higher than in the first experience. They are well informed about advances in eye surgery and demand or expect to have results that meet or exceed their expectations[1].

Another characteristic is related to the cornea that usually shows a progressive central flattening, with fluctuation of the visual acuity.When submitted to lens surgery may have a significant flattening, though temporary, which may compromise the final result[2].

Refractive[1] predictability and reproducibility of IOL calculation may be difficult due to the peculiarities of the cornea previously submitted to keratotomy.

The objective of this study is to analyze the cataract surgery postoperative refractive results in eyes previously submitted to keratotomy, using Haigis formula and the data provided by IOL Master® optical biometer.

Methods

This is a retrospective, non-comparative study of 20 eyes which were submitted to keratotomy in the past and have cataract with an indication for intraocular lens implantation by phacoemulsification.

All the eyes underwent a complete ophthalmologic examination with emphasis on the biomicroscopy of the anterior segment, for analysis of radial cuts in the cornea, IOL calculation, analysis of vision potential (PAM) and evaluation of retina.

The measurements for IOL calculation were obtained from the optical biometry based on partial coherence interferometry (IOL Master®, Zeiss, version 5.4, 5.5). This equipment provides:

1. Axial length
2. Central keratometry of 2.50mm
3. White-to-white diameter
4. Anatomic depth of the anterior chamber.

To obtain more detailed analysis of the corneal surface,the eyes were submitted to corneal topography (Tomey - TMS) and corneal tomography (Pentacam - Oculus).

The keratometry used for the calculation of IOL was the one provided by IOL Master® that when compared to Pentacam®, module Holladay Report, the 3mm does not present a significant difference.

The biometric formula used was Haigis. The surgical technique was with scleral incision 1.50mm from the limbus, with sclero-corneal tunnel of 2.2mm wide, phacoemulsification using Alcon INFINITI equipment and implantation of hydrophobic acrylic aspheric intraocular lens - SN60WF - Alcon. All surgeries were performed by one surgeon (VC). The refraction studied was collected between the third and the sixth months postoperative. The chosen preoperative target refraction in biometric calculation was for emmetropia (plano).

All patients signed an inform consent about the procedure.

The statistic method used was the T Student.

Table1
Data of eyes with previous keratotomy submitted to cataract surgery

Nº	K1K2 Pre	Axial L	ACD	IOL	RX Post	S.E.	UDVA	LogMAR	CDVA	LogMAR	Formula
1.	33.35 x 83 / 37.63 x 173M = 35.49	27.48	3.50	21.00SN60WF	+0.50-2.50 90º	-0.75	20/60	0.48	20/20	0.00	Haigis
2.	43.44 x 14 / 43.83 x 104M = 43.63	23.97	3.32	18.50SN60WF	Plana	Plano	20/20	0.00	20/20	0.00	Haigis
3.	42.75 x 16 / 43.44 x 106M = 43.10	24.57	3.26	18.00SN60WF	Plana	Plano	20/30	0.18	20/30	0.18	Haigis
4.	35.20 x 180 / 36.20 x 90M = 35.70	25.79	3.20	25.00SN60WF	-1.75140º	-0.87	20/40	0.30	20/20	0.00	Haigis
5.	35.00 x 55 / 34.40 x 145M = 34.70	25.64	3.27	27.00SN60WF	-0.50160º	-0.25	20/30	0.18	20/20	0.00	Haigis
6.	36.25 x 104 / 37.09 x 14M = 36.67	27.03	3.77	20.00SN60WF	+0.50	+0.50	20/30	0.18	20/20	0.00	Haigis
7.	34.23 x 129 / 44.53 x 39M = 39.38	25.59	3.58	20.00SN60WF	-5.00120º	-2.50	20/100	0.70	20/30	0.18	Haigis
8.	35.83 x 85 / 36.64 x 175M = 36.23	26.04	3.51	23.00SN60WF	-1.00115º	-0.50	20/40	0.30	20/20	0.00	Haigis
9.	31.96 x 119 / 37.84 x 29M = 34.90	26.95	2.87	23.00SN60WF	Plana-5.50 105º	-2.75	20/200	1.00	20/40	0.30	Haigis
10.	30.00 x 94 / 35.00 x 4M = 32.50	28.87	2.86	21.00SN60WF	+1.00-4.50 92º	-1.25	20/200	1.00	20/40	0.30	Haigis
11.	35.53 x 17 / 37.38 x 107M = 36.45	27.43	3.06	20.00SN60WF	+0.50-1.50 15º	-0.25	20/60	0.48	20/20	0.00	Haigis
12.	34.62 x 88 / 36.06 x 178M = 35.34	26.50	3.10	23.00SN60WF	+0.50-0.75 105º	+0.25	20/40	0.30	20/20	0.00	Haigis
13.	35.87x 98 / 36.76 x 8M = 36.31	26.12	3.48	23.00SN60WF	Plana	Plano	20/30	0.18	20/20	0.00	Haigis
14.	36.93 x 146 / 37.46 x 56M = 37.19	25.83	4.96	22.50SN60WF	Plana	Plano	20/30	0.18	20/20	0.00	Haigis
15.	35.38 x 123 / 35.83 x 33M = 35.60	29.38	3.19	16.50SN60WF	Plana	Plano	20/50	0.40	20/30	0.18	Haigis
16.	34.97 x 151 / 35.71 x 61M = 35.34	27.19	3.40	21.00SN60WF	-1.00145º	-0.50	20/50	0.40	20/30	0.18	Haigis
17.	35.94 x 172º / 39.06 x 82ºM = 37.50	26.75	3.67	20.00SN60WF	+0.50-0.50 70º	+0.25	20/30	0.18	20/30	0.18	Haigis
18.	35.60 x 11 / 37.01 x 101ºM = 36.30	26.56	3.76	23.00SN60WF	Plana	Plano	20/20	0.00	20/20	0.00	Haigis
19.	41.11 x 5 / 41.93 x 95ºM = 41.52	23.37	3.09	24.50SN60WF	Plana	Plano	20/20	0.00	20/20	0.00	Haigis
20.	41.82 x 151 / 42.13 x 61ºM = 41.97	23.29	2.97	24.50SN60WF	-1.00120º	-0.50	20/40	0.30	20/20	0.00	Haigis

Table 2

Average preoperative keratometry

32.50 to 34.00	1	5%
34.25 to 36.00	7	35%
36.25 to 38.00	7	35%
38.25 to 40.00	1	5%
40.25 to 42.00	2	10%
42.25 to 44.00	2	10%
Total	20	100%

Table 3

Postoperative refraction (spheric equivalent)

Plano	8	40%
+0.50 a -0.50	7	35%
-0.75 a -1.00	2	10%
> -1.00	3	15%
Total	20	100%

Table 4

Preoperative refraction and preoperative spheric equivalent, postoperative refraction and postoperative spheric equivalent

Nº	RX Pre	S.E. Pre	RX Post	S.E. Post
1.	-0.50 -1.75 70º	-1.37	+0.50 -2.50 90º	-0.75
2.	+1.50	+1.50	Plano	Plano
3.	+1.50	+1.50	Plano	Plano
4.	+2.75 -0.50 30	+2.50	-1.75 140º	-0.87
5.	+4.00 -1.00 180	+3.50	-0.50 160º	-0.25
6.	+0.50	+0.50	+0.50	+0.50
7.	+2.00 -5.00 135º	-0.50	-5.00 120º	-2.50
8.	+1.50 -1.00 85º	+1.00	-1.00 115º	-0.50
9.	-1.00 145º	-0.50	Plano -5.50 105º	-2.75
10.	-1.00 -4.00 90º	-3.00	+1.00 -4.50 92º	-1.25
11.	-4.00 -2.00 35º	-5.00	+0.50 -1.50 15º	-0.25
12.	-1.00 80º	-0.50	+0.50 -0.75 105º	+0.25
13.	+1.00 -0.50 90º	+0.75	Plano	Plano
14.	+2.00	+2.00	Plano	Plano
15.	-4.75 -0.75 180º	-5.12	Plano	Plano
16.	-2.00 -0.50 45º	-2.25	-1.00 145º	-0.50
17.	-0.50 70º	-0.25	+0.50 -0.50 70º	+0.25
18.	+1.50 -0.25 50º	+1.38	Plano	Plano
19.	+3.50	+3.50	Plano	Plano
20.	+3.00 -1.00 110º	+2.50	-1.00 120º	-0.50

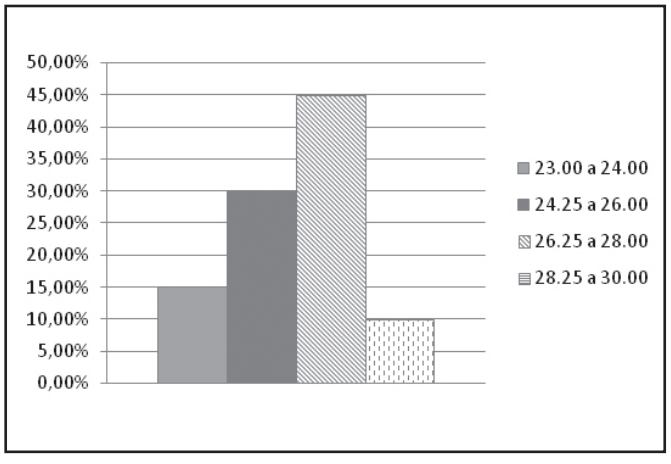

Figure 1: Axial length

Table 5

Postoperative UDVA

20/20	3	15%
20/30	6	30%
20/40	4	20%
20/50	2	10%
20/60	2	10%
20/100	1	5%
20/200	2	10%
Total	20	100%

Table 6

Postoperative CDVA

20/20	13	65%
20/30	5	25%
20/40	2	10%
Total	20	100%

Results

Table 1 shows the relationship of the eyes studied with the following data: preoperative keratometry, axial length, anterior chamber depth (ACD), implanted IOL, postoperative refraction, spherical equivalent (SE), postoperative visual acuity with and without correction and formula used.

Preoperative keratometry varied from 32.50 D to 43.63 D (Table 2).

Axial length varied from 23.00mm to 29.38mm (Figure 1).

Average spheric equivalent in postoperative refraction was plano in 40% of the eyes and lower than -1.00 in 85% of the eyes (Table 3).

Statistical analysis

Applying the T test in relation to a previously planned refraction, if it is plano = 0, one obtains statistical $t = 2.3941$ with $p = 0.02714$ which means that the mean random variable of post-surgical spheric equivalent is statistically different from zero.

The uncorrected distance visual acuity is shown in table 5.

Postoperative CDVA is shown in table 6.

Discussion

The calculation of IOL power depends on the method used, data on axial length, data on corneal power and biometric formula[3].

The method used in this study was optical biometry with the IOL Master - Zeiss® (5.4 - 5.5) which makes the calculation of axial length by partial coherence interferometry and has proved more efficient than contact ultrasonic biometry[4].

Corneal power, the focus of major controversy in the eyes with keratotomy[2] scar, is obtained by the autorefractor biometer in a central area of 2.50mm (different from manual keratometry that provides values of an area of 4.00mm[5]).

In addition to our routine corneal power provided by the biometer, we obtained an extra keratometry with topographer (Pentacam - Oculus) that in the module Holladay Report allows us to choose the keratometric value in a central area of 3.0mm[6]. In the latest versions of the IOL Master® Zeiss (5.4 and 5.5), this double control is not necessary, because the results are extremely consistent.

We completed the propaedeutics of anterior corneal surface with topography (Tomey, TMS) that facilitates the interpretation of the irregularities of corneal surface, in particular, by the presence of irregular astigmatism[7].

We must remember that the keratotomy alters the curvature of the anterior and posterior central cornea, keeps the parallelism of the two faces, therefore, it does not alter the refractive index of the cornea[8].

In relation to biometric formula, our choice is Haigis, which using the data provided by thebiometer has shown an excellent refractive predictability[3,6,8]. This predictability is attributed to the fact that Haigis formula "does not depend on" the corneal power directly, but on the anatomic depth of the anterior chamber and its relationship to axial length. According to Aramberri, it is the only formula that excludes the Double-Kmethod[9]. IOL constants should be updated monthly on specific sites, thus optimizing IOL diopter, IOL model and the appropriate formula.

Our results prove the efficacy of Haigis formula in eyes post keratotomy.

We have no doubts in stating that the measurement of axial length by optical method is the best option, not only in routine cases as well in challenging cases.

Among the last generation formulas, we highlight Haigis that has been very predictable and reproducible in terms of refraction.

However, IOL calculation in eyes previously submitted to keratotomy, is a challenge to obtain a precise and real keratometry of the smaller central area of the cornea, which is supposed to be the location through which passes the visual and anatomic axis of the eye.

A simplified explanation of what happens to the cornea after keratotomy, is the transformation of the physiological prolate corneal dome (central portion more curved than periphery) on an oblate surface (flattening of the central portion maintaining pheripheral curve)[1].

Specifically in eyes after keratotomy, central corneal flattening happens both in its anterior and the posterior faces, not changing the refractive index (n = 1.3375).

The total power of the cornea has been calculated since the nineteenth century by using a value n = 1.3375, called standard keratometricindex, which compensates for the negative power of the posterior face of the cornea, which placido keratometer sand topographers cannot calculate.

This K value calculated with n = 1.3375 provides a power greater than the real one in eyes submitted to lasik, PRK, keratotomy, etc. Haigis proved that with 1.3375 what is actually calculated is the back vertex power, while with 1.3315 it is obtained the equivalent power of the cornea[10].

This characteristic definitely changes the ELP calculation (effective lensposition) when compared with corneas which have not undergone corneal refractive procedures.

It is important to note that the Haigis formula uses anterior chamber axial length and anatomic depth, not depending on corneal height.

By using three constants (a0 = related to nominal constant provided by the manufacturer, a1 = anterior chamber measure and a2 = axial length measure) instead of one, like the other formulas, Haigis has the ability to estimate the actual position of the lens in the anterior segment. There is no need for correction factor or to use double-K method, as it is not dependent on the corneal power to calculate the IOL[1].

The surgical technique, with scleraldelamination at 1.5 mm from the limbus, with sclero-corneal tunnel of 2.2m wide, contributed to not modify the already changed corneal surface and with this technique we have not had secondary hyperopia that can last up to ±8 weeks postoperative[11], not even being necessary to suture radial incisions that occur during surgical manipulation.

We must be aware that corneas submitted to keratotomy suffer central flattening, going from prolate to oblate, and that this flattening can be progressive, therefore, interfering with the postoperative refraction target[12].

Many of these corneaspresent refractive diuturnal fluctuations, beingflatter in the morning and with the greater curvature in the afternoon[9].

Another interesting fact is the appearance in the immediate postoperative period of a hyperopic refraction (up to +3.50 D), perhaps due to corneal edema at the site of radial incisions, which leads to a flattening of the central cornea. Not to perform any surgical intervention like IOL exchange, because in most cases there is an involution of this hyperopia and it is not rare for the eye to get close to an emmetropia. Wait about 8 weeks[11,13,14].

During the preoperative examination, take into consideration the number of incisions, because the higher the number the greater the possibility of refractionalinstability[15]. It is also important the optical zone size; and the smaller, the greater the difficulty in calculating cornealpower[15].

There are reports on the influence of height above sea level, which may influence the final result and visual fluctuation[16].

Regarding the choice of IOL there are no standards or consensus in the literature[4,12,15]. Better an aspheric IOL to reduce spherical aberrations induced by keratotomy.Better monofocal.The toric IOL may be indicated if the astigmatism was stable, central and symmetrical. We must consider that astigmatism may change over time. Multifocal IOLs, refractive or diffractive, have formal counter-indication, because we believe that the undesirable optical lens phenomena added to the keratotomy scars may compromise the quality of vision.

Theoretically, some models of single piece accommodative IOL may perhaps be implanted without visual impairment.

In conclusion, optical biometry by partial coherence interferometry associated with the Haigis formula is presented as a valid alternative in the calculation of IOL in eyes submitted to keratotomy. The refractive results are highly predictable and reproducible.

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Corresponding Author:
Juan Carlos Sánchez Caballero
Av. Ibirapuera, nº 624 - Ibirapuera
CEP 04028-000 – São Paulo (SP), Brasil
E-mail: juancaballero@imo.com.br

Effects of certain drugs on the in vitro proliferation of fibroblasts in primary pterygium

Efeitos de algumas drogas sobre a proliferação de fibroblastos de pterígio primário in-vitro

Juliana Almodin[1], Flavia Almodin[2], Edna Almodin[3], Vânia Cibele Minguetti-Câmara[4], João Paulo Neves[5], Ana Karina Teixeira Bezzon[6],Carla Emília Diniz Maciel Safar[7], Helaine Belato Bertanha Amadeu[8]

ABSTRACT

Objective: *This study aims at observing the inhibition of cell proliferation in primary pterygium by the use in vitro of mitomicyn C, cyclophosphamide, methotrexate.* ***Methods:*** *Pterigyum was removed from seven pacients between 30 and 60 years and were submitted to culture of epithelial cells. Later the effect of drugs was tested on the cells: cyclophsphamide, methotrexate, mitomicyn. The cells were observed for five days under the microscope to assess cellular proliferation, and the experiments were repeated five times.* ***Results:*** *When mitomicyn was used, a marked inhibition of cellular proliferation was observed. When cyclophosphamide was used there also was inhibition of cellular proliferation, 50% within 24 hs of the culture exposition to the drug increasing in the following days.* ***Conclusion:*** *The inhibition effects in the cellular proliferation by the use of mitomicyn C was already expected, but the use of cyclophosphamide was also very effective. The cyclophsphamide inhibitory action on fibroblastic proliferation in vitro lead us to believe that it may be used to prevent pterygium recurrence after incision. However, tests in animals and later in humans are necessary.*

Keywords: *Cell proliferation/drug effects; Mitomycin/therapeutic use; Cyclophosphamide/; Pterygium/drug therapy; Methotrexate/ therapeutic use; Recurrence/prevention & control*

RESUMO

Objetivo: Este estudo tem por objetivo observar a inibição da proliferação celular in vitro em pterígios primários utilizando mitomicina C, ciclofosfamida e metotrexato. **Métodos:** Os pterígios foram retirados de 7 pacientes com idade entre 30 e 60 anos e foram submetidos à cultura de suas células epiteliais. Foi então verificado o efeito de drogas sobre as células: ciclofosfamida, metotrexato e mitomicina. As células foram observadas por 5 dias ao microscópio para avaliar a proliferação celular e os experimentos foram repetidos 5 vezes. **Resultados:** Quando a mitomicina foi utilizada observou-se importante inibição da proliferação celular. Quando a ciclofosfamida foi utilizada houve também inibição do crescimento, 50% após 24 horas de cultura após a exposição da droga aumentando nos dias subsequentes. Nenhum efeito foi observado quando o metotrexato foi utilizado. **Conclusão:** Os efeitos de inibição da proliferação celular pela mitomicina C já eram esperados, porém a ciclofosfamida também apresentou-se bastante eficaz. A ação inibitória da ciclofosfamida sobre a proliferação fibroblástica in vitro nos leva a acreditar que ela possa ser usada para prevenir a recorrência do pterígio depois da excisão. Entretanto, testes em animais e posteriormente em humanos se fazem necessários para se chegar a essa conclusão.

Descritores: Proliferação celular/efeito de drogas; Mitomicina/uso terapêutico; Ciclofosfamida; Pterígio/quimioterapia; Metotrexato/uso terapêutico; Recidiva/prevenção & controle

[1] Glaucoma Department, Próvisão Eye Hospital – Maringá/PR, Brazil.
[2] Tadeu Cvintal Ophthalmology Centre – São Paulo/SP, Brazil.
[3] Próvisão Eye Hospital – Maringá/PR, Brazil.
[4] Biochemistry Department, Maringá University Hospital – Maringá/PR, Brazil.
[5] Retina and Vitreous Department, Hospital de Base – São José do Rio Preto/SP, Brazil.
[6] Visclin Ophthalmology Clinic – São Paulo/SP, Brasil.
[7] Oncoclínica – Maringá/PR, Brasil.
[8] Post-graduation Programme (Master's Degree), Maringá State University (UEM) – Maringá/PR, Brazil.
Redentora Eye Hospital – São José do Rio Preto/SP, Brazil.

The authors declare no conflicts of interest

Received for publication: 20/10/2011 - Accepted for publication: 14/10/2012

Introduction

Pterygium, from the Greek *pterygos*, meaning "arm", is a fibrovascular, degenerative, elastotic, basophilic subepithelial tissue of triangular shape which grows from the bulbar conjunctiva toward the cornea. It can be primary or recurrent; the latter is defined as the proliferation of fibrovascular tissue similar to a previously removed primary pterygium and secondary to an inflammatory reaction. Recurrence is associated with conjunctival inflammation and pronounced corneal involvement. Multiple surgical interventions in the limbic area lead to severe local dysfunction and growth of fibrous tissue, which can result in the formation of symblepharon.

