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Covid-19 set to change ophthalmology as we know it

Our second issue of 2020 is being published at a strange, unprecedented and unique time in the history of the world due to the current Covid-19 pandemic. This pandemic is changing our world in ways that we could not have imagined. It has practically brought several aspects of our lives to a standstill. Apparently, the ‘Spanish Flu’ after World War One, which killed about 3% of the population of the world, had a similar effect, but most of us or those that we know did not witness that time.

Ophthalmologists are known to be in a high-risk category for contracting Covid-19 because of close contact with patients during eye examination (conjunctival, tear and aerosol secretions). Also, our daily outpatient clinics and theatre lists have high patient volumes. In fact, all healthcare workers in the ophthalmology service, as well as patients, are at risk. Our outpatient clinic waiting rooms are usually crowded, especially with elderly people, many with comorbidities. Most national ophthalmology societies have recommended avoiding any treatment other than urgent or emergent care, in order to reduce virus transmission. It has become common practice to risk assess and postpone outpatient visits and delay elective surgical procedures, having taken individual patient medical and social circumstances into account. The safety of patients and staff is our priority and we face the challenge of achieving a balance between patient risk of significant visual loss without treatment and the increased risk of coronavirus infection from leaving home to attend hospitals and clinics.

It seems that the world, as we know it, will be changing and will probably not be the same again. Measures to maintain physical distancing between patients and staff will be required for a long time to come. This may involve reconfiguring our clinics or offices and will affect appointment scheduling in order to limit the number of patients in waiting areas. All patients will have to be screened for symptoms of Covid-19 before being allowed entry, and testing for Covid-19 may become part of routine presurgical workups. Universal precautions will have to be applied during examinations, special investigations and surgery for the foreseeable future. Travelling to international conferences and other events will most likely be restricted until a vaccine becomes available. Vaccination will probably be a requirement for travel to most countries. Meetings, conferences and even CMSA exams are already moving to the virtual realm and this will most likely continue in future. The WOC scheduled for Cape Town in June this year will now be run on a virtual platform. Face masks will become the order of the day – masks ranging from basic and cheap to personalised and costly will likely become money spinners.

Soon, we will enter the phase when the pandemic subsides. Telemedicine may be more widely adopted for certain tasks. There will still be the need for in-person visits, but numerous changes will have to be implemented. In an interview, glaucoma specialist from New York, Dr Liebmann pointed out that, as examples, pneumotonometers and air-puff tonometers may need to be avoided because they might generate viral particles from the tear film. The use of automated perimetry presents a challenge since the perimetry bowl is a potential source for viral spread and is difficult to clean without causing damage. Equipment manufacturers will have to help with designing new care protocols for their products. Research to develop as well as validate new diagnostic and monitoring paradigms will need to begin. These are just a few of the challenges that we will be facing.

It is coincidental that our review article for this issue is on the topic of the ocular findings of Ebola virus disease. This epidemic caused havoc mainly in West Africa and affected international travel a few years ago. We have also included four other original articles and studies on various topics in this issue.

On another note, regarding the aims that were set for the South African Ophthalmology Journal since mid-2017, namely achieving peer-review status (done by September 2018), DHET accreditation (achieved December 2019) and academic online indexing, we are pleased to report that Google Scholar listing should be achieved with our current issue. The actual process takes 4–6 weeks after publication and if this proves successful, then we will also retrospectively list all our issues that were peer-reviewed on Google Scholar. We now turn our focus to indexing with SciELO, Pubmed/Medline and Scopus, which are more lengthy processes with minimum application times of two years. We thank you for your continued support and encourage you to please increase your valuable submissions to the journal.

The South African Ophthalmology Journal team encourages all our readers to stay safe during the Covid-19 crisis.
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South African Ophthalmology Journal

Guidelines for authors

The SA Ophthalmology Journal is a peer-reviewed scientific journal and the official mouthpiece of the Ophthalmological Society of South Africa. It appears on a quarterly basis.

1. A cover sheet is to be submitted with each manuscript. It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. The main author should include his/her name, address, phone and email address.

2. Articles should be the original, unpublished work of the stated author. All materials submitted for publication must be submitted exclusively for publication in this journal. Written permission from the author or copyright holder must be submitted with previously published figures, tables or articles.

3. The Editor reserves the right to shorten and stylise any material accepted for publication.

4. Authors are solely responsible for the factual accuracy of their work.

5. Articles should be between 2 000 and 3 000 words in length. A 200-word abstract should state the main conclusions and clinical relevance of the article.

6. All articles are to be in English and are to follow the Vancouver style.

7. Abbreviations and acronyms should be defined on first use and kept to a minimum.

8. Tables should carry Roman numerals, I, II etc., and illustrations Arabic numbers 1, 2 etc.

9. References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance. Identify references in the text by Arabic numerals in superscript after punctuation, e.g. ...trial.15

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Articles:

Chapter in a book:

11. Articles are to be submitted by email to the Editor-in-Chief, Prof Nagib du Toit at the following email address: journaleditor@ossa.co.za

The text should be in MS Word. Pages should be numbered consecutively in the following order wherever possible: Title page, abstract, introduction, materials and methods, results, discussion, acknowledgements, tables and illustrations, references.

12. All figures, tables and photographs should also be submitted electronically. Each figure must have a separate self-explanatory legend. The illustrations, tables and graphs should not be imbedded in the text file, but should be provided as separate individual graphic files, and clearly identified. The figures should be saved as a 300 dpi jpeg file. Tables should be saved in a PowerPoint document or also as a 300 dpi jpeg.

13. Authors should declare any interests, financial or otherwise, regarding the publication of their article.

The CPD questions now have to be completed online.

To complete the questionnaire, go to https://www.medicalacademic.co.za/courses/sa-ophthalmology-journal-cpds-autumn-2020
Abstract

Ebola virus disease is a highly virulent infection occurring exclusively and sporadically across various tropical regions of sub-Saharan Africa. In recent years there has been increasing recognition of the pathological effects of Ebola on the human eye. The 2013–2016 West African epidemic cast Ebola into the global spotlight and provided the first real opportunity for sustained clinical research into Ebola-related eye disease. Ocular involvement occurs during both the acute illness and after apparent clinical recovery, affecting thousands of survivors in outbreak zones. A review of published clinical, epidemiological and laboratory-based research is provided and aims to bring all those working in African eye care up to date on what is currently known about the ocular manifestations of Ebola.

Keywords: Ebola virus disease, ocular manifestations, uveitis, ophthalmology, review

Introduction

In 1977, two South African ophthalmologists published a unique report in which a case of unilateral, hypertensive, acute anterior uveitis in a survivor of the 1975 Marburg virus outbreak in Johannesburg was described. Symptoms developed three months after recovery from the initial viral infection and a full uveitis battery of tests was negative. Tissue culture performed on an aqueous sample subsequently revealed live Marburg virus to be the causative agent behind the intraocular inflammation.

Almost 40 years later, a near identical presentation was described in an American physician who contracted Ebola while working in Sierra Leone during the 2013–2016 West African Ebola epidemic. This case has sparked significant interest in the underlying mechanisms of Ebola-related eye disease.

The ocular manifestations of Ebola have been the subject of much research in recent years and provide an interesting perspective on what is undoubtedly a uniquely African pathology.

This article aims to review the available literature and summarise what is currently known about the ocular manifestations of Ebola, including both acute presentation and long-term complications. A discussion of the relevance and implications of these findings, as well as of animal models and laboratory studies that offer some insight into disease pathogenesis, is also presented.

Background

Ebola virus disease (EVD) is a severe, acute illness caused by various species of the genus *Ebolavirus* (EBOV) (Figure 1). Together with Marburg virus, EBOV falls under the *Filoviridae* virus family. EVD is a complex zoonosis with high virulence...
in human hosts. Fruit bats are thought to be the natural viral reservoir, and introduction into human populations is facilitated by close contact with a variety of infected animals, including non-human primates, fruit bats and certain antelope.\textsuperscript{3} Human-to-human transmission occurs through direct contact with bodily fluids of infected individuals.