Pterygium affects a large number of people worldwide, especially in areas closer to the equator, tropical and subtropical regions where the climate is warmer and ultra-violet rays are more intense. This, together with the higher prevalence in individuals who work outdoors, points to a strong relationship with exposure to actinic radiation — specifically, UV-A and UV-B rays[1]. In fact, UV radiation induces damage to limbal stem cells thus increasing the risk of pterygium, which is one of the most frequent reasons for visits to ophthalmologists. Pterygium is a multifactorial disease which is also associated with chronic inflammation, repeated microtrauma, heredity, age, exposure to wind, sand, dust, and immune disorders[2].

Its course is slow and progressive, often associated with irritative symptoms (burning, foreign body sensation, redness) and decreased visual acuity (VA), which can occur due to invasion of the visual axis (pupillary area), changes in the tear film, and induced irregular astigmatism (which can reach 3 diopters)[1].

Currently, the only available treatment for complete resolution is surgical removal, which is indicated in cases with impaired VA, chronic inflammation, cosmetic changes, restriction of ocular motility, and persistent irritative symptoms[2]. The high rates of recurrence after excision have led to the development of various surgical techniques and adjuvant therapies[3]. Among the techniques employed for removal are conjunctival flap, autologous conjunctival graft[4], oral mucosa graft[5], lamellar keratoplasty, penetrating keratoplasty[4], scleral keratoplasty, and amniotic membrane graft[4]. Excision with the bare sclera technique, first described by D'Obraim (1948), is the most common procedure for treating pterygium. However, this technique is associated with a recurrence rate of 5-89%. Different adjuvant therapies have been shown to decrease the rate of recurrence, but various complications have been reported with their use[3]. Our work aims to find new drugs that can help reduce the recurrence of pterygium. To this end, we examined the in vitro inhibition of pterygium fibroblast growth in the presence of certain drugs.

Methods

Patients

Pterygia were removed from 7 patients (3 men and 4 women) aged 30-60 years, after informed consent. All pterygia were primary, with no associated eye disease.

Culture of pterygium epithelial cells

The protocol for cell culture was based on modifications to the technique developed by Kria et al.[6], where immediately after removal of the pterygium, it was washed in Earle's balanced salt solution (Materbaby, Maringá, PR, Brazil) containing penicillin (200 ìg/ml), streptomycin (100 ìg/ml) (Sigma, St. Louis, MO, USA), amphotericin B (100 ìg/ml), and Fungizone (5 ìg/ml) (GIBCO, Grand Island, NY, USA). Pterygia were cut into pieces of approximately 2x2 or 2x3 mm and placed in 60-mm plastic plates containing "Minimal Essential Medium" (MEM) (Fundação Ezequiel Dias, Belo Horizonte/MG, Brazil) supplemented with 10% foetal bovine serum (Nutricell, Campinas/SP, Brazil) and antibiotics at the concentrations described above. The plates were then incubated at 37ºC in a humidified incubator containing 5% CO_2. The medium was changed twice a week, with 70% of the medium removed and replaced with fresh medium.

Testing the effect of drugs on cells

After the first layer of cells was formed, these were detached using a trypsin solution (0.25% EDTA without Ca^{++} and Mg^{++} [GIBCO, Grand Island, NY, USA]) at room temperature for 1 minute. After trypsinisation, trypsin was inactivated by adding MEM with 10% foetal bovine serum and the cells were washed with the same medium, centrifuged and resuspended for primary counting. Cells were then added to four-hole plates at a density of 2 x 10^4 cells/ml to be subcultured. After 2 days of growth, drugs were added to the cells at the following concentrations: 1000 ìg/ml or 20 mg/ml: cyclophosphamide (Baxter Oncology GmbH, Frankfurt, Germany), 500 ìg/ml or 10 mg/ml; methotrexate (Galena Química e Farmacêutica Ltda, Campinas/SP, Brazil), 1000 ìg/ml or 20 mg/ml; and mitomycin (Bristol-Myers Squibb Brasil S.A, Santo Amaro/SP, Brazil), 20 ìg/ml or 0.4 mg/ml. Drugs were diluted in MEM medium with 10% serum placed in an incubator for 12 hours before use to stabilise its pH. Immediately after dilution the drugs were added to the cells and the plates were returned to the incubator. The cells were observed daily for 5 days on a phase contrast microscope to assess proliferation. Negative control was performed by adding no drugs. The experiments were repeated 5 times.

Results

With mitomycin, a significant inhibition of cell proliferation was observed. In the first 24 hours the cells were almost completely detached from the plate. With cyclophosphamide, growth inhibition was also observed. Cells were approximately 50% detached from the plate 24 hours after exposure to the drug and detachment increased in the following days, with cells being almost completely detached after 72 hours. However, the cells showed no apparent degeneration even after 120 hours of culture in the presence of the drug. No effect was observed with methotrexate, even after 120 hours of culture; the cells remained attached to the plates and growth was observed. The same was observed in the control plate, with cell growth and cells attached to the plates. The pH of the plates was measured after 24 hours; plates with mitomycin, methotrexate and cyclophosphamide had a pH around 7.0 (Figures 1-9).

Discussion

Mitomycin C has been widely used either intraoperatively or postoperatively as an adjuvant therapy of pterygium excision to prevent recurrence. Singh et al. reported a recurrence rate of 2.2% after pterygium resection with the bare sclera technique and mitomycin C eye drops, compared with 88.9% in placebo-treated controls[7]. Thereafter this antimitotic agent became more popular and is currently indicated to reduce the postoperative recurrence of pterygium. However, serious visual complications following this approach cause concern among many surgeons. Effects such as conjunctival irritation and complications such as keratitis, necrosis of the sclera with or without

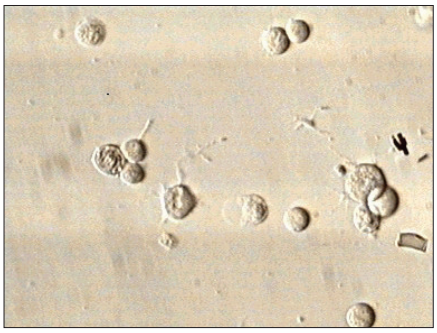
Figure 1 - Cyclophosphamide 24h


Figure 2 – Methotrexate 24h

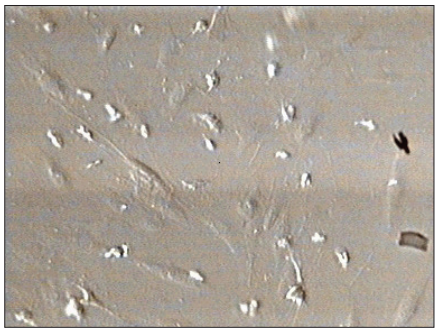
Figure 3 - Mitomycin 24h


Figure 4 - Control 24h

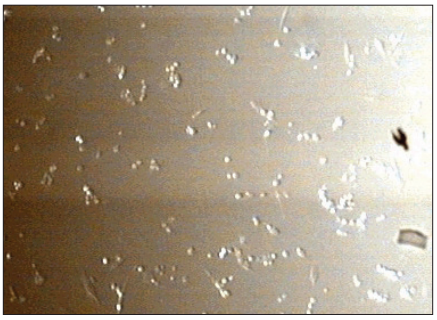
Figure 5 - Cyclophosphamide 72h


Figure 6 - Methotrexate 120h


Figure 7 - Cyclophosphamide 72h


Figure 8 - Mitomycin 72h


Figure 9 - Control 72h

inflammation (scleromalacia), secondary glaucoma, cataract, corneal oedema and perforation, and calcification of the sclera have been reported[8]. Mitomycin C is a radiomimetic agent that can cause avascular necrosis similar to beta irradiation.

In 1992, Rubinfeld et al. reported 10 cases of serious complications related to topical mitomycin C after pterygium surgery using the bare sclera technique. This technique predisposes the eye to the avascular effects of mitomycin, which can lead to corrosion of the sclera, but it is still the most used technique, since it is the easiest to perform[9].

The search for greater safety in the use of mitomycin C has led to increasingly lower concentrations of the drug, which are still effective in reducing recurrence. However, a case was recently reported where a low dose (0.02%) of mitomycin C, used for only 3 min, led to perforation of the cornea and sclera[10].

Mitomycin has been widely used, but some precautions are needed. The drug should not come into contact with de-epithelised areas, and the sclera should not be left exposed after its use. When mitomycin comes into contact with areas with corneal epithelial defects, such as those produced during pterygium removal, regeneration is delayed[11]. Excessive cauterisation of the sclera should be avoided, and the resected area should not be left exposed at the end of the surgical procedure. Scleral damage due to delamination and excessive cauterisation, as well as the vessel occlusion effect of mitomycin C and tear film instability, may predispose to thinning and necrosis of the sclera in these areas[11-13]. Also, mitomycin C should be avoided in the elderly and in patients with atrophic pterygium, where the chance of recurrence is low. The drug should not to be used in dry eyes or in eyes with surface changes[9].

Beta irradiation also reduces recurrence rates to 5-33%, but it is also associated with serious complications[14]. Because of the unsatisfactory results with mitomycin and other adjuvant therapies, we decided to investigate other drugs that could help reduce the recurrence of pterygium. Since recurrence does not seem to be associated with exposure to ultraviolet light but to rapid fibroblast proliferation produced by the surgical trauma[15], we decided to conduct in vitro experiments to assess pterygium fibroblast growth inhibition with certain drugs. These drugs, which are used in the treatment of cancer, were chosen because they are not vesicant[16], as we believe that the unwanted ocular effects of mitomycin are mainly due to its vesicant effect. Vesicant drugs

are those that cause severe irritation with blistering and tissue destruction when infiltrated outside blood vessels, and they may cause necrosis.

The inhibition of pterygium fibroblast proliferation with mitomycin in our experiments was already expected, but cyclophosphamide also showed to be very effective. Cyclophosphamide belongs to the group of chloroethylamines and is a bifunctional alkylating agent with no specificity for any phase of the cell cycle[17]. On the other hand, mitomycin is an alkylating antimetabolite agent which binds to the DNA causing anomalous bonds and breaks in its structure, inhibiting mitosis and protein synthesis, and leading to cell death[18]. The inhibitory action of cyclophosphamide on the in vitro proliferation of fibroblasts suggests that it could be used to prevent the recurrence of pterygium after its removal. In 1983 mitomycin C was first described as a potent fibroblast inhibitor in filtration surgery. Since then, several authors have reported excellent results with its intraoperative use, especially in refractory glaucoma[19]. This suggests that cyclophosphamide could also be used in filtration surgery as a substitute to mitomycin. Cyclophosphamide is a cyclic phosphamide ester of mechlorethamine which prevents cell division primarily by crosslinking DNA strands. It was used at larger doses than mitomycin C, since the concentrations used in this study were the same as those indicated for cancer, where the dose of mitomycin is always much lower than cyclophosphamide.

The observed effect of cyclophosphamide on cell proliferation was not seen with methotrexate, showing that not every antimitotic drug affects pterygium growth. It is still unclear whether cyclophosphamide will produce any adverse effects that contraindicate its use for the prevention of pterygium recurrence or even for filtration surgery. To clarify this issue, tests in animals and later in humans are needed.

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Corresponding author:
Juliana Almodin
Rua Silva Jardim, 359 Maringá (PR), Brazil
Cep 87013-000
Tel: +5544 3262 2061
e-mail: juliana_almodin@hotmail.com.br

Fluency of laser and surgical downtime, loss of fixation, as factors related to the precision refractive

Fluência do laser e tempo de parada cirúrgica, por perda de fixação, como fatores relacionados à precisão refracional

Abrahão da Rocha Lucena[1], Newton Leitão de Andrade[2], Descartes Rolim de Lucena[3], Isabela Rocha Lucena[4], Daniela Tavares Lucena[5]

ABSTRACT

***Objective**: To evaluate the correlation of flow and stopping time intraoperative loss of attachment factors as hypertension or hipocorreções of refractive errors after Lasik. **Methods**: The age ranged between 19 and 61 years (mean= 31.27 ± 9.99). The minimum follow-up period was 90 days. Individuals with: corneal topography preoperative maximum keratometry greater than 46.5D or presence of irregularities, corneal curvature postoperative simulated smaller 36.0D, pupils more 6mm; corneal thickness smaller 500 µm; Myopia more -8.0, hyperopia more +5.0DE and astigmatism more -4.0DC. The laser was used with Esir Schwind Eye-Tracking and 350Hz scanning spot of 0.8 mm. The microkeratome used was the Moria M2 with programming 130µm thick. **Results**: The visual acuity logMAR preoperative correction ranged from 0.40 to 0 (mean= 0.23 ± 0.69) and postoperative uncorrected 0.40-0 (x= 0.30 ± 0, 68). The Median= 0 logMAR for both time points (p= 0.424). For spherical equivalent before and after surgery, we found an obvious difference, with the pre (mean= -4.09 ± 2.83) and post (mean= -0.04 ± 0.38). The Median was -4.75 in the pre and zero postoperatively (p <0.0001). Sixty-nine cases (78.3%) were plan ± 0.25. Fluency minimum= 0.513 mJ/cm2 and maximum= 0.581 mJ/cm2 (mean= 0.545 ± 0.01), no correlation (r = -0.03266, 95% CI -0.241 to 0.178, p = 0.762) between the flow and spherical equivalent (mean = -0.04 ± 0.38) in eyes operated. The minimal downtime during surgery was 02 seconds and maximum was 12 seconds (mean= 4.90 ± 3.47). Making a correlation (r = 0.08865, 95% CI = -0.123 to 0.293, p = 0.411) between the postoperative spherical equivalent and downtime during surgery, not perceived differences. **Conclusion**: There was no correlation between the fluency of the laser during surgery and downtime due to loss of fixation with hipocorreções in hyper-or post-Lasik ametropia.*

***Keywords**: Keratomileusis, laser in situ; Refractive erros; Visual acuity*

RESUMO

Objetivo: Avaliar a correlação da fluência e o tempo de parada transoperatória por perda de fixação, como fatores de hiper ou hipocorreções das ametropias pós-Lasik. **Métodos:** A idade variou entre 19 e 61 anos com média de 31,27 ± 9,99. O tempo mínimo de acompanhamento pós-operatório foi de 90 dias. Foram excluídos indivíduos com topografia corneana pré-operatória com ceratometria máxima maior que 46,5D ou presença de irregularidades; ceratometria média pós-operatória simulada menor que 36,0D; pupilas maiores que 6mm; paquimetria menor que 500 µm; miopia maior que -8,0DE, hipermetropia maior que +5,0DE e astigmatismo maior que -4,0DC. O laser utilizado foi o Esiris Schwind com Eye-Tracking de 350Hz e *scanning spot* de 0,8 mm. O microcerátomo utilizado foi o M2 da Moria com programação de 130µm de espessura. **Resultados:** A acuidade visual logMAR pré-operatória com correção variou de 0,40 a 0 com média de 0,23 ± 0,69; a pós-operatória sem correção foi de 0,40 a 0 com média de 0,30 ± 0,68. A mediana foi de 0 logMAR para os dois momentos (p=0,424). No equivalente esférico pré e pós-operatório, notou-se uma óbvia diferença (p< 0,0001), no pré-operatório com média de -4,09 ± 2,83 e o pós com média de -0,04 ± 0,38. A mediana foi de -4,75 no pré e de 0 no pós-operatório. Sessenta e nove casos (78,3%) ficaram plano ± 0,25. A fluência mínima foi de 0,513 mJ/cm^2 e a máxima de 0,581 mJ/cm^2 com média de 0,545 ± 0,01, não se percebendo correlação (r= -0,03266; IC 95% -0,241 a 0,178; p= 0,762) entre a fluência e o equivalente esférico final (média= -0,04 ± 0,38) nos olhos operados. O tempo mínimo de parada transoperatória foi de dois segundos e o máximo de 12 segundos com média de 4,90 ± 3,47. Fazendo-se uma correlação (r= 0,08865; IC 95%= -0,123 a 0,293; p= 0,411) entre o equivalente esférico pós-operatório e o tempo de parada transoperatória, não se percebeu diferenças. **Conclusão**: Não houve correlação entre a fluência do laser e o tempo de parada transoperatória por perda de fixação, com hiper ou hipocorreções nas ametropias pós-Lasik.

Descritores: Ceratomileuse assistida por Excimer laser in situ; Erros de refração; Acuidade visual

[1]Cataract and refractive surgery department, Fortaleza Ophthalmology Centre and Oftalmolaser Clinic – Fortaleza/CE, Brazil.
[2]Cataract and refractive surgery department, Leiria de Andrade Eye Hospital, Fortaleza/CE, Brazil.
[3]Medical Doctor, graduated from the Juazeiro do Norte Medical School (FMJ) – Juazeiro do Norte/CE, Brazil.
[4]5th year medical student at the Juazeiro do Norte Medical School (FMJ) – Juazeiro do Norte/CE, Brazil.
[5]5th year medical student at the Christus Medical School – Fortaleza/CE, Brazil.
Work conducted at the Ophthalmology Reference Centre, Ceará School of Ophthalmology, Fortaleza/CE, Brazil. Data collected at VISIONLASER.

O autor declara não haver conflitos de interesse

Received for publication: 8/11/2011 - Accepted for publication: 20/01/2013

Introduction

The Laser was created in 1960, and its first medical use in the area of ophthalmology occurred in the same decade[1]. Pallikaris was the first to promote the removal of corneal stromal tissue with excimer laser to correct refractive errors[2].

The use of excimer laser to correct myopia, hyperopia and astigmatism evolved in recent years, mainly due to the technological advancement of devices.

Laser-assisted in situ keratomileusis (LASIK) is still the most widely used technique; it is a painless, safe, and accurate method for treating refractive errors with quick recovery[3-5]. By preserving epithelial integrity in the central region of the cornea, it promotes a milder wound healing reaction. The healing response triggered by the laser and the creation of a flap are important to the safety and efficacy of the procedure. However, it is a significantly complex event[6].

The literature reports great refractive stability from the 3rd month after surgery[7-9]. However, do intraoperative factors such as daily variations in laser fluence and interruptions during laser application due to loss of fixation influence the refractive outcome?

The aim of this study was to evaluate the correlation of laser fluence and intraoperative stopping time due to loss of fixation with over- or undercorrection of refractive errors after LASIK.

Methods

We reviewed the medical records of 83 patients in a reference service in the city of Fortaleza, Brazil, in 2009, in order to assess the refractive accuracy of excimer laser in correcting myopia, hyperopia and astigmatism.

The study's protocol was approved by the Research Ethics Committee of the Integrated Faculty of Ceará (Of. No. 214/10).

Of the 83 medical records, 47 (56.6%) were considered eligible according to the aims of the study. We examined data such as gender, age, pre- and postoperative spherical equivalent (SE) and visual acuity (VA), preoperative corneal topography and pachymetry, laser fluence (mJ/cm^2), and intraoperative stopping time due to loss of fixation.

A total of 88 eyes were evaluated among the 47 medical records, of which 31 (65.9%) were female and 16 (34.1%) were male. Patient age ranged between 19 and 61 years with a median of 29 years.

Preoperative refraction was assessed under cycloplegia after refractive stabilisation for at least three years. The refractive outcome was then evaluated 90 days after surgery.

Exclusion criteria for surgery included: a) Pre-operative corneal topography showing maximum keratometry higher than 46.5D or areas with irregularities; b) Average simulated postoperative keratometry lower than 36.0D; c) Pupils larger than 6mm; d) Pachymetry under 500 micrometres; e) Myopia greater than -8.0D, hyperopia greater than +5.0D, and astigmatism greater than -4.0D; f) Eyes in which, during the loss in fixation, the stromal bed had to be wiped.

The study used an Esiris Schwind laser with 350Hz eye-tracking and a 0.8 mm scanning spot. For the laser to operate within the desired standards of accuracy, a fluence of 0.555 nn, ranging from 0.495 to 0.605 nn, was considered adequate. A Moria M2 microkeratome with a 130ìm head was used to create the flap. For myopia alone and myopia associated astigmatism a 6-mm optical zone was used with a 1.25-mm transition zone (total ablation zone, 8.5 mm). For hyperopia alone and hyperopia associated astigmatism a 6.25-mm optical zone was used with a 1-mm transition zone (total ablation zone, 8.25 mm).

Table 1

Nomogram for correction of refractive errors for the Esiris Schwind device

Hyperopia	Real diopter x 30.0%
Astigmatism	Real diopter x 25.0%
-1.00 to -2.00	Real diopter x 20.0%
-2.25 to -3.00	Real diopter x 15.0%
-3.25 to -4.00	Real diopter x 10.0%
-4.25 to -5.00	Real diopter x 5%
-5.25 to -6.00	Real diopter
-6.25 to -7.00	Real diopter x -5.0%
-7.25 to -8.00	Real diopter x -10.0%
-8.25 to -9.00	Real diopter x -20.0

The operations were performed by a single surgeon who used the same intraoperative criteria for all eyes. After the blepharostat was placed, four markings were done in the corneal surface with gentian violet: a lower, an upper and two lateral marks. After creating the flap (with a medial pedicle), the upper and lower fornices were cleaned with a Merocel sponge to remove the excess liquid and then raised. After lifting the flap the stromal bed was dried with a Merocel sponge only once and then the laser was applied. The flap was then repositioned and the interface was cleaned with sterile ringer lactate using an appropriate cannula mounted on a 5ml syringe. Finally, the edge of the flap was dried with a Merocel sponge and a bandage contact lens was placed, being removed the next day.