After an incubation period of 2–21 days, the disease typically presents as an acute influenza-like illness, followed by severe gastrointestinal symptoms with associated dehydration and hypovolaemia. Neurological involvement and haemorrhagic complications follow, with progression to multi-organ dysfunction and death, usually within two weeks. The average case fatality rate is approximately 50%.\textsuperscript{4}

EVD was first described in 1976 following simultaneous outbreaks in Nzara, Sudan and Yambuku, Zaire (now the Democratic Republic of Congo). Between 1976 and 2013, 23 sporadic outbreaks occurred in various tropical regions of sub-Saharan Africa, involving 2 345 laboratory-confirmed cases and 1 546 deaths.\textsuperscript{4} The 2013–2016 West African epidemic was by far the largest outbreak to date, with more than 28 600 documented cases and 11 300 deaths, occurring predominantly in Sierra Leone, Guinea and Liberia.\textsuperscript{5} The recent outbreak in the Democratic Republic of Congo is recognised as the second largest EVD outbreak in recorded history (Figure 2).\textsuperscript{6}

### Acute presentation

When considering the acute ocular manifestations of EVD, it is important to note that most outbreaks have occurred in rural and/or under-resourced settings, with limited availability of equipment and personnel trained in ophthalmic examination. Given the severity of the disease, as well as the high risk of transmission that would be associated with conducting such an examination, it is not surprising that data on acute eye disease are extremely limited.

The most common acute ocular sign reported is that of bilateral red or injected eyes. This is variably described as ‘conjunctivitis’, ‘conjunctival injection’, ‘conjunctival haemorrhage’, or simply as ‘redness’ or ‘injection’.

Early studies conducted during the 1976 Yambuku\textsuperscript{7} and 1995 Kikwit\textsuperscript{8} outbreaks found the prevalence of red/injected eyes in EVD cases to be 43–51%. More recent results from the West African epidemic, however, report prevalence of 30–34%.\textsuperscript{9–12}

### Clinical significance

Given the various challenges described above, the precise clinical implication of acutely red eyes in EVD is still uncertain. Possible explanations include one or more of the following:

- **Conjunctivitis:** Primate models have demonstrated EBOV immune-positivity in conjunctival tissue\textsuperscript{13} and EBOV RNA can be detected by reverse transcription polymerase chain reaction (RT-PCR) assays of human conjunctival swabs.\textsuperscript{14} Thus, red eyes in the acute setting may represent a direct viral conjunctivitis, similar to that seen in other systemic viral infections, like measles.

- **Uveitis:** Alternatively, red eyes may indicate the presence of intraocular inflammation. EVD survivors are at increased risk of uveitis during convalescence,\textsuperscript{15–20} while evidence of intraocular inflammation and EBOV immune-positivity of uveal tissue has been demonstrated on necropsy of EBOV-infected rhesus macaques.\textsuperscript{21,22} EVD-associated uveitis is discussed in more detail later in the paper.

- **Conjunctival haemorrhage:** Conjunctival bleeding, another possible cause for red eyes, has also been described.\textsuperscript{23,24} This may be due to direct viral infection of the conjunctiva (similar to acute haemorrhagic conjunctivitis seen with coxsackievirus and enterovirus); secondary to associated vomiting; or represent an underlying bleeding

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**Figure 1. Transmission electron micrograph of an Ebola virus virion**  
Source: CDC Global. Ebola virus [Internet]. 2014 (cited 31 March 2020). Available at: https://flickr.com/photos/cdcglobal/14907212221. [Creative Commons Agreement CC BY 2.0]

**Figure 2. Ebola virus disease outbreaks in Africa by species and size (1976–2020)**  
diathesis, which may develop in the late stages of the disease.

- Keratitis/scleritis: EBOV immune-positivity has also been demonstrated in corneal and scleral tissue of primate models, suggesting that viral involvement of the outer coat of the eye may also be responsible for the observed acute ocular manifestations (Figure 3).

Regardless of the underlying aetiology, acutely red eyes in the context of EVD has been shown to have numerous important clinical implications.

During the 1995 Kikwit outbreak, bilateral conjunctival injection was noted to be an early sign (together with maculopapular rash and sore throat) suggestive of acute EVD. Presence of conjunctivitis during the West African outbreak was found to be significantly associated with a confirmed EVD diagnosis. The predictive value of conjunctivitis was further improved when used in combination with other ‘major symptoms’ of EVD (confusion, intense fatigue, hiccups, diarrhoea and vomiting). Although often limited by small sample size, most studies show a trend towards a higher frequency of conjunctivitis in EVD fatalities compared with survivors, with one study reporting a significant association between conjunctivitis and death.