A local nomogram was developed for the correction of refractive errors, initially based on existing nomograms for same device used in other regions of Brazil (Table 1). In the presence of astigmatism of spherical diopter, a 30.0% correction of the hyperopic effect of astigmatism was used.

Even though the literature shows no significant changes in pachymetry with age[10,11], thus maintaining stromal hydration, at the end of the calculation for myopia and hyperopia 0.75 was subtracted in patients over 40 years, as we observed overcorrection upon improving the nomogram.

Postoperatively, antibiotic eye drops (4th generation quinolone) associated with prednisolone 1.0% were used. Artificial tears were prescribed only in cases of foreign body sensation or postoperative dryness.

Data were analyzed with SPSS version 15.0. To check for normal distribution of continuous data the Shapiro-Wilk test was used. In continuous data with non-normal distribution, the Wilcoxon test for paired samples was used. Bivariate correlation was used to assess the association between continuous variables. We adopted a significance level (p) of 0.05.

Results

The minimum follow-up period was 90 days and the maximum was 402 days (median, 143 days). The minimum preoperative pachymetry was 500ìm and the maximum was 629ìm (mean, 547.23 ± 30.91). Regarding the mean preoperative keratometry, a minimum of 40.0D and a maximum 45.0D were observed (mean, 42.74 ± 1.25 D).

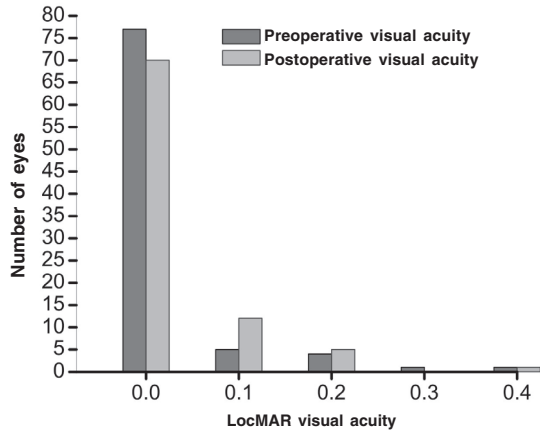

Figure 1 - Pre- and postoperative logMAR visual acuity in eyes submitted to LASIK

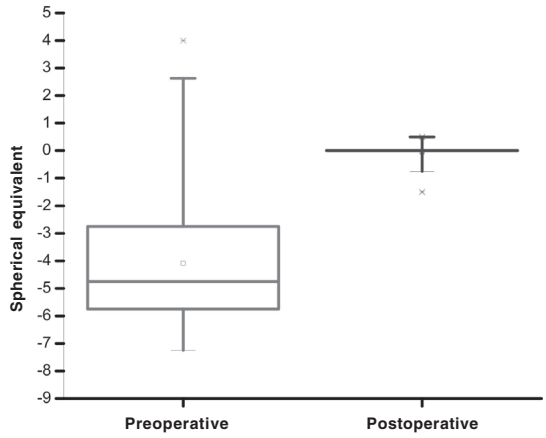

Figure 2 - Pre- and postoperative spherical equivalent in patients submitted to LASIK

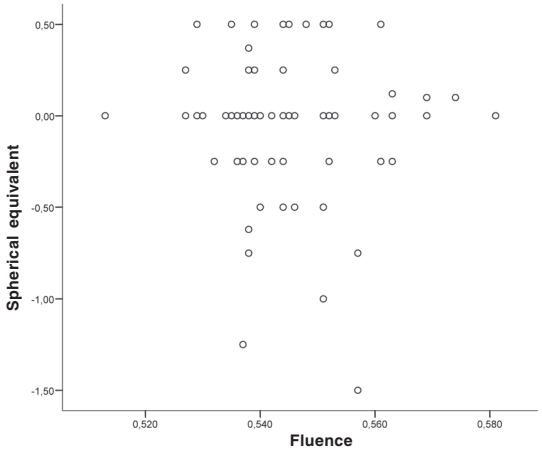

Figure 3 - Fluence of Isiris Schwind excimer laser (mJ/cm^2) versus final spherical equivalent (SE) in each eye

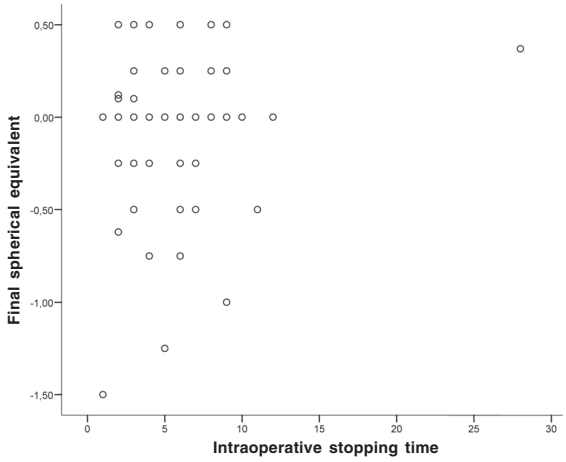

Figure 4 - Correlation between intraoperative stopping time due to loss of fixation and final spherical equivalent (SE) in each eye

The preoperative corrected logMAR VA ranged from 0.40 to 0, with an average of 0.23 ± 0.69. The postoperative values ranged from 0.40 to 0, with an average of 0.30 ± 0.68 (Figure 1). The median logMAR was 0 for both time points, with no statistically-significant differences (p = 0.424).

Regarding pre- and postoperative SE, a clear difference was noted between the two time points (p <0.0001), with mean values of -4.09 ± 2.83 and -0.04 ± 0.38, respectively (Figure 2). Postoperatively, three (3.4%) cases showed undercorrection between -1.50 and -1.00, seven (7.9%) showed undercorrection between -0.75 and -0.50 and nine (10.2%) showed overcorrection of +0.50. The remaining 69 (78.3%) cases had a SE of 0 ± 0.25.

The minimum observed fluence was 0.513 mJ/cm^2 and the maximum was 0.581 mJ/cm^2 (mean, 0.545 ± 0.012). Figure 3 shows that there was no correlation (r = -0.03266, 95% CI, -0.241 to 0.178, p = 0.762) between fluence and final SE (mean, -0.04 ± 0.38).

The minimum intraoperative stopping time due to loss of fixation was 2 seconds and the maximum was 12 seconds (median, 4.0 seconds). No correlation was found between postoperative SE and intraoperative stopping time (r = 0.08865, 95% CI, -0.123 to 0.293, p = 0.411) (Figure 4).

Discussion

The literature reports refractive stabilisation 90 days after refractive surgery[7,12,13,14]. In our study, the minimum follow-up period was 90 days and the maximum was 402 days (median, 142 days) with no observed regression, even in cases of hyperopia. The cases of undercorrection (23.9%) were observed since the first days after surgery and thus were not considered as cases of regression.

According to the literature, the loss of lines of vision is more frequent in cases of myopia of moderate to high degree[7,12]. Despite the use of a centering mechanism (eye tracking)[15], slight decentration may occur, predisposing to the loss of lines of vision. Decentration can occur in up to 6.5% of cases[4,7,12] and may induce irregular astigmatism[16]. The experience of the surgeon and cooperation by the patient can help prevent decentration[18]. In our study, even though no statistical difference was found between preoperative corrected and postoperative uncorrected VA (p = 0.483), there was a trend towards a lower postoperative VA: 87.5% of eyes had a corrected VA of 0 LogMAR preoperatively, compared with 79.5% postoperatively; this was more common in hyperopic eyes (6.4%). Another factor that

contributed to the loss of lines of vision were striae, which were observed in 3.0% of operated eyes.

As in other studies[18,19], a line of vision was gained in 11.5% of eyes compared to preoperative corrected VA. This was more common in myopic eyes, regardless of the degree of myopia. Laser devices have evolved significantly in recent years, and spot size has been decreasing in size, thus increasing the accuracy of the procedure and improving visual quality.

Despite the significant accuracy of laser devices, potential candidates should be informed about the possibility of under- or overcorrection. Despite the procedure's irreversibility, small adjustments can be made from the third month after surgery by elevating the corneal disc and performing photoablation of the cornea[7,20,21]. In our study, as was previously reported in the literature[7,12,13,18,19], the correction of refractive errors of any type and magnitude proved accurate, provided adjustment was made using a nomogram (Table 1). Comparing the spherical equivalent pre- and postoperatively, a clear difference can be noted between the two time points (p = 0.000), with mean values of -4.09 and -0.04, respectively.

Laser fluence reflects the amount of energy per area in a single pulse and it has a direct relationship with the amount of ablated stromal tissue[22]. If the fluence is higher than the recommended value, overcorrection can occur; if it is lower, undercorrection is expected. In our study, despite daily fluctuations in fluence (minimum of 0.513 and maximum of 0.581 mJ/cm^2), no correlation was found between fluence and final SE (r = -0.03266, 95% CI, -0.241 to 0.178, p = 0.762) (Figure 3).

The hydrated corneal stroma has more separated lamellae, and water uptake is done by its constituent proteoglycans. Such a rearrangement, with intrinsic modification of the extracellular matrix, can alter the rate of corneal ablation, with loss of energy due to water destruction. On the other hand, dehydration makes the lamellae more compact, which can potentiate the treatment[23]. Thus, intraoperative interruptions due to loss of fixation, with a greater exposure of the stromal bed to the environment, would lead to dryness and consequent overcorrection. In our study, the minimum intraoperative stopping time was 2 seconds and the maximum was 12 seconds. As shown in Figure 4, no correlation was found between postoperative SE and intraoperative stopping time (r = 0.08865, 95% CI = -0.123 to 0.293, p = 0.411).

This study involved a specific brand of laser device, and the results should be restricted to the studied model.

Conclusion

No correlation was found between variations in laser fluence or intraoperative stopping time due to loss of fixation and over- or undercorrection of refractive errors after LASIK treatment.

Acknowledgements: Dr. André Messias (USP- FMRP)

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Corresponding author:
Abrahão da Rocha Lucena
abrahaorlucena@gmail.com
Av. Santos Dumont, 5.753 - Torre Saúde, 15º Andar,
Complexo São Mateus – Papicu
CEP: 60822-131- Fortaleza (CE), Brazil.

Asymptomatic ocular sarcoidosis

Sarcoidose ocular assintomática

Luiz Guilherme Azevedo de Freitas[1], Luiz Alexandre Rassi Gabriel[2], David Leonardo Cruvinel Isaac[3], Clovis Arcoverde de Freitas[4], Marcos Pereira de Ávila[5]

ABSTRACT

Sarcoidosis is an idiopathic systemic granulomatous disease. It commonly affects the skin, lungs, kidneys, and central nervous system. In the eyes it primarily affects the uveal tract, conjunctiva, lacrimal glands and optic nerve. Here in we describe the case of a patient with systemic sarcoidosis and asymptomatic eye inflammation.

Keywords: *Sarcoidosis; Eye infections; Retinal vasculitis; Retina; Fluorescein angiography; Case reports*

RESUMO

Sarcoidose é uma doença granulomatosa sistêmica idiopática. Afeta comumente pele, pulmões, rins e sistema nervoso central. Nos olhos afeta primariamente a úvea, conjuntiva, glândulas lacrimais e nervo óptico. Descrevemos o caso de um paciente portador de sarcoidose sistêmica com acometimento ocular assintomático.

Descritores: Sarcoidose; Infecções oculares; Vasculite retiniana; Retina; Angiografia fluoresceínica; Relatos de casos

[1]Fellowship of the Department of Retina and Vitreous, Universidade Federal de Goiás (UFG) – Goiânia (GO), Brazil;
[2]Ophthalmologist and Professor and head of the Department of Eye Genetics, Universidade Federal de Goiás (UFG) – Goiânia (GO), Brazil;
[3]Ophthalmologist and Professor and head of the Department of Retina and Vitreous, Universidade Federal de Goiás (UFG) – Goiânia (GO), Brazil;
[4]Fellowship of the Department of Uveitis of The São Geraldo Hospital, Universidade Federal de Minas Gerais (UFMG) – Belo Horizonte (MG), Brazil;
[5]Chairman of Ophthalmology; Head of the Department of Ophthalmology Universidade Federal de Goiás (UFG) – Goiânia (GO), Brazil.

Study carried out at the Department of Ophthalmology, Universidade Federal de Goiás (UFG) – Goiânia (GO), Brazil

The authors declare no conflicts of interest

Received for publication: 6/4/2011 - Accepted for publication: 26/6/2011

Introduction

Sarcoidosis is an idiopathic systemic granulomatous disease[1]. Sarcoidosis is an ubiquitous disease, although not uniform, presenting heterogenous incidence and prevalence rates. Its annual incidence is higher in Sweden and Norway. In Brazil, a prevalence below 10/100,000 persons is estimated[2]. Papers show that the disease is more commonly seen among young adults in their third to fourth decade of life[3,4].

Eye involvement happens in 25 to 50% of patients presenting systemic sarcoidosis[5]. The retinal features are: vasculitis with vascular sheathing, nodular granulomatous phlebitis with a candle wax dripping pattern[6], granulomatous chorioretinitis, and papilledema usually related to simultaneous central nervous system involvement, which may occur in the absence of additional eye inflammation.

Currently there is no curative treatment available for sarcoidosis. Immunosupresants, and/or immunomodulators may be used to control the disease. Corticosteroids are the first-line therapy in the majority of cases. For instance, when eyes or lungs are involved glucocorticoids are indicated[7].

Case report

A 46-year old white male, from the city of Goiania in the center of Brazil was referred by the infectologist for ophthalmological evaluation because of a prior diagnosis of systemic sarcoidosis.

The patient was being followed up since January of 2010 in the Hospital das Clínicas da Universidade Federal de Goiás (HC-UFG) when he was admited the emergency room with fever and joint pain complaints. Besides being treated by the infectologist and ophthalmologist, he has concomitantly being followed by the rheumatology, and hematology departments due to his additional systemic findings.

Abdominal computed tomography performed in may/2010 showed mild to moderate homogenous hepatosplenomegaly, small cortical cysts, and presence of cortical scar in the left kidney. The chest X-ray, performed in june of 2010, exhibited bilateral hilar lymphadenopathy. Hystopathological analysis of the lung biopsy, made in august of 2010 revealed: granulomatous chronic inflammatory reaction making it impossible to rule out sarcoidosis. We could also appreciate leucocytosis (60,000) with left deviation, and thrombocytosis (507,000).

The patient did not have ocular complaints in his first ophthalmological evaluation, and denied high blood pressure and diabetes mellitus.

At the eye examination, his best corrected visual acuity (BCVA) was 20/20 on both eyes (OU). Biomicroscopic evaluation was unremarkable. His eye fundus showed normal optic nerves, mild venular dilation, and normal macula OU.

Fluorescent angiography revealed leakage and venous staining suggesting periphlebitis OU, which were compatible with ocular sarcoidosis (Figure 1).

According to the presented case the patient was oriented to maintain the multidisciplinary follow up.

In his follow up visit, 90 days past his first visit, his BCVA was 20/20 OU, as well as unremarkable biomicroscopy and fundoscopy OU. Fluorescent angiography was also normal OU (Figure 2).

The patient was advised to keep regular ophthalmic evaluations every six months and, in the case of any unexpected visual alteration, to come back immediately.

Discussion

The prevalence of sarcoidosis in Brazil was estimated in 10/100,000 persons, which is quite uncommon when compared with other countries that can show a prevalence twice as high, and also with an increased incidence in afro-descendants.

Brazil, due to its mixed population, cannot consider for its own population, epidemiologic studies performed by countries that show homogenous ethnic populations. In this case report, we are righteously describing one example of this situation: a patient with white skin, but not necessarily Caucasian.

On the other hand, it is important to highlight that in Caucasian countries like Norway and Sweden, the incidence is almost three times higher than in Brazil. This fact may find an answer in a poorly organized national public health system, that may underestimate the real Brazilian prevalence and incidence of sarcoidosis.

The ocular sarcoidosis can show low vision, floaters, pain, and photophobia, which are usually brought up by anterior uveitis.

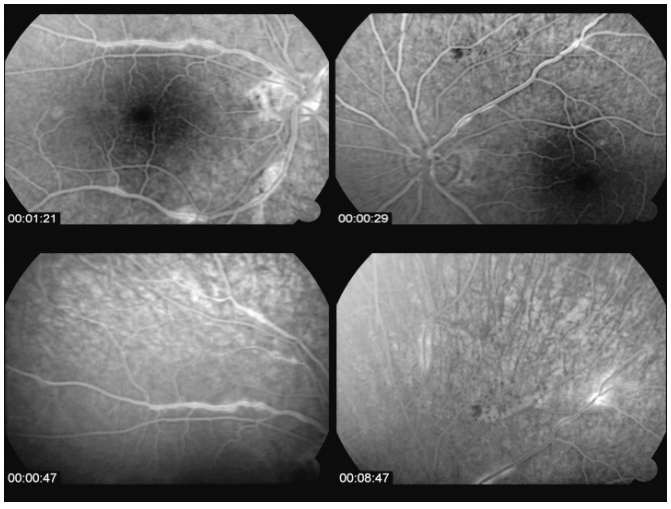

Figure 1: Leakage and venous staining suggesting periphlebitis

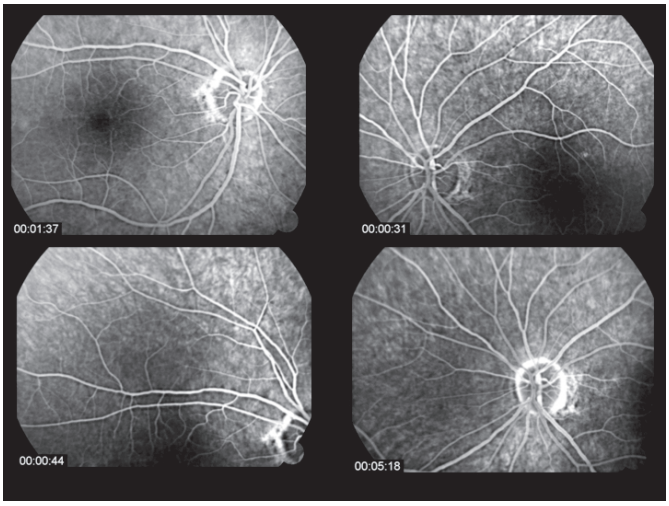

Figure 2: Fluorescent angiography after treatment

The posterior segment inflammation is restricted to one third of the sarcoidosis patients, that present retinal vasculitis and granulomatous periphlebitis[8].

Herein, the patient has not shown any findings in the anterior segment, like keratic precipitates, synechiae, or iris nodules, anterior or intermediate uveitis. He has not showed low visual acuity or eye pain as well. The evolution of this ocular sarcoidosis was restricted to the posterior segment, presenting solely as retinal periphlebitis OU, constituting an atypical case.

The diagnosis of ocular sarcoidosis can become tricky because its features may resemble closely those from other causes. It is important to put together a multidisciplinary medical evaluation and a proper laboratory investigation in order to reach the precise diagnosis. Ophthalmologists have an important task in the diagnosis of sarcoidosis, since the eyes are affected in the beginning of the disease in up to 50% of cases[5], and not always the patient shows eye abnormalities as his first sign.

Conclusion

Ocular sarcoidosis may be underdiagnosed when asymptomatic. It is very well known that patients with extra-ocular sarcoidosis may have concomitantly the ocular form in 50% of cases which may be missed due to the absence of an ocular fundus examination. The ophthalmologic evaluation of a patient with sarcoidosis is, therefore, indispensable.

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Corresponding author:
Luiz Guilherme Azevedo de Freitas
Av. T-2 nº 401 - Setor Bueno
CEP 74210-010 - Goiânia (GO), Brazil
Tel: (62) 3252-5566 - Fax (62) 3252-5500
E-mail: luizgfreitas@gmail.com

Intravitreal ranibizumab as adjuvant treatment for neovascular glaucoma

Ranibizumabe intravítreo como tratamento adjuvante para glaucoma neovascular

Flavia Gazze Ticly[1], Rodrigo Pessoa Cavalcanti Lira[1], Enzo Augusto Medeiros Fulco[1] , José Paulo Cabral de Vasconcelos[1]

ABSTRACT

The purpose of this study was to describe a prospective case series of 5 eyes treated with intravitreal ranibizumab injection for neovascular glaucoma (NVG). Five patients with clinically uncontrolled NVG secondary to proliferative diabetic retinopathy (4 patients) and central retinal vein occlusion (1 patient), non-responsive to maximal tolerable medication and panretinal photocoagulation, received intravitreal ranibizumab injection (0.5 mg). Patients were seen at 1st, 3rd and 7th day after the ranibizumab injection and when it was necessary. Success was defined as intraocular pressure (IOP) <d" 21mmHg, with or without medication. Those with persistent IOP > 21, despite maximal tolerable medication, underwent trabeculectomy with 0.5mg/ml mitomycin C (MMC) for 1 minute. Failure was defined as IOP > 21 mmHg, phthisis bulbi, loss of light perception or additional glaucoma surgery. The primary outcome was 6-month IOP control. Mean IOP before the ranibizumab injection was 37 mmHg (7 mmHg SD). Two out of five eyes underwent only ranibizumab injection, having an IOP control after the procedure. Three patients were submitted to trabeculectomy with MMC on the 7th day after the injection. At 6-month follow-up, the mean IOP was 12mmHg (3 mmHg SD). All eyes showed regression of rubeosis iridis and IOP control. Visual acuity improved in 2 eyes worsened in 1 eye, and remained stable in 2 eyes. These data suggest that intravitreal ranibizumab injection may be a useful tool in the treatment of NVG.

Keywords: *Neovascular, glaucoma/drug therapy; Chemotherapy, adjuvante; Intraocular pressure; Intravitreal injections; Antibodies, monoclonal/therapeutic use; Case reports*

RESUMO

O objetivo deste estudo foi descrever uma série de casos prospectivos de 5 olhos tratados com ranibizumabe intravítreo para glaucoma neovascular (GNV). Cinco pacientes com GNV refratário, secundário a retinopatia diabética proliferativa (4 pacientes) e oclusão de veia central da retina (1 paciente), não responsivos a terapia medicamentosa máxima tolerada e panfotocoagulação da retina, receberam ranibizumabe intravítreo (0,5 mg). Os pacientes foram vistos no 1º, 3º e 7º dia após a aplicação e conforme necessário. O sucesso foi definido como pressão intraocular (PIO) d"21 mmHg, com ou sem uso de medicação antiglaucomatosa. Aqueles com PIO > 21 mmHg, apesar da medicação máxima tolerada, foram submetidos à trabeculectomia com mitomicina C (MMC) 0,5mg/mL por 1 minuto. Falência foi definida como PIO > 21 mmHg, phthisis bulbi, perda da percepção de luz ou necessidade de cirurgia antiglaucomatosa adicional. O resultado primário avaliado foi o controle da PIO após 6 meses do procedimento. A PIO média antes da injeção era de 37 mmHg (DP=7 mmHg). Dois pacientes foram submetidos somente a injeção intravítrea de ranibizumabe, obtendo controle da PIO após o procedimento. Três pacientes foram submetidos à trabeculectomia com MMC no 7º dia após a injeção. Após 6 meses de seguimento, a PIO média era de 12 mmHg (DP=3 mmHg). Todos os olhos mostraram regressão da rubeosis iriana e controle da PIO. A acuidade visual melhorou em 2 olhos, piorou em 1 olho e permaneceu estável em 2 olhos. Estas informações sugerem que a injeção intravítrea de ranibizumabe pode ser uma ferramenta útil no tratamento do GNV.

Descritores: Glaucoma neovascular/quimioterapia; Quimioterapia adjuvante; Pressão intraocular; Injeções intravítreas; Anticorpos monoclonais/uso terapêutico; Relatos de casos

1.Department of Ophthalmology, Universidade Estadual de Campinas (UNICAMP) – Campinas (SP), Brasil.

Study carried out at department of Ophthalmology, Universidade Estadual de Campinas (UNICAMP) – Campinas (SP), Brasil.

The authors declare no conflicts of interest

Received for publication: 5/10/2011 - Accepted for publication: 12/1/2012

Introduction

Neovascular glaucoma (NVG) is a severe form of glaucoma characterized by rubeosis iridis and intraocular pressure (IOP) elevation. Hypoxic disease of the retina such as diabetic retinopathy and occlusion of major retinal vessels account for more than one half of this glaucoma**.** Once retinal hypoxia is established the natural history of neovascular glaucoma can be divided in four stages: prerubeosis stage, preglaucoma stage, open-angle glaucoma stage, and angle-closure glaucoma stage.[1]

Panretinal photocoagulation has been shown to significantly reduce or eliminate anterior neovascularization and may reverse IOP elevation in the open-angle glaucoma stage. When the IOP begins to rise, medical therapy is required to control the pressure during the open-angle glaucoma stage. The mainstays of the therapy at this stage are drugs that reduce aqueous production such as carbonic anhydrase inhibitors, topical beta-blockers and alpha agonists. Although surgical intervention is often necessary, trabeculectomy alone and other shunt-tube drainage procedures for NVG are challenging because new vessels tend to recur, bleed easily, are always associated with postoperative inflammation and have higher rate of failure to control IOP.[2] Recent case series have demonstrated a role for bevacizumab in reducing rubeosis iridis and as an adjunct treatment for NVG.[2-4]

Intravitreal ranibizumab is the standard of care for the treatment of exudative macular degeneration. This pharmacologic agent, which selectively inhibits vascular endothelial growth factor (VEGF), might be an important adjunctive therapy in the management of NVG by causing rapid and consistent regression of neovascularization in the anterior segment.

The purpose of this study is to describe a prospective case series of five eyes treated with intravitreal ranibizumab injection for NVG.

Cases report

A total of 5 patients with clinically uncontrolled NVG, secondary to proliferative diabetic retinopathy (PDR) (4 patients) and central retinal vein occlusion (CRVO) (1 patient), non-responsive to maximal tolerable medication and panretinal photocoagulation, received intravitreal ranibizumab (0.5 mg) injection via the pars plana and if necessary were scheduled for trabeculectomy, at University of Campinas - Brazil. Ethics committee approval was obtained and all participants gave informed consent.

Table 1

Clinical data of cases of intravitreal ranibizumab injection as adjuvant treatment for neovascular glaucoma

Patient number	1	2	3	4	5
Age (years)	50	42	57	56	61
Diagnosis	PDR	PDR	CRVO	PDR	PDR
Pre-injection IOP (mmHg)	48	32	28	40	38
Pre-injection BCVA	HM	20/200	HM	HM	CF
Trabeculectomy	Yes	No	Yes	Yes	No
6-month IOP (mmHg)	13	15	9	16	10
6-month BCVA	CF	CF	HM	HM	20/400
6-month number of antiglaucoma medications	0	2	0	1	1

IOP – intraocular pressure; BCVA – best corrected visual acuity; CF – count fingers at 1 meter; HM – hand movements; PDR – proliferative diabetic retinopathy; CRVO – central retinal vein occlusion

We excluded patients with cloudy media, previous surgery on the superior conjunctiva, history of uveitis, infectious retinopathy, retinal detachment, hemoglobinopathy, trauma or previous vitreoretinal surgery.

After discussing treatment options and obtaining informed consent, a single injection of intravitreal ranibizumab (0.5 mg) was administered (Figure 1). Patients were seen on 1st, 3rd and 7th day after the ranibizumab injection and when it was necessary. Success was defined as IOP ≥ 21mmHg with or without medication. Those with persistent IOP > 21, despite maximal tolerable medication, underwent trabeculectomy with 0.5mg/ml mitomycin C (MMC) for one minute. Failure was defined as IOP > 21 mmHg, phthisis bulbi, loss of light perception or additional glaucoma surgery. The primary outcome was 6-month IOP control.

All patients were on the open-angle glaucoma stage. Mean IOP before the injection was 37 mmHg (7 mmHg SD). Two of them underwent only intravitreal ranibizumab injection, having an IOP control after the procedure with 2 anti-glaucoma medications. Three patients were submitted to trabeculectomy with MMC on the 7th day after the injection. At 6-month follow-up, the mean IOP was 12mmHg (3 mmHg SD). Other outcome

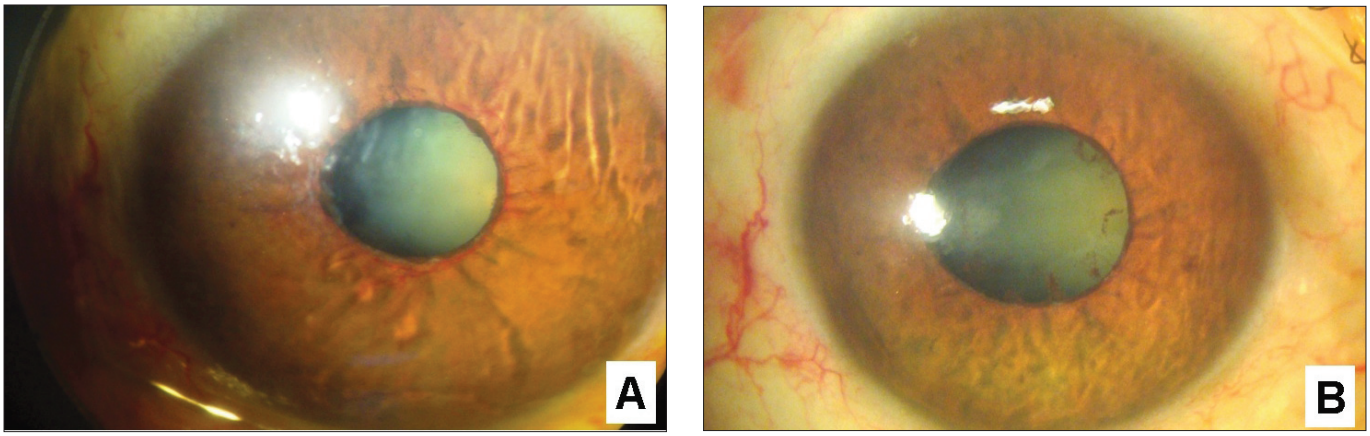

Figure 1: (A) Right eye of a 56-year-old male with neovascular glaucoma secondary to proliferative diabetic retinopathy; (B) Three-day follow-up of the same eye after intravitreal ranibizumab injection; note the rubeosis iridis regression

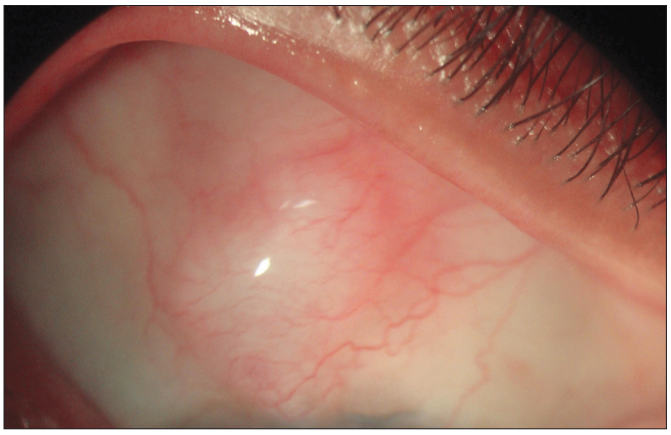

Figure 2: Right eye of a 56-year-old male with neovascular glaucoma secondary to proliferative diabetic retinopathy, submitted to intravitreal Ranibizumab and trabeculectomy with 0.5% C mitomycin; note the partially encapsulated bleb with good IOP control under one antiglaucoma medication (6-month follow up)

measures included 6-month best correct visual acuity (BCVA) and anti-glaucoma medications to control IOP at 6-month follow up (Table 1). All eyes showed regression of rubeosis iridis and IOP control. Visual acuity improved in two eyes, worsened in one eye, and remained stable in two eyes. There were no treatment-related adverse effects.

Discussion

This article describes a consecutive case series of 5 eyes (5 patients) with NVG. Two patients underwent only intravitreal ranibizumab injection and obtained IOP control after the procedure under anti-glaucoma medications. Beutel et al. evaluated the long-term effects of intraocular bevacizumab injections as adjuvant treatment in patients with neovascular glaucoma and hypothesized that bevacizumab may be beneficial as adjuvant treatment because of its anti-angiogenic properties, its ability to induce new vessels regression and to prevent progression of angular obstruction.[2,3]

Three patients underwent trabeculectomy with mitomycin C on the 7th day after the intravitreal ranibizumab injection, with successful IOP control, two eyes without antiglaucoma medication and one under one antiglaucoma medication at 6-month follow up (Figure 2). There are reports that intravitreal bevacizumab injection may be an effective adjunct to trabeculectomy in NVG.[5] Although there was no improvement in visual acuity due to patients' severe disease, the IOP reduction was achieved with treatment, which traditionally does not occur with standard filtering procedures without anti-VEGF. Trabeculectomy for NVG eyes has been described as a challenging treatment with a poor surgical success rate.[1]

We are unaware of previous reports using ranibizumab as an adjuvant treatment in patients with neovascular glaucoma. This antibody fragment inhibits all forms of biologically active VEGF and its use is specifically intraocular, with known local and systemic safety but we should concern about the cost of therapy and the benefit to the patient.

These data suggest that ranibizumab may also be a useful tool in the treatment of this devastating disease. Randomized clinical trials are necessary to confirm the importance of this adjuvant therapy for the treatment of NVG.

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Corresponding Author:
Flavia Gazze Ticly
Rua Izabel Negrão Bertotti, nº 100 - apto. 112B
CEP 13087-508 - Campinas (SP), Brazil
Tel: (19) 8177-3499
email: flaviaticly@yahoo.com.br

Association of macular microhole and optic disc pit

Associação de microburaco macular e fosseta de papila

Renata Leite de PinhoTavares[1], Fernando José de Novelli [2], Mário Junqueira Nóbrega[1], Evandro Luis Rosa[2]

ABSTRACT

Optic disc pit and macular microhole are two rare pathologies with an extremely low likelihood of coexistence, this paper will report an association of both pathologies in the same eye with the purpose of analyzing clinical manifestations, tests, angiography, OCT, retinography, biomocroscopy, treatment outcome and the connection between the optic disc pit and macular microhole.

Keywords: *Retinal perforations/therapy; Fundis oculi; Optic disc/abnormalities; Tomography, optical coherence; Case reports*

RESUMO

A fosseta de papila do nervo óptico e o microburaco macular são duas patologias raras, cuja probabilidade de coexistência se torna extremamente baixa, embora não haja relação fisiopatológica entre ambas, descreveremos um caso de associação das mesmas, acometendo comumente um olho, a fim de analisar as manifestações clínicas, os exames de OCT, angiografia, retinografia, biomocroscopia, o tratamento e a correlação entre ambas patologias.

Descritores: Perfurações retinianas/terapia; Fundo de olho; Disco óptico/anormalidades; Tomografia de coerência óptica; Relatos de casos

[1]Medical School, Joinville Regional University (Univille), Joinville/SC, Brazil.
[2]Sadalla Amin Ghanem Eye Hospital, Joinville/SC, Brazil.

The authors declare no conflicts of interest
Received for publication: 12/9/2011 - Accepted for publication: 14/10/2012

Introduction

Optic disc pit maculopathy and macular microhole are two uncommon diseases whose chance of co-occurring appears to be extremely low.

Optic disc pit has an incidence of 1:11.000 and is a congenital malformation secondary to a developmental disorder of the primitive epithelium of the optic disc which occurs in the fifth week of embryogenesis[1,2]. Usually unilateral (in 95% of cases), this excavation of the optic nerve has an oval shape and is most often located in the temporal region of the optic disc; its colour ranges from shades of gray to yellow to black[1]. Symptoms occur only in the of presence serous macular detachment, which occurs in 25-75% of cases and affects visual acuity[3].

The aetiology of serous macular detachment related to optic disc pit is undetermined. There are three possible sources of subretinal fluid: The movement of vitreous humour through the pit fissure to the subretinal space; the flow of cerebrospinal fluid from the subarachnoid space into the subretinal space; and the leakage of fluid through peripheral choriocapillaris into the subretinal space[4].

First described by Cairns and McCombe, macular microhole is a retinal defect consisting of a reddish lamellar fissure with well-defined edges. It is located in the inner layer of the retina, in the central region of the fovea, corresponding to the inner and outer segments of photoreceptors[5]. Its aetiology is undetermined, and since there is no causal factor directly related to its formation, it may be a primary condition. Symptoms usually include: central scotoma, mild to moderate impairment of visual acuity, and metamorphopsia. However, many patients remain asymptomatic. Diagnosis can be made by combining the findings of posterior pole biomicroscopy and optical coherence tomography (OCT). The prognosis is good, as the condition usually progresses with stability of symptoms and anatomic appearance[5-8].

Even though optic disc pit and macular microhole have a low incidence, we describe a case where both conditions occurred simultaneously in the same eye. The aim of this paper is to describe the clinical manifestations, OCT scans, angiography, retinography, biomicroscopy, and treatment of the conditions.

Case report

VL, 30-year-old white female born in Nova Trento, Brazil, was diagnosed 3.5 years ago at another service with serous retinal detachment in the left eye (LE). Initial ophthalmic examination showed a visual acuity of 20/20 in the right eye (RE) and 20/40 in the LE. Biomicroscopy of the anterior segment showed no changes in both eyes. Fundoscopy showed the presence of a temporal optic disc pit in the RE. Evaluation of the fovea in the RE showed a reddish spot suggestive of macular microhole.

In the LE, detachment of the sensory retina was observed, affecting the macular region and reaching the temporal edge of the optic disc. The patient then underwent an OCT scan (Figures 1 and 2), which confirmed the temporal optic disc pit and the presence of a macular microhole in the RE. In the LE, the OCT clearly showed the optic disc pit with a communication between the subretinal space and the inferior temporal region of the optic disc, indicating a possible orifice communicating these structures. Furthermore, a loss of foveal contour was observed with serous detachment of the neurosensory retina, more pronounced in the region nasal to the fovea, and a content of average reflectivity was seen in the central macular region (Figure 1).

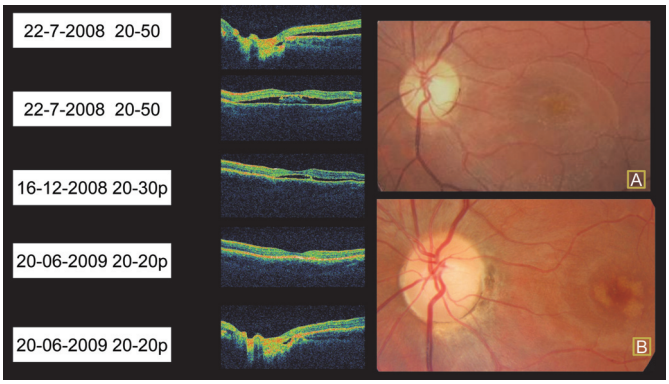

Figure 1. Evolution of sensorydetachment of the retina over months after laser photocoagulation. The top right retinography shows the area of sensorymacular detachment. The bottom right retinography shows the resolution of the detachment, with macular pigment alteration and juxta papillary scarring as a result of laser photocoagulation. The sequence of OCTs shows a gradual resolution of the detachment. The upper image shows the optic discpit by the nerve and the sensory detachment at the temporal edge of the papilla. The bottom image shows the increased reflectivity of the subretinalfluid which is likely due to a change in sub retinalfluid throughout the long period of detachment.

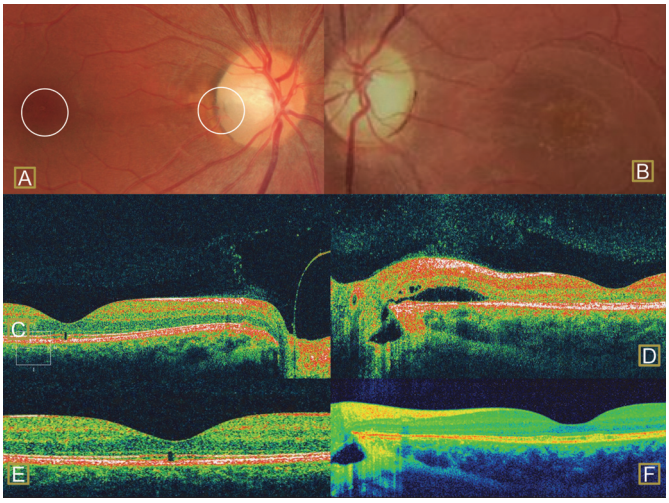

Figure 2. The top left-hand image is a retinography of the right eye where a papillary pit with optociliary vessel and foveal punctiform pigment alteration (both highlighted) can be observed. The OCT shows the defect in the foveal region, at the transition line between the internal and external segments of photoreceptors, referring to a macular microhole. In the OCT of the left eye on the bottom right-hand side, vitreous adherence at the area of sensory detachment can be observed. The lower OCT shows resolution of detachment after vitrectomy.

In the RE the approach toward the diagnosis of optic disc pit associated with macular microhole was expectant management, with frequent ophthalmic evaluations using Amsler grid every month and OCT every two months.

In the LE we performed laser photocoagulation in the temporal edge of the optic disc, with slow but the gradual improvement of the detachment; after five months, the macula was completely attached (Figure 1B).