Survivors were also found to be ten times more likely to develop subsequent uveitis if they presented with red/injected eyes in the acute setting.

### Pathophysiology

The significance of these findings may be explained by scientific insights into the pathophysiology of EBOV infection.

After host entry, EBOV is able to rapidly infect a variety of cell types and tissues, with highly efficient intracellular replication and a high peak viraemia. In animal models, when death occurs during this acute phase of illness, typical targets identified on histological examination include the liver, spleen, adrenals and lymph nodes. However, when death is delayed, the virus appears to be cleared fairly rapidly from these primary sites and develops tropism for secondary sites, including the eyes and brain.

It is proposed that barriers to EBOV entry into these secondary organs are overcome by prolonged duration of infection or by a high viral load. A higher EBOV viral load has indeed been shown to be independently associated with the subsequent development of new ocular symptoms or diagnoses in a cohort of West African EVD survivors. A high EBOV viral load has also been shown to be a risk factor for death, possibly accounting for the observed association between red eyes and death in EVD.

Recent non-human primate models suggest that EBOV may gain access to the eye via the blood vessels of the choroid and optic nerve leptomeninges, with subsequent progressive involvement of the uvea, sclera, retina and vitreous over time. This suggests that acute ocular disease in EVD may in fact be a dynamic process with involvement of various and/or multiple ocular structures, depending on the temporal course of viral infection.

EBOV has also been shown to persist within the eye and other immune-privileged sites of the body (specifically the brain and testes), despite apparent clinical recovery and clearance from other tissues. This viral persistence may be in part responsible for the chronic sequelae of EVD, including the long-term ocular manifestations of the virus. Retinal pigment epithelial (RPE) cells and CD68+ vitreous macrophages/monocytes have been identified as potential intraocular reservoirs of EBOV. Importantly, EBOV-infected RPE cells exhibit a robust type-1 interferon response and continue to express multiple immunomodulatory molecules linked to ocular immune privilege, which may contribute to the persistence of live virus within the eye.

### Long-term complications

**Post-EVD syndrome**

EVD survivors are at increased risk for the development of a number of chronic medical sequelae in the months and years following acute infection. These long-term complications, termed the post-EVD syndrome (PEVDS), include a multitude of ocular, rheumatological and neuropsychiatric conditions, and are responsible for significant post-convalescent morbidity. Although better characterised in recent years, the exact pathogenesis of PEVDS remains unclear. Proposed hypotheses include molecular mimicry, viral persistence with direct tissue damage, and elevated inflammatory cytokines. With more than 17 000 survivors of the 2014–2016 West African outbreak, PEVDS poses a significant public health burden.

**Ocular disease**

Post-convalescent eye-related complaints

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*Figure 3. Diffuse immunopositive staining demonstrating the presence of Ebola virus in the cornea of a rhesus macaque*

*Adapted from: Larsen T, Stevens EL, Davis KJ, Geisbert JB, Daddario-DiCaprio KM, Jahrling PB, et al.*

are extremely common, affecting up to 76% of EVD survivors.\textsuperscript{19} Frequently described symptoms include blurry vision, photophobia, tearing, pain, redness, floaters and foreign body sensation.\textsuperscript{16,18,29,37} These have been documented to begin as early as two weeks post-recovery and in some cases, while still receiving acute critical care for EVD,\textsuperscript{18} suggesting at least some degree of overlap with the acute ocular disease process. Follow-up of survivors of the West African outbreak has shown that symptoms may persist for up to two years after recovery\textsuperscript{18} but may prove to be far longer as results from ongoing prospective studies become available.