The clinical picture remained stable for 1 year and 7 months. However, fundus examination showed a recurrence of the sensory detachment near the optic disc, affecting the inferior

macula in the LE. OCT confirmed the sensory detachment, with attachment of the posterior vitreous exactly in the region where the retina was elevated, suggesting the possibility of localised traction (Figure 2D). Serial OCTs showed the progression of the detachment; we then performed posterior vitrectomy with C3F8 gas infusion at a concentration of 12%. The patient recovered satisfactorily, with gradual decrease of the subretinal fluid and complete resolution of the condition in 6 months. After a follow-up of 9 months, the patient had stable vision (20/20) and an attached macula.

The RE had a 20/20 vision without visual impairment.

Discussion

The optic disc pit is an uncommon congenital anomaly presenting as a yellow or gray oval lesion. It is usually unilateral and is found primarily in the temporal region of the optic disc. In more than 50% of cases, one or two cilioretinal arteries can be seen in the pit area[3]. Changes in the colour of the pigment epithelium along the temporal edge of the disc and posterior vitreous detachment are findings associated with the condition[2].

In cases where an abnormal communication exists between the optic nerve and the retina, the passage of fluid between the two structures can occur. The origin of the fluid, whether from the vitreous humour, the cilioretinal arteries or the cerebrospinal fluid, remains unclear. The resulting maculopathy caused by fluid leakage can be observed on OCT as a separation of the retina in a two-layered structure. The fluid coming from the optic disc pit can accumulate in different layers of the retina, most commonly in the inner and outer nuclear layers. The appearance is reminiscent of retinoschisis, i.e. it overlies the sensory macular detachment[9]. The latter occurs in 40-60% of patients and is considered the primary cause of visual impairment in patients with optic disc pit[2,3].

Macular microhole is a little known and infrequently diagnosed disease. It is identified by fundoscopy and confirmed by OCT and is described as a small red spot in the centre of the fovea measuring between 50 and 150 microns on average; it can lead to a mild loss of visual acuity, central scotoma and metamorphopsia[4-8].

In our case, the patient had optic disc pits in both eyes. In the RE, which had a 20/20 vision without symptoms or visual changes, fundus examination showed a reddish foveal spot suggestive of macular microhole, which was confirmed by OCT. Given this diagnosis, we explained the patient that the condition generally does not progress and indicated a follow up with complete eye examinations and OCTs. In the literature there are no reports relating the two diseases. Despite their presentation in the same eye, the two conditions possibly have different physiological mechanisms.

The LE presented with an optic disc pit and serous macular detachment. Several types of treatment are proposed for this condition: laser photocoagulation alone, intravitreal gas injection, laser photocoagulation combined with intravitreal gas injection, and vitrectomy combined with gas injection, with or without laser photocoagulation[10].

In a joint decision with the patient, we opted for the simplest and less invasive alternative: laser photocoagulation in the temporal edge of the optic disc, in the region of fluid passage to the subretinal space. After laser therapy, the detachment improved slowly but completely. However, after a few months, the detachment recurred. The patient then underwent posterior vitrectomy with C3F8 gas infusion at a concentration of 12%.

The option to perform vitrectomy was based on the tomographic finding of vitreous attachment in the exact area of the retinal detachment, suggesting the possibility of localised traction. This, together with the other anatomical conditions present in cases of optic disc pit, is the aetiology of sensory retinal detachment. This traction effect had been previously mentioned by other authors[11,12]; in our case, the OCT was very helpful in revealing the condition and was therefore essential for the decision to perform surgery.

Macular serous detachment associated with optic disc pit has a poor prognosis in untreated patients; chronic macular detachment can lead to visual acuity lower than 20/200 in 80% of cases[1].

In our case, the OCT was essential to confirm the diagnosis of macular microhole in the RE and to guide treatment in the LE, allowing detailed evaluation and monitoring of the improvement of sensory macular detachment after laser therapy. It also allowed us to observe the onset of recurrence and to diagnose the presence and the precise location of the traction, having been a key tool for choosing the appropriate type of treatment.

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Corresponding author:
Fernando José de Novelli,
Hospital de Olhos Sadalla Amin Ghanem
Rua Carlos Eberhardt 321
CEP- 89218-160 Joinville (SC), Brazil.
e-mail: Fernando.novelli@gmail.com

Double ring capsulorhexis: clinic opathologic study

Capsulorrexe em duplo anel: estudo clínico patológico

Eduardo Ferrari Marback[1], Marcelo Siqueira de Freitas[2], Fernanda Tanajura Spínola[3], Luciano Espinheira Fonseca Junior[4]

ABSTRACT

We present a case of double ring capsulorhexis in a 81 year-old female patient. Surgical specimen was submitted to histopathologic study resulting in typical double ring capsulorhexis findings. We discuss the questioned relation to true capsular exfoliation. We call attention to the fact that it is possible to obtain a good surgical result even when the double ring is not complete – as the case presented –, since both capsular flaps are fused in a continuous form.

Keywords: *Cataract extraction; Cataract/pathology; Capsulorhexis; Lens capsule/surgery; Lens capsule/pathology; Case reports*

RESUMO

Apresentamos caso de capsulorrexe em duplo anel em paciente feminina de 81 anos. O espécime cirúrgico foi submetido a estudo anatomopatológico que evidenciou os achados típicos da capsulorrexe em duplo anel. Comentamos a possível relação com a exfoliação capsular verdadeira. Salientamos que é possível realizar a cirurgia com bom resultado mesmo que o duplo anel não seja completo – como no caso apresentado –, porém desde que os folhetos capsulares estejam fundidos de forma contínua.

Descritores: Extração da catarata; Catarata/patologia; Capsulorrexe; Cápsula do cristalino/cirurgia; Cápsula do cristalino/patologia; Relatos de casos

[1]PhD in Ophthalmology, Adjunct Professor of Ophthalmology at the Federal University of Bahia (UFBA), Salvador/BA, Brazil; Surgeon at the Freitas Eye Institute, Salvador/BA, Brazil.
[2]MSc in Ophthalmology, Medical Director of the Freitas Eye Institute, Salvador/BA, Brazil.
[3]Medical Doctor, 3rd-year student at the Specialisation Course on Ophthalmology, Federal University of Bahia (UFBA), Salvador/BA, Brazil.
[4]PhD in Human Pathology, Adjunct Professor of Pathology at the Federal University of Bahia (UFBA), Salvador/BA, Brazil.

*Work conducted at the Federal University of Bahia and the Freitas Eye Institute.

The authors declare no conflicts of interest

Received for publication: 5/10/2011 - Accepted for publication: 21/12/2011

Introduction

With the popularisation of capsulorhexis as the preferred capsulotomy technique for cataract surgery, reports began to emerge of the double-ring sign (DRS) during capsulorhexis.[1-3] Some authors question whether such patients have subclinical true exfoliation and whether the DRS would be a possible sign of capsular weakness potentially associated with surgical complications.[2-4]

This article presents a case of DRS, describing its clinical presentation and pathological findings.

Case report

Our patient was an 81-year-old female housewife who presented with progressive worsening of vision in both eyes (BE). On examination, her best corrected visual acuity was "hand motion" in the right eye (RE) and 20/100 in the left eye (LE). Biomicroscopy showed nuclear cataract ++/IV in BE. Retinal mapping showed nonexudative age-related macular degeneration in BE, more pronounced in the RE. The patient underwent phacoemulsification with intraocular lens implantation in the RE, without complications and with improvement of visual acuity to 20/400. When the LE was operated, a double ring was noted during capsulorhexis, starting at the 10 o'clock meridian (Figure 1). When the second ring was noted, care was taken to maintain the integrity and continuity of the two flaps, which reunited at the 3 o'clock meridian. The excised portion of the anterior capsule was fixated with 10% formaldehyde and sent to pathology. The remainder of the procedure was uneventful, with good positioning of the intraocular lens within the capsular bag. Postoperative visual acuity improved to 20/50.

Pathological examination of the anterior capsule fragment revealed the presence of surface delamination, areas of epithelial thinning and intraepithelial vacuoles (Figure 2), findings similar to those of true exfoliation of the lens capsule, which, from the pathological point of view, is characterised as the DRS.

Discussion

The incidence of the DRS is unclear. There is significant disagreement in the literature, with different studies reporting that 5-40% of cataract surgeries are affected by the condition.[2,3] We believe that this variation may be due to the fact that some surgeons are unaware of the existence of the DRS, since it is not easily identified in lower magnifications, especially if a vital dye such as trypan blue is not used to highlight the anterior capsule.

Some authors consider that the DRS represents a subclinical stage of true exfoliation of the capsule.[1-3] This is based on pathological appearance, which is indistinguishable between the two conditions.[1-5] Despite the similarity, Yamamoto et al., examining 13 eyes with true capsular exfoliation and 11 with DRS, argue that the DRS would be a iatrogenic condition caused by mechanical action on the lamellar structure of the lens capsule.[5] To support this idea, the authors point to the presentation of cases of capsular delamination induced by the injection of viscoelastic into the anterior chamber.[6] Moreover, upon examining a number of capsules from patients without the DRS, the authors found vacuoles in the capsular epithelium and considered the presence of fissures in the capsular structure and areas of epithelial thinning as fixation artifacts.[5]

Although there are no known environmental risk factors predisposing to the DRS, such as exposure to high temperatures, which predisposes to true exfoliation, patients with the DRS are usually over 80 years old.[1-6] In this age group, true exfoliation affects as many as 3.6% of individuals, and these patients have even higher rates of capsular pseudoexfoliation and zonular weakness.[5]

Despite the uncertainties surrounding the nature of the DRS as a precursor of true exfoliation, pathological examination of this and other cases of DRS leaves no doubt regarding the presence of capsular weakening.[1-3,5] This weakening, caused by a thinning of the anterior capsule after delamination, was the basis for our decision to perform continuous capsulorhexis in both rings.[1-3] In our case, the double ring was not complete, with visible delamination starting at the 10 o'clock meridian and continuing until the 3 o'clock meridian. From there, the anterior cap-

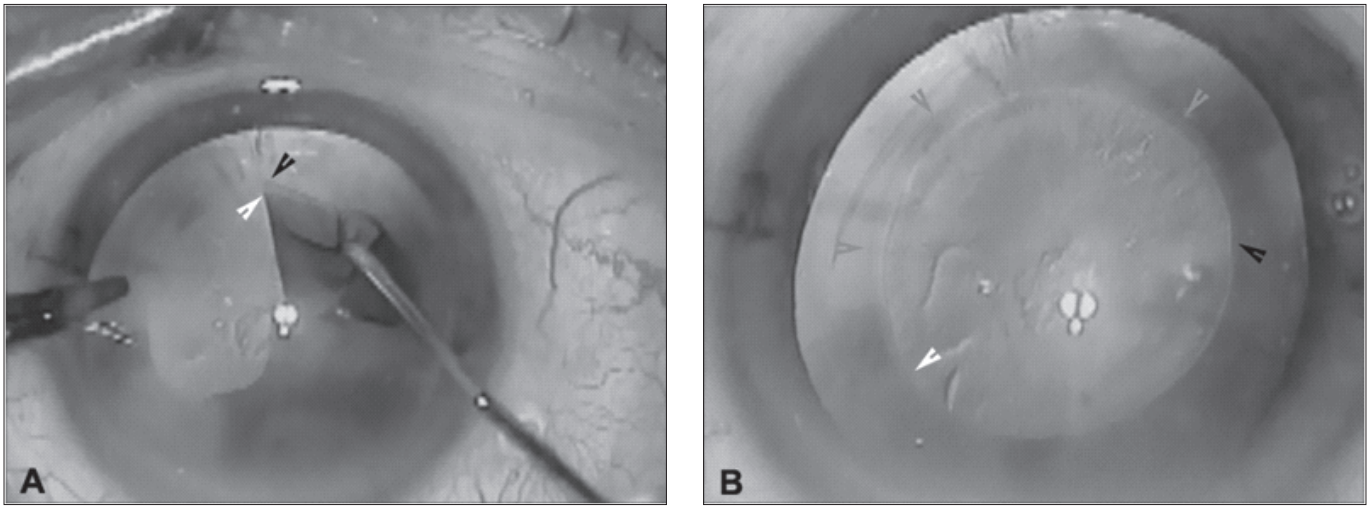

Figure 1: Intraoperative appearance. a) Double ring seen during the procedure. Inner layer (white arrow); outer layer (black arrow). b) Finished capsulorhexis; note the beginning of the double ring (white arrow), the end of the double ring with fused layers (black arrow), and the limits of the double ring (grey arrows).

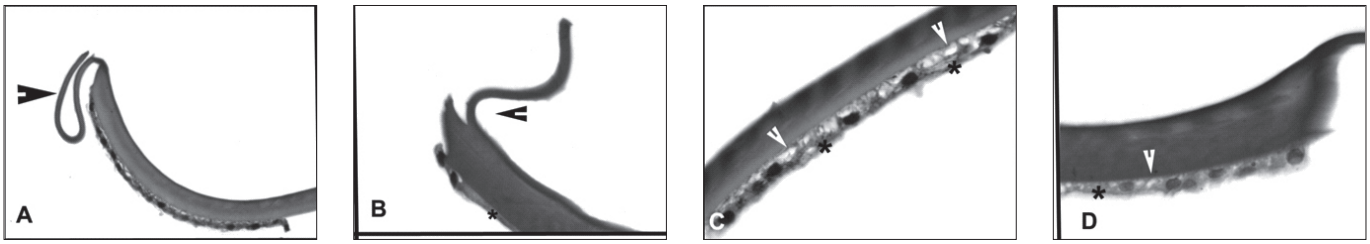

Figure 2. Microscopic images. a) Delamination of the superficial capsule (arrow) (PAS 200X). b) Detail of capsule delamination (arrow) and epithelial thinning (asterisk) (PAS 400X). c) and d) Presence of clear vacuoles in the epithelial cytoplasm (arrows) and thinning of epithelial cells (asterisks) (PAS 400X).

sule flap had a single contour, which allowed the operation to proceed and to be concluded with implantation of the intraocular lens in the capsular bag. Given this, we do not emphasise the need to perform a complete double ring, but to continue the incision without damaging the superficial lamella before the end of delamination, thus avoiding an isolated weak point that predisposes to peripheral tear-out of the capsulorhexis.

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Corresponding author:
Eduardo Marback
Rua Eduardo José dos Santos, 147, Sala 808
CEP: 41940-455 – Salvador (BA), Brazil.
Tel/Fax: (71) 3235-9368
E-mail: eduardomarback@uol.com.br

Neurofibromatosis type I

Neurofibromatose tipo I

Flávia Souza Moraes[1], Weika Eulálio de Moura Santos[2], Gustavo Henrique Salomão[3]

ABSTRACT

The neurofibromatosis type 1 is a autosomal dominant disease which the diagnosis is made based on clinical criteria. Its three main features - neurofibromas, cafe au lait macules and Lisch nodules occur in up to 90% of the pacients until puberty. We documented a clinical case of a young male pacient who had the diagnosis of neurofibromatosis type 1 and family history, describing its clinical aspects and radiological features.

Keywords: *Neurofibromatosis type 1; Glioma; Magnetic resonance imaging; Case reports*

RESUMO

A neurofibromatose tipo I é uma doença autossômica dominante cujo diagnóstico presuntivo é feito com base em critérios clínicos. As três principais manifestações: neurofibromas, manchas café com leite e nódulos de Lisch ocorrem em mais de 90% dos pacientes até a puberdade. Relatamos o caso de um paciente jovem com diagnóstico de neurofibromatose tipo I e história familiar positiva para a doença, comentando seus aspectos clínicos e achados nos exames de imagem.

Descritores: Neurofibromatose tipo I; Glioma; Imagem por ressonância magnética; Relatos de casos

[1] 1st year resident physician at the Ophthalmology Department, ABC Medical School (FMABC), Santo André/SP, Brazil.
[2] Physician at the Paediatric Ophthalmology and Strabismus Departments, ABC Medical School (FMABC), Santo André/SP, Brazil.
[3] Chief physician at the Paediatric Ophthalmology Department, ABC Medical School (FMABC), Santo André/SP, Brazil.

Work conducted at the Ophthalmology Service of ABC Medical School (FMABC), Santo André/SP, Brazil.

The authors declare no conflicts of interest

Received for publication: 10/8/2010 - Accepted for publication: 5/12/2012

Introduction

Neurofibromatosis type 1 (NF1), also called peripheral neurofibromatosis or von Recklinghausen disease, is an autosomal dominant (AD) disease with a highly variable clinical presentation.[1,2] Its incidence ranges from 1/2000 to 1/7800 live births, making it one of the most frequent autosomal dominant genetic diseases. It has been observed in different parts of the world, in all races and in both sexes.[1]

Half of the cases are caused by new mutations. The mutation rate for the NF1 gene is 1/10,000; this is due to the large size and unusual internal structure of the gene, which predispose it to deletions and mutations.[1]

A correlation has not been established between the mutated region of the NF1 gene and the phenotype of patients with the syndrome. Variable expression is one of the most striking features of NF1.[1]

Presumptive diagnosis of NF1 is based on clinical criteria. Its three main features — neurofibromas, café-au-lait spots and Lisch nodules — occur in over 90% of patients until puberty.[1-3]

Currently there is no cure for NF1, but mitigation measures can improve the prospects of life of affected individuals. These patients generally have a normal life expectancy, lead productive academic and professional careers and have a regular affective life. Genetic counselling is important to guide the parents of affected children and to inform them about the risk of recurrence in other pregnancies.[1]

Case report

Male, 16-year-old patient born and raised in Santo André/SP, Brazil, referred to the paediatric ophthalmology service of the ABC Medical School under investigation for neurofibromatosis type 1. The patient had no ocular symptoms and no history of ophthalmic disease, obstetric complications or neuropsychomotor development deficits. Family history revealed a maternal grandmother and mother with neurofibromatosis. The patient's mother died of lung cancer, and his sister was under investigation for NF1.

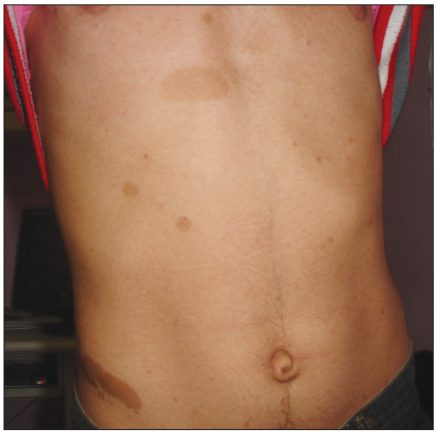
On general examination, café-au-lait spots were seen on the trunk and abdomen. (Figure 1)

Ophthalmic examination showed a corrected visual acuity of 20/30 in both eyes. The patient used corrective lenses of +0.25 SD, - 0.75 CD, 5º in the RE and 0 SD, -0.75 CD, 165º in the LE. Symmetrical pupils, normal pupillary light reflexes, no relative afferent pupillary defect, extrinsic muscles without alterations. Biomicroscopy showed Lisch nodules in both eyes, without other changes. Fundus examination showed a fully attached retina, an optic disc with sharp edges and mild temporal pallor, a physiologic cup and a normal macula in both eyes.

Perimetry showed a loss of sensitivity in the temporal hemifields compatible with the suprachiasmatic lesion observed on an MRI brain scan, without signs of deterioration when compared to the first studies.

Optical coherence tomography (OCT) showed no changes.