**Uveitis**

Numerous studies have shown post-convalescent uveitis to be the most well-documented ophthalmic manifestation of PEVDS, affecting 13–34% of EVD survivors.\textsuperscript{18,20,33} Diagnosis occurs on average 53–64 days post discharge from an Ebola treatment unit (ETU)\textsuperscript{20} but has been documented to occur after as long as 13 months post negative EBOV serology.\textsuperscript{17} Conversely, in many survivors, symptoms of uveitis were already present at the time of ETU discharge.\textsuperscript{17}

Established risk factors include higher EBOV viral load\textsuperscript{20} and conjunctival injection\textsuperscript{39} during the acute illness, as well as younger age and longer ETU admission.\textsuperscript{19}

Although unilateral anterior uveitis appears to be the predominant disease entity, there is significant variability in clinical presentation: uveitis may occur bilaterally; and intermediate-, posterior-, and panuveitis have all been documented to occur at varying frequencies (Figure 4).\textsuperscript{18,20} Relapses can occur, sometimes as long as a year after initial presentation.\textsuperscript{17}

Although EVD-associated uveitis is well described, the exact pathological mechanisms behind the intraocular inflammation remain unclear. Proposed theories include viral persistence with direct cytotoxic effects; an inflammatory response to live virus or residual viral antigens; and autoimmune-mediated mechanisms.

Live, actively replicating EBOV has been cultured from the eye of an American physician who developed a unilateral hypertensive acute anterior uveitis (with subsequent progression to a sight-threatening panuveitis) 14 weeks after apparent recovery from acute EVD.\textsuperscript{2,17} Both conjunctival swabs and peripheral blood specimens tested negative for EBOV RNA on RT-PCR testing, suggesting isolated intraocular viral persistence.

Parallels can be drawn with infectious uveitis syndromes caused by *Herpesviridae*, in which clinical manifestations are known to be directly caused by active viral replication.\textsuperscript{29} However in a recent study, ocular fluid samples from 50 EVD survivors with either active uveitis or uveitic cataracts all tested negative for EBOV on RT-PCR,\textsuperscript{37} suggesting the possibility of a variety of pathological processes underlying EVD-associated uveitis.

**Visual outcomes**

Structural complications secondary to intraocular inflammation account for significant visual morbidity in EVD survivors. Documented sequelae include keratic precipitates, band keratopathy, posterior synchiae, uveitic cataract, vitreous opacities, macular oedema, chorioretinal scars, tractional retinal detachment and phthisis bulbi.\textsuperscript{70,72,37} Visual acuity (VA) in affected eyes was <3/60 in 38% of participants in a Liberian study conducted in the first year of the West African outbreak.\textsuperscript{18} In a study conducted one to two years later however, more than 70% of affected eyes had a VA <3/60, with a median VA in affected eyes of logMAR 3 (Snellen equivalent: hand movements),\textsuperscript{37} highlighting the public health need for appropriate, early interventions to prevent progressive visual morbidity in populations after EVD outbreaks.

**Cataracts**

Lens opacification has been shown to occur following EVD-associated uveitis and at a higher frequency than uninfected matched controls (Figure 4).\textsuperscript{17,18,20,35,37} Safety concerns about the infection transmission risks associated with performing intraocular surgery in these cases have been raised. However, EBOV has not yet been detected in ocular fluid samples of any EVD survivor with cataracts;\textsuperscript{22,33} and the recent EVICT study has shown manual small incision cataract surgery to be a safe and effective intervention in such cases, with excellent visual outcomes and no concerns about EBOV transmission.\textsuperscript{37}

**Neuro-ophthalmological sequelae**

A variety of different retinal lesions...
have been documented to occur in EVD survivors. However, given the high background rate of viral, parasitic and fungal disease in study populations (most notably toxoplasmosis and onchocerciasis), it is difficult to attribute causality to EBOV. A novel retinal lesion, which follows the anatomic distribution of optic nerve axons, has been reported to be specific to EVD survivors and suggests that neuronal transmission via the optic nerve may be a route of ocular entry (Figure 5). This is supported by primate models, which demonstrate EBOV immune-positivity in perioptic tissue; and by a recent study in which EVD survivors were found to have a significantly higher frequency of optic disc swelling and colour vision deficits than controls.

EVD-associated meningo-encephalitis has also been reported in numerous previous outbreaks and EVD survivors have been shown to be affected by a multitude of residual neurological deficits. Up to two-thirds show impairment of pursuits and saccades after recovery; and various other neuro-ophthalmological manifestations, including optic neuropathy, nystagmus, Argyll Robertson pupils, internuclear ophthalmoplegia, homonymous hemianopia and cranial nerve palsies have all been described. Magnetic resonance imaging (MRI) of a healthcare worker with acute EVD and nervous system involvement has suggested that microvascular ischaemia and occlusion may be the pathophysiological basis for some of these signs.