A head and brain MRI showed a mass involving the optic



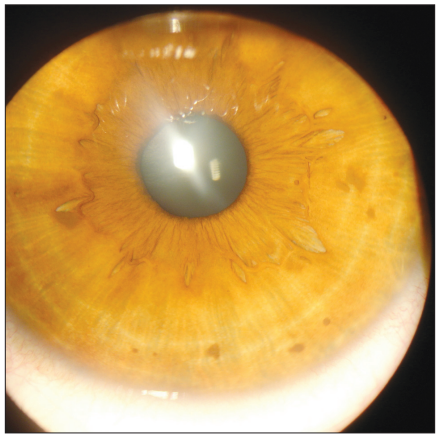
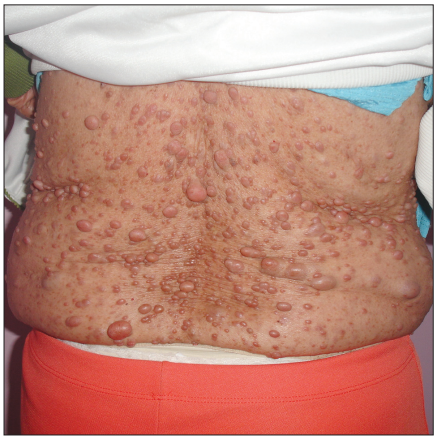


Figure 1: A) Images of the patient showing café-au-lait spots and Lisch nodules



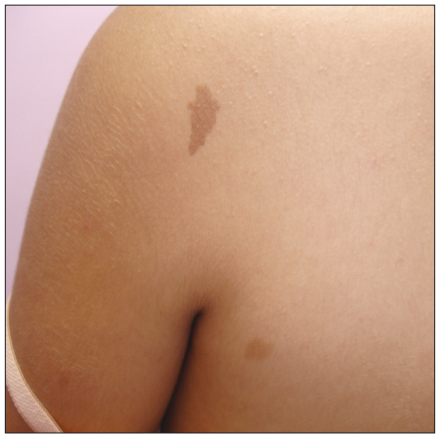


Figure 1: B) Maternal grandmother with neurofibromas and sister with café-au-lait spots

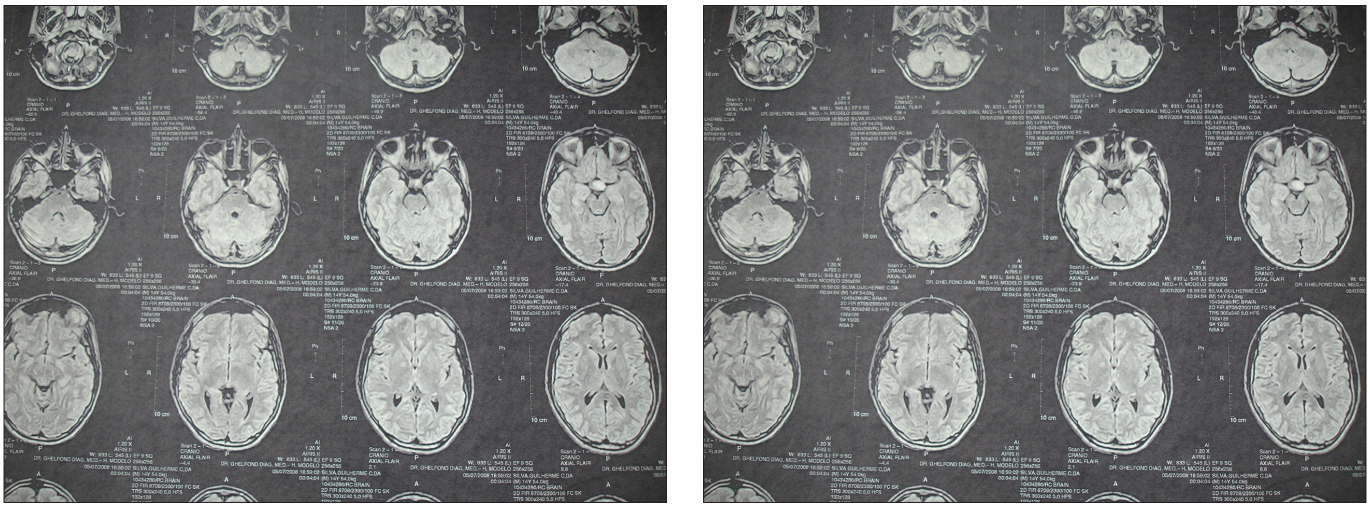


Figure 2. MRI of the brain on T2 and FLAIR sequences showing an optic chiasm mass compatible with glioma

chiasm and hypothalamus, with hyperintense signal on T2-weighted images and flair measuring 1.4 x 1.4 cm in its greatest paramagnetic contrasts, without mass effect on adjacent structures. (Figure 2)

The patient continues to undergo follow-up in both the ophthalmology and the neurology services, performing serial perimetries and MRIs to monitor the tumour.

Discussion

Neurofibromatosis type I is a genetic disease characterised by progressive systemic involvement; it presents with physical and neurological changes and ocular findings.[3.4]

It is an autosomal dominant disease, and the NF1 gene can suffer mutations which lead to a variety of clinical presentations among affected patients.[1.2]

The diagnosis of neurofibromatosis type 1 should be done as early as possible through clinical examination and family history.[4] In our case, the patient has a strong family history with a maternal grandmother and mother diagnosed with NF1 and a sister under investigation for the disease.

Refractive errors can be associated with the condition, with frequent cases of anisometropia, astigmatism and amblyopia. To prevent amblyopia and for early correction of refractive changes, patients should be properly screened before the age of 3 years.[5] In our case, the patient had a visual acuity of 20/32 in both eyes, with low hyperopia in the right eye and slight astigmatism in both eyes.

The most frequent ocular manifestations of the disease include Lisch nodules, hypertelorism, motor disorders, disorders of the optic nerve, and glioma. Of these, Lisch nodules are the most frequent, corresponding to approximately 75% of ocular manifestations and predominantly located in the lower iris.[2.6] Our patient had Lisch nodules in both eyes, slight temporal pallor of the optic nerve and changes on MRI consistent with glioma.

Optic glioma, although benign, can present aggressively in children. Tumour growth is variable and unpredictable, especially in younger patients.[7] Clinical, neurological and ophthalmic follow-up with serial imaging is recommended to monitor tumour growth. Visual evoked potential can be used as a non-invasive screening method for early detection of glioma in patients with NF1 and normal visual acuity.[8.9]

In paediatric patients with NF1 and optic glioma, visual loss depends on tumour size and location, which can be observed on MRI. Visual loss is more common when post-chiasmatic structures are involved.[10]

Typically, only cases of symptomatic optic gliomas whose expansion is seen on imaging studies require treatment. Both chemotherapy and radiotherapy can stabilise tumour growth and even reduce its size. For younger patients, chemotherapy is the first line of treatment, as it shows better effects on tumour growth than radiotherapy.[8.11] Resection is an alternative for tumours involving the optic nerve, but it is only used in patients with loss of visual function or severe proptosis causing pain or exposure keratopathy.[8.12]

Spontaneous tumour regression can occur; it is seen as a decrease in tumour size on MRI and a remission of symptoms. The possibility of regression should be discussed when deciding the treatment plan.[13]

Tumour location determines the prognosis. Optic nerve gliomas have fewer complications and a lower mortality compared to tumours in the optic chiasm, especially those involving post-chiasmatic structures.[10]

In our case, the MRI showed an optic chiasm tumour. The patient also had a loss of sensitivity in the temporal hemifields compatible with the location of the tumour. Serial MRIs and perimetries did not show progression of the lesion. Thus, the patient has been undergoing clinical follow-up with serial studies for close monitoring of the tumour and symptoms.

Due to the tumour's potential to affect visual function severely, regular long-term ophthalmic follow-up is recommended.[14] The approach toward patients with glioma should be decided case by case and is based on tumour location and clinical and imaging progression. The risks and benefits of treatment should be weighted.[8]

Children with NF1 should be examined as early as possible, preferably before puberty. Early diagnosis through clinical examination, family history and imaging studies is essential for therapeutic monitoring and control of the tumour. NF1 management should aim to anticipate major complications and provide early treatment. In genetic counselling, it is important to inform parents and relatives about the general features of the disease and its complications, emphasising that most patients lead healthy and productive lives.[1.15]

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Corresponding author:
Flávia Souza Moraes,
Rua Rui Barbosa, 451, apto 72,
Santo André (SP), Brazil CEP: 09190370

Antifungals in eye infections: drugs and routes of administration

Antifúngicos em infecções oculares: drogas e vias de administração

Guilherme Gubert Müller[1], Newton Kara-José[2], Rosane Silvestre de Castro[2]

ABSTRACT

Treatment of fungal eye infections represents a challenge to the ophthalmology practice. For an adequate therapeutic response, besides correct drug choice, it is necessary an effectively administration. This script gathers information about the major antifungal drugs used in eye infections, their concentrations and main administration routes.

Keywords: *Antifungal agents/therapeutic use; Fungal eye infections; Mycoses; Yeasts; Filamentous fungi*

RESUMO

O tratamento das infecções oculares por fungos representa um desafio à prática oftalmológica. Para obtermos resposta terapêutica adequada, além do uso da droga correta, é necessária a administração desta de forma eficaz. Este manuscrito reúne informações a respeito das principais drogas antifúngicas utilizadas em infecções oculares, suas concentrações e principais vias de administração.

Descritores: Antimicóticos/uso terapêutico; Infecções oculares fúngicas; Micoses; Leveduras; Fungos filamentosos

[1]Post-graduation Programme in Ophthalmic Medical Sciences, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas/SP, Brazil.
[2]Department of Ophthalmology, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas/SP, Brazil.
Institution:
Work conducted at the University Hospital of the State University of Campinas (UNICAMP), Campinas/SP, Brazil.

The authors declare no conflicts of interest

Received for publication: 28/11/2011 - Accepted for publication: 02/02/2012

INTRODUCTION

Fungal eye infections are important causes of ocular morbidity. Since the first report of a fungal keratitis by Leber in 1879[1], an increasing number of cases has been observed. Factors such as corticosteroid use, which facilitates the penetration of pathogens, and the popularisation of topical antibiotics, which create an environment of lower competition among microorganisms on the ocular surface, as suggested as key factors for such increase.

Despite the emergence of new drugs, cure remains difficult in many cases. Compared to antibacterials, antifungals have a lower efficacy due to their mechanism of action (usually fungistatic, with fungicidal action being dose dependent), lower tissue penetration, and the indolent nature of the infection[4].

This paper aims to present information on the main antifungals currently used for the treatment of fungal keratitis and endophthalmitis, highlighting their advantages and disadvantages in order to facilitate the choice of the most appropriate therapy for each case.

POLYENES

This class of antifungal agents includes amphotericin B (AMB), nystatin and natamycin (NTM). Nystatin has not been used to treat eye infections for several decades due to its low tissue penetration, toxicity, and reports of resistance[5,6]. However, AMB and NTM remain as the primary drugs in the treatment of fungal eye infections.

- Amphotericin B

AMB belongs to the family of polyene macrolide antibiotics and was the first broad-spectrum antifungal agent to be discovered. Isolated in the 1950s, AMB is produced by the actinomycete *Streptomyces nodosus*. It became popular after approval by the FDA in the 1960s due to its great efficiency in controlling disseminated fungal infections[4,6-8]. In ophthalmology, it is still the reference drug.

AMB acts by increasing cell permeability through the formation of pores or channels in the fungal cell membrane upon binding to ergosterol and by promoting oxidative action on cells, thus altering their metabolic functions. It also binds to cholesterol in human cells, which is the main reason for its side effects[8,9].

The drug's name is derived from its amphoteric properties (soluble in extreme pHs, both acidic and basic). It has low water solubility and needs to be diluted in deoxycholate for administration. AMB has long molecules that, when infused, coalesce into a colloid. It is photo- and thermosensitive and should be stored in a dark and refrigerated place (2-8°C)[4,6,7,10]. Its action is primarily fungistatic, with fungicidal action depending on the concentration reached in the target tissue[11].

In internal medicine, its use is limited due to its toxicity and side effects. During infusion, fever, chills, hyperventilation, hypotension, nausea, and vomiting may occur, among others. It always causes tubular injury with loss of kidney function in patients with previous kidney disease. It is also partly eliminated by the liver[8,11,12]. AMB should not be diluted in saline solution, as aggregation of colloids can occur, thus reducing the drug's bioavailability.

AMB acts on both yeasts and filamentous fungi. It has an excellent spectrum, being effective against *Candida* spp., *Aspergillus* spp., *Penicillium marneffei*, *Criptococus* spp. and the causative agents of mucormycosis. It is also effective, to a lesser extent, against the main *Fusarium* species. It has no antibacterial activity[4].

AMB also promotes immunopotentiation by binding to cholesterol on the cell membrane of lymphocytes. Suppressor T lymphocytes have higher concentrations of cholesterol in their cell membrane than B and T helper lymphocytes, therefore AMB leads to a reduction in suppressor cells with a relative increase in pro-inflammatory cells[13,14].

Systemic administration of AMB produces little penetration into ocular tissues and does not reach therapeutic levels in the cornea, aqueous or vitreous humour[4,10,15-17]. Furthermore, its side effects discourage systemic administration. Direct in situ administration is therefore the main form of treatment. It is one of the few drugs described in the literature as being used through the subconjunctival, intrastromal, intracameral, and intravitreal routes, as well as topically.

Topical administration in concentrations of 1.5 to 5 mg/ml is commonly the first choice in the treatment of fungal keratitis. The product has to be prepared from the intravenous formulation (Fungizone™ - Bristol-Meyers Squibb, New York, NY) diluted in distilled water. It is used at hourly intervals at the beginning of treatment, and then every 4 hours after the therapeutic response is observed. Periodic debridement of the corneal epithelium is recommended during treatment, because the molecule's large size hinders penetration into the cornea if the epithelium is intact. After topical administration of AMB in rabbits whose corneal epithelium had been removed, therapeutic levels were reached in the corneal stroma. However, in corneas with intact epithelium, concentrations were low or undetectable[18-21]. The drug showed good tolerability and efficiency when used both as eye drops and ointment[22,23].

Subconjunctival administration can be used in patients with low adherence to treatment, but it is limited due to reports of conjunctival necrosis, scleritis and scleral thinning[24,25].

Intracorneal administration, on the other hand, provides better results. There are few reports of complications with this route of administration; also, it provides higher and more sustained corneal concentrations than topical or intracameral administration. Several cases of keratitis unresponsive to topical treatment are successfully resolved after intrastromal administration[18,26], but further controlled studies are still needed. Intrastromal administration of AMB at a concentration of 5 to 10 ìg is suggested for deep infections affecting the stroma that do not respond well to topical treatment[2]. The interval between doses should be at least seven days and the drug should be administered under peribulbar block, as it causes intense pain. Doses above 15 to 20 ì g can cause endothelial cell loss and persistent corneal oedema[18].

Intracameral injection can also be used at a concentration of 5 to 10 ì g/0.1ml. It is administered at least once daily, due to the rapid removal of the drug, without significant endothelial loss. It is indicated in deep infections that penetrate Descemet's membrane and affect the anterior chamber and/or the lens. There are reports of cataract after administration and of a transient increase in chamber reaction within 24 hours due to the immunopotentiating effect of AMB. Other side effects such as iritis and corneal oedema may occur, but they are reversible[27-31].

For the treatment of fungal endophthalmitis, intravitreal injection of AMB is the therapy of choice. The recommended dose ranges from 1 to 10 ì g/0.1ml and may be repeated weekly. In vitrectomised patients, the dosing regimen should be reduced to every 3 or 4 days[32]. Clinical and experimental studies demonstrate the safety and efficacy of this route of administration; however, there are reports of toxicity and retinal necrosis, which are probably dose dependent[3,33].

In eye infections caused by yeasts (especially *Candida* spp.), AMB is still the drug of choice. Although therapeutic success depends on using the drug for a long period (at least 4 weeks), there are few reports of drug resistance by these organisms[34]. Among filamentous fungi, especially *Fusarium* spp., there are reports of drug resistance[3,10].

- Natamycin

Similar to AMB, natamycin (NTM) or pimaricin is a polyene antifungal used only in the treatment of fungal keratitis. It is also used as a pesticide and as a preservative in the food industry [3,35].

NTM has a long molecule with low water solubility. Presented as a suspension, it needs to be shaken before administration. It is the only drug approved by the Food and Drug Administration (FDA) for the treatment of fungal keratitis. In some countries, the drug is commercially available (Natacyn™, Alcon Laboratories, Fort Worth, TX). In Brazil, it needs to be compounded[3,10].

Used at a concentration of 5% (50 mg/ml), it had good stability and is well tolerated when used topically. Due to its high molecular weight, NTM has low corneal penetration and is only indicated as a monotherapy in the treatment of superficial infections[10,36]. In deep infections or those involving intraocular structures, NTM should be associated with other antifungal agents using a different route of administration[2,37-39].

Due to its low corneal penetration, therapeutic success requires long term use of the drug, averaging 39 days[37]. Epithelial debridement is recommended as an adjuvant therapy so that higher concentrations can be achieved in the corneal stroma. This provides a greater adherence of the drug to the de-epithelised surface [3,40]. However, in a study by Prajna et al. epithelial scraping did not improve healing time. In fact, in this study epithelial scraping was associated with lower visual acuity after healing[41].

The dosing interval is similar to AMB, and can be increased once symptoms improve. Some infections require sustained treatment for longer periods; doses every 4 hours maintain therapeutic concentrations in the cornea with good long-term tolerability[42].

Subconjunctival administration is discouraged due to serious complications, such as scleritis and conjunctival necrosis[3,24,43]. There are no reports of administration of NTM through other routes (intracameral, intravitreal, intrastromal, or systemic).

NTM is a broad-spectrum agent, especially against filamentous fungi. Although NTM can also be used in yeast infections, AMB remains the drug of choice due to its wider spectrum against *Candida* species[39,44].

Fusarium infections are usually treated successfully with NTM, especially superficial infections[45,46]. Lalitha et al., in a comparative study on the minimum inhibitory concentrations (MIC) of different antifungal agents, reported that NTM has a lower relative MIC than AMB both against *Fusarium* and *Aspergillus* species[47]. In another clinical trial comparing the efficacy of NTM versus voriconazole (VCZ), no difference was found between the two groups in terms of healing time and final visual acuity [41]. Kalavathy et al. compared the efficacy of NTM and fluconazole (FCZ) and found better results in the group treated with NTM, although the difference was not significant[45]. Several other studies also highlighted the superiority of NTM in the treatment of infections by *Fusarium* spp.[48-50]. Nevertheless, certain authors have shown that about one third of *Fusarium* infections do not respond to NTM[37,51,52]. In such cases, NTM should be replaced by or associated with another drug.

AZOLES

Introduced into medical practice in the 1970s, azoles represented an important advance in antifungal therapy. Compared to AMB, they have a broader spectrum of action and cause fewer adverse effects. Their use spread rapidly, especially in the treatment of infections of the skin and mucous membranes[8].

Azoles act on fungal cytochrome P450 enzymes by blocking the synthesis of ergosterol in the plasma membrane, thus inhibiting fungal growth. Azoles are divided into two major classes — imidazoles were the first to be introduced, followed by triazoles. Both have similar antifungal spectra, but triazoles have the advantages of being metabolised more slowly and exerting less influence on the metabolism of steroids in humans[4,8]. These drugs are metabolised primarily in the liver, therefore control of liver enzymes is recommended. They have teratogenic activity (class C) and should not be used during pregnancy[4,53].

The imidazoles used more often in ophthalmology include miconazole (MCZ), econazole (ECZ) and ketoconazole (KCZ). Among the first-generation triazoles, the most used are itraconazole (ICZ) and fluconazole. Second-generation triazoles were introduced into clinical practice in the past decade and include voriconazole and posaconazole (PCZ).

- Miconazole

MCZ has been developed for use as a topical cream to treat diseases of the skin and mucous membranes and is used primarily in the treatment of superficial mycoses. It is effective against several strains of *Candida*, being used primarily in the treatment of dermatophitosis and oral and vaginal candidiasis, due to its rapid fungicidal action[54]. Systemic administration produces good results but is in disuse due to its cardiovascular and hepatotoxic side effects[55,56].

MCZ not only acts on the synthesis of ergosterol, similar to other azoles, but also promotes the inhibition of peroxidases, resulting in an accumulation of free radicals in the fungal cytoplasm which leads to cell death[57-60].

Topical use at a concentration of 10 mg/ml has good penetration, particularly if associated with epithelial scraping[61-63]. Topical MCZ was also effective in an experimental study where therapeutic concentrations were maintained even with less frequent dosing[64]. It is notably effective and safe when used subconjunctivally (1.2 to 10 mg) in the treatment of infections caused by *Candida*, *Fusarium*, *Curvalaria*, and *Aspergillus*[2,61,65,66]. Systemic use does not reach therapeutic corneal concentrations and is discouraged due to its adverse effects[61,67].

Compared to polyenes, MCZ is less effective but provides better penetration into ocular tissues[5,61]. In vitro, it was more effective than KCZ and ICZ against *Aspergillus* spp., *Candida albicans* and non-*albicans*[50,68]. Further comparative controlled studies are needed to demonstrate the real benefits of this drug.

- Econazole

ECZ, an imidazole with a similar molecular structure to MCZ, is used primarily in the treatment of superficial mycoses, with some studies involving systemic use[69].

It has been little studied in the treatment of eye infections, but there are some reports of topical administration to treat fungal keratitis. In a controlled clinical trial comparing eye drops of ECZ 2% (20 mg/ml) with NTM 5%, there was no statistical difference between the rates of therapeutic success in the two groups; both groups had with good results with no reports of adverse reactions[42]. Mahashabde et al. suggest the use of ECZ ointment 1% as prophylactic treatment after ocular trauma with risk of fungal infection[70]. Unfortunately, the drug is not com-

mercially available for ophthalmic administration, which prevents its use.

- Ketoconazole

KCZ was the first systemic imidazole to be used successfully, but its use is now uncommon in internal medicine. It has been replaced by ICZ due to the latter's milder influence on the metabolism of glucocorticoids and extended antifungal spectrum[4]. It is used at a dose of 100 to 400 mg every 12 hours; its oral absorption depends on gastric pH (below 3), therefore it should be taken without food or gastric acid-suppressive agents. It can be associated with gastric intolerance, hepatotoxicity, gynecomastia, and menstrual changes[8,10].

Although its penetration into the cerebrospinal fluid and urine is low, its penetration into ocular tissues is significant when used systemically. There are numerous reports of therapeutic success with oral KCZ with or without topical NTM or AMB in the treatment of fungal keratitis. Some authors suggest its routine use in all cases of fungal keratitis[71-73], but this is not supported by controlled studies.

There are reports of cases treated exclusively with topical KCZ (10 to 50 mg/ml)[74], but other drugs have been shown to be superior in comparative studies. Komadina et al. and Singh et al., comparing topical and oral KCZ with NTM, showed that the latter is superior. A partial response was also achieved with isolated oral administration, with increased effect when combined with topical NTM[75,76].

In vitro studies with strains of *Aspergillus* spp. and *Fusarium* spp. exhibited a lower susceptibility of these organisms to KCZ compared to NTM and VCZ[50]. Other laboratory studies also showed similar results with strains of *Aspergillus*, *Fusarium* and *Candida* spp., which were susceptible to KCZ only at high doses[34,77].

Currently, systemic KCZ is indicated only for the adjuvant treatment of deep fungal keratitis.

- Itraconazole

ICZ is more frequently used in general practice than KCZ and has fewer side effects when administered systemically. However, when administered orally it exhibits lower bioavailability, solubility and penetration into ocular tissues than other azoles[3,10,78,79]. Similar to KCZ, gastric absorption depends on a low pH. Studies in rats showed that ICZ has a lower teratogenic risk than KCZ[53].

Systemic administration at 400 mg/day was effective in the treatment of infections by *Candida* spp.[80]. However, in infections by *Fusarium* spp., some studies suggest that ICZ is ineffective. Topical use at a concentration of 10 mg/ml was not as effective as NTM 5%[45]. In vitro studies found that ICZ had a higher MIC than AMB and NTM[48,78], and even found some drug resistance among all analysed strains[47]. ICZ was effective against *Aspergillus* spp., but not as effective as KCZ[77].

Systemic use should be limited only to the adjuvant treatment of eye infections by yeasts.

- Fluconazole

Unlike ICZ and KCZ, FCZ shows excellent absorption from the gastrointestinal tract and is not influenced by gastric acidity. Its plasma concentrations with oral use reach almost the same levels as with intravenous administration. Penetration into ocular tissues is effective, reaching aqueous concentrations similar to those in the plasma[4,81].

Oral use at 200 to 400 mg per day was effective in the treatment of eye infections, with or without topical NTM[82,83]. When used subconjunctivally in association with topical AMB, a broader antifungal spectrum was observed with less toxicity than isolated AMB[84]. Yilmaz and Maden managed to treat 60% of cases of fungal keratitis with subconjunctival injections of FCZ alone[85]. A subconjunctival dose of 2 mg in 1 ml administered daily for 10 days is recommended, followed by every 48 hours until remission[86].

FCZ eye drops achieved good intracorneal therapeutic levels against strains of *Aspergillus fumigatus* in rabbits. Used at a concentration of 2 mg/ml, its penetration was better after epithelial scraping[87,88].

FCZ is less effective than other drugs in the treatment of fungal endophthalmitis. Despite its good vitreal penetration when administered orally, its ineffectiveness against filamentous fungi discourage its use as an adjuvant. However, there are reports of successful treatment of endogenous endophthalmitis by *Candida* spp. with FCZ[89-91].

Even though its ocular penetration is superior to KCZ, in vitro and in vivo studies showed that the antifungal spectrum of FCZ is narrower. In several studies that evaluated the susceptibility of causative agents of fungal keratitis and endophthalmitis, only *Candida* species were susceptible to FCZ, and filamentous fungi (*Aspergillus* and *Fusarium* spp.) exhibited marked resistance[34,48,77,92].

- Voriconazole

VCZ has the same mechanism of action than first-generation triazoles, but is more effective in blocking the synthesis of ergosterol. VCZ was developed from the FCZ molecule and presents better efficacy at lower MICs than the first triazoles, which increases its effectiveness against filamentous fungi[8]. Because of its great efficacy in treating disseminated fungal infections, with lower toxicity compared to AMB, VCZ is currently the drug of choice in the treatment of invasive aspergillosis[93].

VCZ is commercially available for oral and parenteral administration (Vfend™ - Pfizer, New York, NY). It is metabolised by the liver, therefore liver enzymes should be controlled during therapy. Among its side effects are visual disorders (blurred vision, change in colour perception and photophobia), which are present in about 30% of patients using the drug and are usually reversible. Similar to FCZ, it presents good gastric absorption and bioavailability[4,92].

Administered orally at a dose of 200 mg every 12 hours, VCZ reaches peak plasma concentrations after 2-3 hours. The drug has been extensively studied in the treatment of keratitis and endophthalmitis due to its good concentrations in several ocular tissues (cornea, vitreous and aqueous)[32,94]. Hariprasad et al. found concentrations of VCZ in the vitreous and aqueous humours corresponding to 38% and 51% of plasma levels, respectively, after oral administration. Although the concentrations achieved in the vitreous were insufficient to treat infections by *Fusarium* spp., the authors argue that the study was conducted in non-inflamed eyes, and that in the presence of inflammation a more permeable blood-ocular barrier would help increase the local concentrations of the drug[95]. Alfonso et al. suggest VCZ as the drug of choice for oral use in the treatment of deep keratitis, scleritis, and endophthalmitis and as prophylaxis after penetrating keratoplasty[2]. Hariprasad et al. also suggest oral VCZ as prophylaxis in cases of ocular trauma with plant material[92].

Intravitreal administration was shown to be safe in an experimental model with rats, with no changes in electroretinography in doses up to 25mg/ml[96].

There are also numerous reports of therapeutic success with topical VCZ. Administered at a concentration of 1 mg/ml, it

was effective in the treatment of keratitis by *Candida*, *Aspergillus*, *Fusarium*, *Scedosporium*, and *Paecilomyces*, among others[97-101]. Its advantages compared to polyenes include its greater stability to light and temperature, remaining effective for up to 30 days[102,103]. Studies in horses showed drug penetration even with epithelial integrity[104].

Some reports support the use of intracorneal VCZ in cases of deep keratitis unresponsive to topical and/or oral administration. Prakash et al. report success in three cases of keratitis unresponsive to topical NTM using VCZ 50 ìg/0.1 ml[105]. Recently Siatiri et al. described 3 cases of *Fusarium* keratitis unresponsive to topical treatment that resolved after intracorneal VCZ[106]. The authors suggest that direct injection of VCZ in the cornea increases its concentration above its minimum inhibitory concentration for *Fusarium* species. Sharma et al., in a series with 13 patients, also suggest the use of intrastromal VCZ in refractory keratitis[107].

However, there are few studies comparing VCZ with other antifungal agents. In a multicenter randomised study VCZ was not found to be superior to NTM, with both groups having similar healing times and final visual acuity[41]. There are even reports of treatment failure with VCZ. Giaconi et al. reported two cases, a keratitis by *Fusarium oxysporum* and another by *Colletotrichum dematium*, which were unresponsive to topical therapy with VCZ[108].

In vitro studies demonstrate the superiority of VCZ to AMB against *Aspergillus* spp.[109-112]. Against *Fusarium* species, the absolute MIC of VCZ, NTM and AMB were similar, with VCZ having a lower relative MIC than the polyenes[47]. Even so, the minimum inhibitory concentration of VCZ for *Fusarium* species was superior to *Candida* and *Aspergillus* species[77].

- Posaconazole

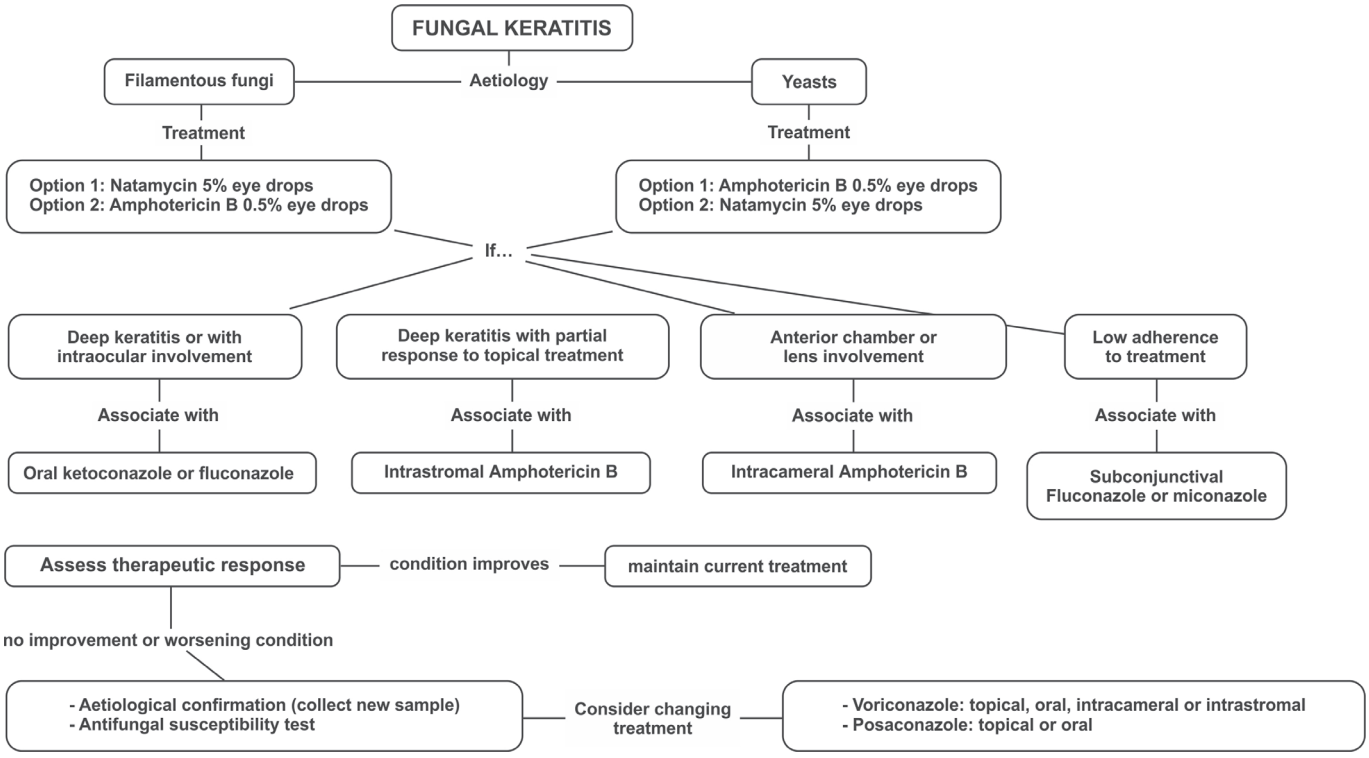
Similar to VCZ, PCZ is a second-generation triazole recently introduced into medical practice. It results from an improvement in the molecule of ICZ and is primarily indicated for the treatment of invasive fungal infections in onco-hematological patients. It is only available as an oral solution (Noxafil™ - Schering-Plough, Kenilworth, NJ) and should be administered at a dose of 200 mg four times daily or 400 mg twice daily. A parenteral presentation is currently being developed. Gastrointestinal complaints are the

Table 1

Antifungal agents and their indications

Drug	Route of administration	Dosing	Indication
Amphotericin B	Topical	1.5-5mg/ml	- First choice in the treatment of keratitis by yeasts - Alternative to NTM in the treatment of keratitis by filamentous fungi
	Intrastromal	5-10µg	- Deep keratitis with partial response to topical treatment
	Intracameral	5-10µg/0.1ml	- Keratitis affecting the internal chamber and/or lens
	Intravitreal	1-10µg/0.1ml	- First choice in the treatment of fungal endophthalmitis (by yeasts or filamentous fungi)
Natamycin	Topical	50mg/ml	- First choice in the treatment of fungal keratitis by filamentous fungi - Alternative to AMB in the treatment of keratitis by yeasts
Miconazole	Subconjunctival	1.2-10mg/1ml	- Associated with topical therapy in patients with low adherence to treatment
Econazole	Topical	20mg/ml	- Alternative to NTM in keratitis by filamentous fungi
Ketoconazole	Oral	100-400mg every 12h	- Associated with topical therapy in deep keratitis or those affecting intraocular tissues
Itraconazole	Oral	400mg/day	- Associated with topical therapy in deep keratitis by yeasts or those affecting intraocular tissues
Fluconazole	Topical	2mg/ml	- Alternative to polyenes in the treatment of fungal keratitis
	Subconjunctival	2mg/1ml	- Associated with topical therapy in patients with low adherence to treatment
	Oral	200-400mg/day	- Associated with topical therapy in deep keratitis or those affecting intraocular tissues
Voriconazole	Topical	1mg/ml	- Fungal keratitis resistant to polyenes and first-line triazoles
	Intrastromal	50µg/0,1ml	- Deep keratitis with partial response to topical drugs or in patients with low adherence to treatment
	Intracameral	50µg/0,1ml	- Fungal keratitis affecting the internal chamber and/or lens
	Intravitreal	50µg/0,1ml	- Alternative to AMB in fungal endophthalmitis
	Oral	200mg every 12h	- Associated with topical therapy in deep keratitis or those affecting intraocular tissues- Prophylaxis after eye trauma with plant material
Posaconazole	Topical	100mg/ml	- Fungal keratitis resistant to polyenes and first-line triazoles
	Oral	200mg every 6h or 400mg every 12h	- Adjunctive therapy in deep keratitis and endophthalmitis by organisms resistant to polyenes and first-line triazoles.
Flucytosine	Topical	10mg/ml	- Associated with topical AMB in fungal keratitis by yeasts
Caspofungin	Topical	1.5-5mg/ml	- Fungal keratitis by yeasts resistant to polyenes and first-line triazoles
Micafungin	Topical	1mg/ml	- Fungal keratitis by yeasts resistant to polyenes and first-line triazoles

Figure 1. Treatment algorithm for fungal keratitis



only adverse effects reported to date[113].

In vitro and in vivo studies show that PCZ has a broad spectrum against *Candida* spp., *Cryptococcus neoformans*, *Aspergillus* spp., and *Fusarium* spp., among others. PCZ was effective against most agents resistant to ICZ and FCZ[114,115] and, together with VCZ, had the lowest MIC against multiple agents[47].

Experience with its use in ocular infections is still limited, but initial results are encouraging. In a series of three cases of *Fusarium* keratitis progressing to endophthalmitis unresponsive to treatment with oral and topical VCZ, a rapid therapeutic response to PCZ was observed[36]. Sponsel et al. also describe a case of keratitis by *Fusarium solani* resistant to AMB and NTM but successfully treated with oral PCZ 200 mg 4 times daily associated with topical use (100 mg/ml prepared from an oral solution)[116]. However, comparative controlled studies with first-line antifungal agents are still lacking.

PYRIMIDINES

Pyrimidines are represented by 5-fluorocytosine (5-FC) or flucytosine, which is the only antifungal agent with intracellular action. After being absorbed by the fungus it is converted into 5-fluorouracil, a powerful antimetabolic which acts by inhibiting the synthesis of DNA[4,117].

Its use in eye infections is restricted due to its narrow antifungal spectrum and low penetration into ocular tissues[17]. It is effective against *Candida* spp., with varied action against *Aspergillus* spp. It is ineffective against *Fusarium* spp. Systemic or topical administration should be associated with AMB, primarily due to its potentiating effect (synergism) and because of induction of resistance when 5FC is used alone[4,6,77,118].

ECHINOCANDINS

Echinocandins are semisynthetic lipopeptides that inhibit the synthesis of glucan in the fungal cell wall through non-competitive inhibition of the enzyme 1,3-â-glucan synthase, causing osmotic imbalance and cell lysis[8,119,120]. This class of drugs includes caspofungin (CFG) and micafungin (MFG).

Used in yeast infections, echinocandins have rapid fungicidal action against most *Candida* species, including strains resistant to FCZ, but not against *Cryptococcus*, *Rhodotorula* and *Trichosporon*[121]. Echinocandins have fungistatic action against some filamentous fungi such as *Aspergillus*, but not against *Fusarium* and *Rhizopus*[47,122]. CFG is administered intravenously (Cancidas™ - Merck & Co - Whitehouse Station, NJ) at a dose of 70 mg on the first day and 50 mg on the following days[4,8]. MFG (Mycamine™ - Astellas Ireland - Killorglin, Ireland) is also administered intravenously at a dose of 100 to 150 mg/day.

Topical CFG at a concentration 1.5 to 5 mg/ml was as effective as AMB in the treatment of corneal ulcer by *Candida albicans* in an animal model[123]. Two other studies involving topical MFG 1 mg/ml found an efficacy comparable or superior to FCZ in the treatment of keratitis by *Candida albicans* and *Candida parapsilosis*[124,125].

ASSOCIATION OF ANTIFUNGAL AGENTS

In order to increase treatment efficiency or even broaden the antifungal spectrum, drugs are commonly associated in the treatment of eye infections. Although some combinations of antifungals such as 5-FC and AMB are widely used[126], other less studied associations may not be as effective as expected.

Azoles are often associated with standard topical antifungal agents such as NTM or AMB. However, several studies

showed an antagonistic effect between these drugs. The introduction of an azole decreases the synthesis of ergosterol in the cell membrane, a binding site for polyenes, whose action is therefore decreased.

Arora et al. observed this antagonistic effect between ECZ and AMB in the treatment of fungal keratitis, whose association produced therapeutic results similar to ECZ alone[127]. In a review article, Sugar et al. showed an in vitro antagonistic effect between AMB and various azoles (MCZ, KCZ, FCZ and ICZ), with decreased polyene action[128]. In a similar study, Li et al. found an antagonistic effect between NTM+ICZ and NTM+FCZ and a synergistic effect between AMB+ICZ[48].

Studies in humans and animals usually do not reproduce these laboratory findings. There are countless reports of improvement with the association of antifungal agents, especially when topical AMB is associated with first- and second-generation systemic triazoles[129,130]. This combination should be used in deep corneal infections or those with intraocular involvement.

The combination of two drugs of the same class is discouraged (e.g. NTM+AMB) because it increases local toxicity and also fails to increase therapeutic efficacy[131].

OTHER DRUGS

Alternatives to antifungal agents have been studied to treat keratitis of unclear aetiology. In a number of cases, povidone-iodine 2.3% was used successfully to treat keratitis by *Candida albicans* and *Acremonium strictum*[132]. However, in a comparative study, povidone-iodine 0.5% showed no benefit compared to NTM 5% in the treatment of experimental keratitis by *Fusarium solani*[40]. In another experimental study, Fiscella et al. showed that polyhexamethylene biguanide (PHBM) 0.02% is effective in the treatment of eye infections by *Fusarium solani* in rabbits[133]. However, there are no comparative studies between PHMB and antifungal agents.

Experimental trials involving topical corticosteroids associated with antifungal therapy found deleterious effects. O'Day et al. showed a modified host response after the introduction of corticosteroids. In their study, in rabbits infected with *Candida albicans*, *Aspergillus fumigatus* and *Fusarium solani* that received subconjunctival corticosteroids corneal sterilisation occurred later than in the control group[134]. Weiyun et al. studied the risk factors for recurrence of the fungal infection after transplantation and found a six-fold increase in the risk of recurrence in patients who received topical steroids prior to transplantation[135].

Conclusion

There are many options of antifungal agents and routes of administration, and the choice depends on both the aetiologic agent and the location and extent of the infection (Table 1).

Standard therapy with polyenes remains effective. Despite the numerous reports of infections that do not respond to first-line drugs and improve after the introduction of other agents, particularly second-generation triazoles, comparative studies demonstrating the superiority of the latter are lacking.

Until the real benefit of the new generation of antifungal agents is demonstrated, we believe such drugs should be used as an alternative to standard therapy (Figure 1).

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Corresponding author:
Guilherme Gubert Müller
Av. Des. Hugo Simas, 333. Curitiba/PR, Brazil
CEP 80520-250
e-mail: guimuller@ig.com.br

Importance of radiofrequency in ophthalmology

Importância da radiofrequência na oftalmologia

José Ricardo Carvalho Lima Rehder[1], Leonardo Verri Paulino[2], Eduardo Paulino[3]

ABSTRACT

This paper reviews and makes a critical analysis of radiofrequency in ophthalmology.

Localized heating of the cornea has been apllied since 1889 for different therapeutic and surgical objectives.The principle that heating corneal tissue causes shrinking of the collagen that changes the corneal curvature. After the approval of FDA in 2004, we initiated a multicenter study in Brazil coordinated by ABC School of Medicine that resulted in an analyses of 258 patients. Inconclusion the study showed that the procedure had a temporary result and the best results were obtained in patients between 45 and 55 years old without optical correction for far.We believe that the problem has not been solved yet and a great deal of research effort should be focused.

Keywords: *Radio waves/therapeutic use; Eye diseases/therapy; Corneal topography*

RESUMO

Este trabalho revisa e faz uma análise crítica da radiofrequência em oftalmologia.

O aquecimento da córnea tem sido realizado desde 1889 com diferentes finalidades terapêuticas e cirúrgicas. O princípio do aquecimento da córnea causa um enrugamento do colágeno que muda a curvatura da córnea. Após a aprovação da FDA em 2004, iniciou-se um estudo multicêntrico no Brasil coordenado pela Faculdade de Medicina do ABC que resultou na análise de 258 pacientes. Como conclusão o estudo mostrou que o procedimento tem um resultado temporário e que os melhores resultados foram obtidos em pacientes entre 45 e 55 anos de idade sem correção óptica para longe.

Acreditamos que o problema ainda não foi resolvido e que novas pesquisas devem ser realizadas.

Descritores: Ondas de rádio/uso terapêutico; Oftalmopatias/terapia; Topografia da córnea

[1]Department of Ophthalmology, ABC Medical School (FMABC), Santo André/SP, Brazil.
[2]Cornea and External Diseases Unit, Department of Ophthalmology, ABC Medical School (FMABC), Santo André/SP, Brazil.
[3]Refractive Surgery Unit, Department of Ophthalmology, ABC Medical School (FMABC), Santo André/SP, Brazil.

The authors declare no conflicts of interest

Received for publication: 7/10/2011 - Accepted for publication: 26/07/2012

Introduction

The first studies on radiofrequency date back to 1864, when the Scottish scientist James Clerk Maxwell, after observing the experiments made by Faraday, managed to produce an electromagnetic radiation that travelled through space with wave-like features and calculated that those waves propagated at the speed of light.[1-4]

The properties of electromagnetic radiation were confirmed in 1888 by the experiments of Heinrich Hertz, who used oscillating charges to produce high frequencies, around 500 Mc/s, for the first time. Due to the importance of Hertz's experiments, the unit c/s (cycles per second) was named after him (Hz).

Further technological developments made it possible to produce higher frequencies up to 300 GHz (300 x 10^6 kHz). Such frequencies, classified as SHF (Super High Frequencies) and EHF (Extremely High Frequencies), can be used for communication and also have the property of being absorbed by water (H_2O) or oxygen (O_2) molecules.[3,4]

Studies on the absorption of electromagnetic waves by water and oxygen showed that waves of shorter wavelength and higher frequency produce heat in the irradiated area.

In ophthalmology, radiofrequency was initially used for refractive surgery in 1980 with the works of Rowsey et al. and Doss and Rowsey, who used it to treat keratoconus. The technology was later used for several conditions, such as ocular plastic surgery, conjunctival surgery, glaucoma surgery and complications of cataract surgery.[5-18]

Radiofrequency for treating refractive errors

In the United States of America, after approval by the Federal Drug Administration (FDA) on April 11, 2002, a device named "ViewPoint™ CK System", from Refractec, Inc., California, was launched in the market. The system, based on the concepts of thermokeratoplasty, applies a high frequency, low energy electrical current to the corneal stroma, producing a temperature sufficient to shrink collagen fibres (Figure 1). The device has been approved by the FDA for the treatment of hyperopia from +0.75 to +3.25D with astigmatism < -0.75 D and a difference up to 0.50D between visual acuity with and without cycloplegia in persons over 40 years of age.[19-31]

On February 6, 2004 the FDA approved the same technology for the correction of presbyopia, aiming at balanced vision.

For the adoption of the technology in Brazil, the Department of Ophthalmology of ABC Medical School, with the approval of the Ministry of Health, prepared a National Protocol for the Study of Radiofrequency in Ophthalmology. The protocol began in 2002 with 300 operations using an animal model. This study established the criteria for optimal power and application time to obtain the best effects on the corneal stroma — a power of 0.6W, with 0.60 seconds per pulse (Figures 1, 2 and 3).

In the second stage of the protocol 40 volunteers were selected, 20 of them hyperopic and 20 presbyopic. The volunteers underwent radiofrequency therapy at the Eye Institute of the ABC Medical School.

After this pilot phase, having established the optimal radiofrequency parameters for the correction of refractive errors, a multicenter study was conducted on the treatment of presbyopia in 45 reference centres throughout Brazil.[27,28,32]

The study, concluded in 2010, assessed the anatomical behaviour of the cornea in 258 patients and showed that, after undergoing radiofrequency therapy, all patients had an abrupt increase in corneal curvature (Chart 1). After this initial peak

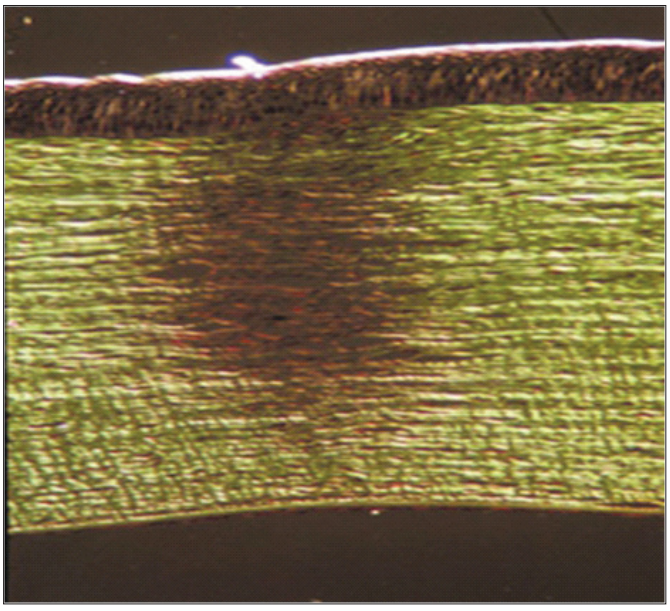


Figure 1: Collagen shrinking

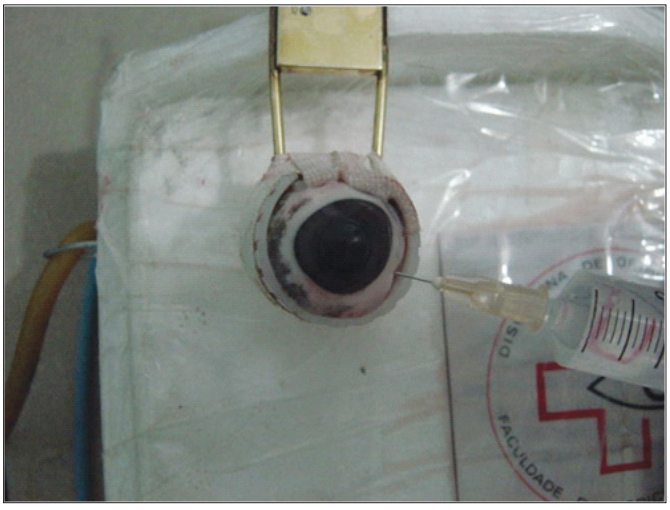


Figure 2: Applying saline solution

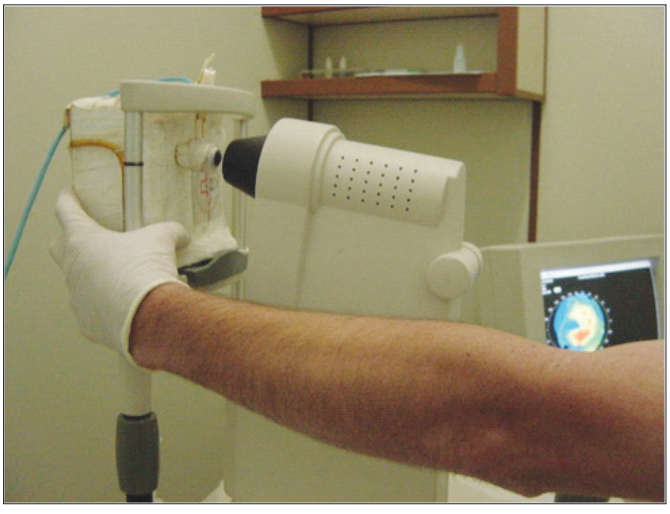


Figure 3: Corneal topography

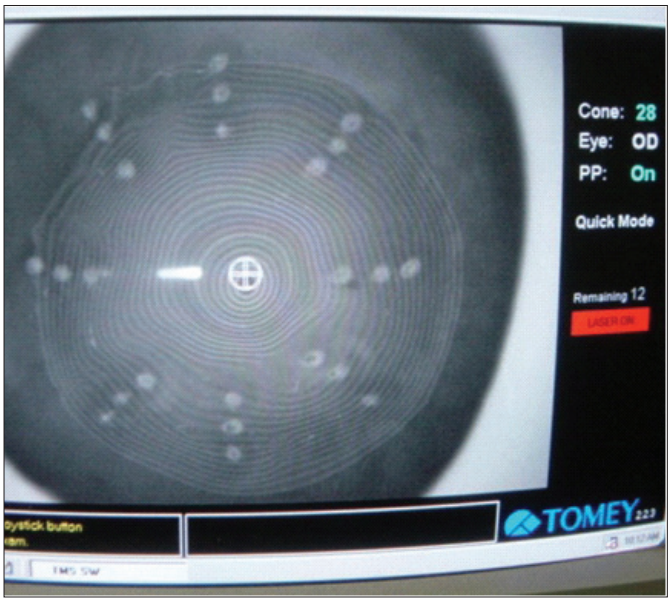
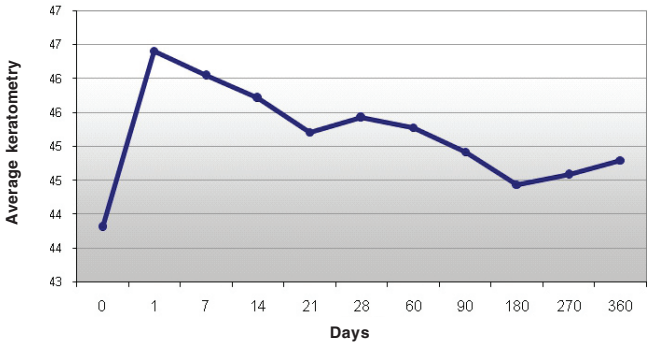


Figure 4: Corneal topographic map

Chart 1

Average keratometry



Days	0	1	7	14	21	28	60	90	180	270	360
Average	43,81	46,41	46,04	45,71	45,21	45,42	45,28	44,92	44,44	44,58	44,79
Stand. Dev.	1,54	1,91	1,84	1,74	2,65	1,64	1,51	1,69	1,66	1,49	1,78
N	159	115	127	114	103	109	88	84	71	34	19

Chart 2

Efficacy in 90 days

Near visual acuity without correction preoperative x Near visual acuity without correction preoperative

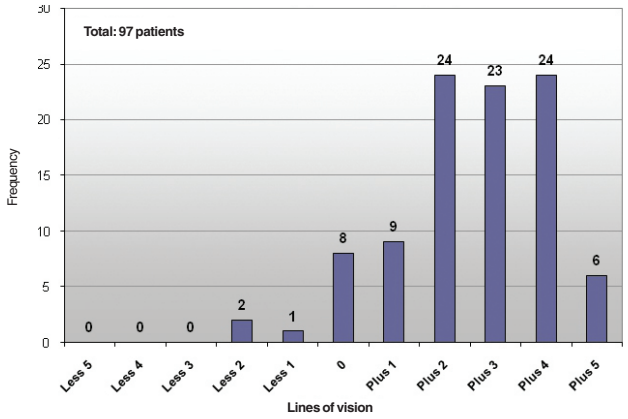
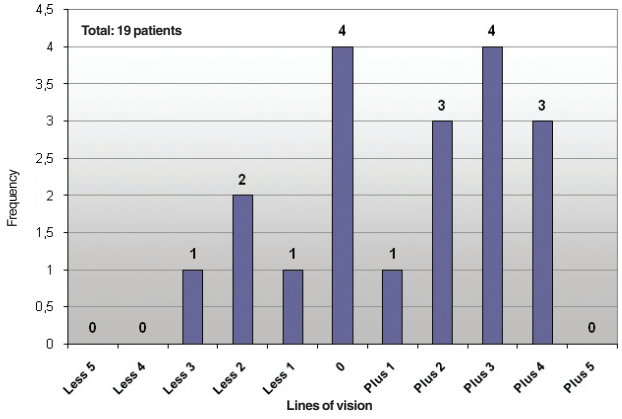


Chart 3

Efficacy in 360 days

Near visual acuity without correction preoperative x Near visual acuity without correction preoperative



increase, the curvature decreased over time, with a loss of therapeutic effect.

The desired effects on near vision were observed in 88% of operated eyes 90 days after the procedure and were maintained in 70% after 360 days (Charts 2 and 3).

Safety analysis showed that 96.8% of patients maintained their preoperative binocular distance vision after 90 days, and 88% did so after 360 days (Charts 4 and 5).

In some cases (26.5%) distance vision improved without correction. It is important to note that in all cases distance vision worsens abruptly in the immediate postoperative period, but as the corneal curvature decreases, distance vision improves progressively without the expected loss of near vision.

The patients who had a greater loss of distance vision were the ones with higher degrees of latent hyperopia.

In the near vision chart (Chart 6) the percentage of patients with vision between J1 and J3 during the period of analysis remained high.

It was therefore concluded that the treatment of presbyopia with radiofrequency is **safe and effective** and that it produces a **temporary effect**.

Regarding the surgical technique, it is clear that the best results are obtained when the corneal surface is kept dry during the procedure and that centralisation and visualisation of corneal marks is facilitated when performed under a microscope with coaxial illumination (microscopes coupled with excimer laser devices hinder marking).

Furthermore it can be stated that this procedure is "surgeon dependent", i.e. the position of the probe and its depth of penetration, as well as corneal compression during application, are important factors for achieving best results, because bad centralisation of corneal marking leads to worse refractive outcomes, with high astigmatism and lower visual acuity.

Regarding the results of the procedure, distance visual acuity tends to be low in the immediate postoperative period, causing discomfort to most patients. On average, this discomfort decreases after 30 days with the stabilisation of corneal curvature. A partial loss of the therapeutic effect occurs approximately 6

Chart 4

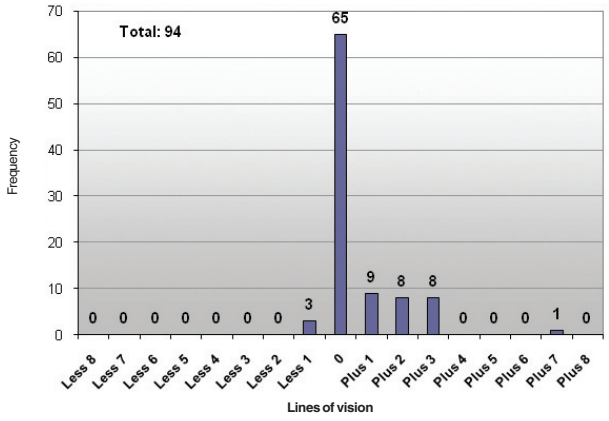


Chart 5

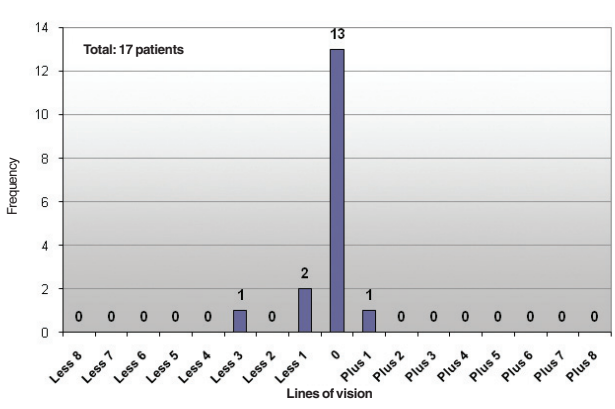
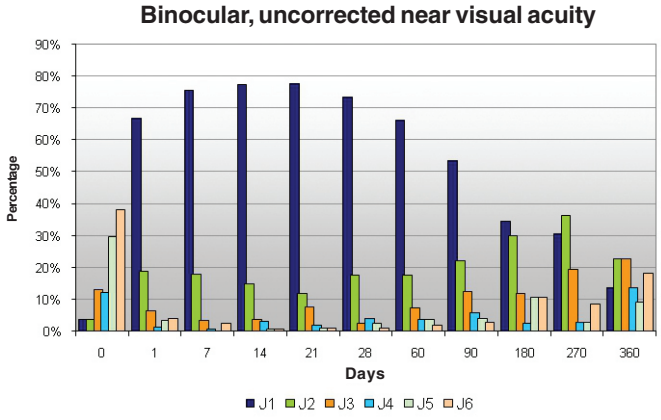


Chart 6



		Days										
		0	1	7	14	21	28	60	90	180	270	360
Lines of Vision	J1	7	104	118	105	93	96	72	56	29	11	3
	J2	7	29	28	20	14	23	19	23	25	13	5
	J3	26	10	5	5	9	3	8	13	10	7	5
	J4	24	2	1	4	2	5	4	6	2	1	3
	J5	59	5	0	1	1	3	4	4	9	1	2
	J6	76	6	4	1	1	1	2	3	9	3	4
Total		199	156	156	136	120	131	109	105	84	36	22

		Days										
		0	1	7	14	21	28	60	90	180	270	360
Lines of Vision	J1	3,5%	66,7%	75,6%	77,2%	77,5%	73,3%	66,1%	53,3%	34,5%	30,6%	13,6%
	J2	3,5%	18,6%	17,9%	14,7%	11,7%	17,6%	17,4%	21,9%	29,8%	36,1%	22,7%
	J3	13,1%	6,4%	3,2%	3,7%	7,5%	2,3%	7,3%	12,4%	11,9%	19,4%	22,7%
	J4	12,1%	1,3%	0,6%	2,9%	1,7%	3,8%	3,7%	5,7%	2,4%	2,8%	13,6%
	J5	29,6%	3,2%	0,0%	0,7%	0,8%	2,3%	3,7%	3,8%	10,7%	2,8%	9,1%
	J6	38,2%	3,8%	2,6%	0,7%	0,8%	0,8%	1,8%	2,9%	10,7%	8,3%	18,2%
Total		100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

months after the procedure, when the patient reports a decrease in near visual acuity. There is also a phenomenon of decoupling between postoperative refraction and visual acuity in operated eyes, i.e., the measured refraction for distance vision does not match the visual acuity. This finding supports the theory of the "blend" effect described by Holladay where a multifocal corneal effect would occur due to the prolate central cornea which would be responsible for the improvement in near vision, and not the initially induced myopia.

With respect to the indications of radiofrequency for the correction of presbyopia, ideally patients should have a preoperative visual acuity of 20/20 in both eyes without correction. Occasional hyperopia with cycloplegia should not exceed +0.50SD with +0.50CD in both eyes, to prevent any loss of distance vision postoperatively. The ideal age for the procedure is between 45 and 55 years due to the progressive nature of presbyopia and accommodative properties. Patients with very functional or completely ineffective accommodation should not undergo the procedure.

The temporary effect should be considered a positive feature of the procedure, because presbyopia may still be progressing at this age, therefore definitive procedures are contraindicated.

Reoperation may be indicated only when the therapeutic effect has remitted completely and, according to the literature, should be performed at the same sites as in the previous procedure.

Definite loss of corneal tissue does not occur with the procedure, the optical centre of the cornea is preserved, and the resulting monovision provides satisfactory distance visual acuity.

Several studies have also assessed the use of thermokeratoplasty with radiofrequency to correct astigmatism. Wen Xuet al. concluded in 2010 that the nomogram for conductive keratoplasty provides good results in the treatment of hyperopic astigmatism.[26]

Other Ophthalmic Indications

In modern medicine, many therapeutic techniques can be used for different purposes. The various types of lasers, as well as the various radiofrequency devices, can be used for cauterisation, coagulation, tissue contraction, vaporisation, and cutting.[33-39]

Radiofrequency can often be used to obtain results similar to lasers, but at lower costs, by simply modulating the frequency, power, exposure time and pulse and by using uni-, bi- or tripolar probes.[25,26,38,39]

Ocular plastic surgery

In ocular plastic surgery, radiofrequency has been used for blepharoplasty, excision of tumours, treatment of xanthelasma, trichiasis, and recanalisation of the nasolacrimal duct.[9.18]

Conjunctiva

In the conjunctiva, radiofrequency is used for coagulation, to treat pterygium and to remove tumours.[10]

Extrinsic ocular muscles

In strabismus, radiofrequency can be used to weaken medial or lateral extrinsic muscles in cases of mild strabismus and even to cut muscles during surgery.

Cornea

In external diseases, radiofrequency is used to treat keratoconus and bullous keratopathy.[11,12,24,30,33-37,40-45]

Cataract surgery

In cataract surgery, radiofrequency is more frequently used to perform anterior capsulorhexis and also posterior capsulorhexis in congenital cataract.[13,14]

Glaucoma

For glaucoma, several studies have shown that radiofrequency can be used to create transconjunctival fistulas in the trabecular meshwork with a device called the trabectome.

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Corresponding author:
José Ricardo Carvalho Lima Rehder
Rua Tucumã 189 apto 92 - Jardim Europa
CEP: 01455-010 - São Paulo/SP, Brazil.

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