Other manifestations
Less frequently described ocular manifestations documented during prospective follow-up of EVD survivors include interstitial keratitis and episcleritis, although whether these represent true ocular manifestations of EBOV or incidental findings remains unclear.

Ongoing studies
The PREVAIL III study is an observational natural history cohort study of Liberian EVD survivors and their close contacts. Follow-up is planned for five years and includes an ophthalmological sub-study. Early results have already been presented and it is hoped that the study will continue to provide further insights into EVD-associated eye disease.

Conclusion
EVD outbreaks continue to pose an ongoing threat to various regions of sub-Saharan Africa. Although outbreaks are often isolated and relatively small in magnitude, they have the potential to escalate to epidemics of global public health significance if not adequately contained.

The acute ocular manifestations of EVD remain poorly defined but may represent a spectrum of virus-associated ocular inflammation affecting a multitude of tissue types and structures. Further research is needed to better elucidate the precise mechanisms underlying acute eye involvement, as well as the feasibility and benefit of ophthalmic treatment in the acute setting of EVD.

Post-convalescent uveitis represents the most significant chronic ocular complication of EVD. If left untreated, the various structural complications of intraocular inflammation lead to significant visual morbidity and pose a significant public health burden to affected populations after EVD outbreaks. Further advances in our understanding of the disease process may lead to targeted therapeutics in the future.

It remains to be seen whether the 2013–2016 West African EVD epidemic was a harbinger of future large-scale outbreaks and ongoing ophthalmological research, or whether advances in EVD prevention, containment and treatment relegate EVD-associated eye disease to an interesting footnote in the annals of ophthalmology.

References

Figure 5. Novel retinal lesion following distribution of optic nerve axons: a) illustration of axon distribution, b) example, right eye


A prospective analysis of infectious keratitis at a tertiary facility in South Africa

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Abstract

Background: The aim of the study was to determine the microbial profile of infectious keratitis and the frequency of viral and bacterial co-infection in these cases.

Materials and methods: A prospective study included 57 patients with microbial keratitis. Corneal scrapings were sent for microscopy, culture and sensitivity (MCS) and herpes virus polymerase chain reaction (PCR) testing.

Results: Males (64.9%) were predominantly affected by infectious keratitis. A positive microbial culture was obtained in 24 of 57 cases (42.1%). Sixteen patients had positive herpes virus PCR results (28.1%) with 21 viruses identified from the 16 samples. Five patients with a positive viral PCR result had more than one virus identified on PCR testing (31.3%). A viral cause of infectious keratitis was suspected clinically before corneal scraping in 11 of 16 patients (68.7%) with a positive viral PCR result.

Conclusion: In our setting, polymicrobial infection is common in patients presenting with infectious keratitis. Viral and bacterial co-infection can be predicted clinically and should prompt clinicians to perform additional sampling for laboratory diagnosis of herpes viruses.

Keywords: infectious keratitis, viral PCR, mixed bacterial and viral infections

Funding: No funding received for this work.

Conflict of interest: The authors declare that they have no competing interests to declare with regard to this study.

Introduction

Infectious keratitis is an infection of the cornea that may be associated with an epithelial defect and signs of inflammation. It can potentially lead to severe visual dysfunction and is considered a leading cause of monocular blindness in the developing world. Infectious keratitis can be suppurative or non-suppurative. Suppurative keratitis is frequently caused by bacteria and fungi, while the aetiology of non-suppurative infectious keratitis could be viral, spirochaetal, parasitic or immune-related stromal necrosis.

Trauma is a common cause of corneal ulceration in adults in the developing world and accounts for up to 60% of cases developing a corneal ulcer. Superficial corneal trauma frequently leads to corneal abrasions that can rapidly progress to corneal ulceration which mostly heals with scarring and may result in permanent vision loss. Polymicrobial keratitis has been widely reported and occurs quite commonly. Effective treatment requires a prompt laboratory diagnosis to accurately identify the causative pathogen/s and minimise complications that may arise from misdiagnosis and inappropriate treatment.

The epidemiology of infectious keratitis is influenced by predisposing risk factors, climatic and geographic factors as well as seasonal variations. In developing countries, most patients with infectious keratitis do not receive medical care due to poor access to medical facilities, lack of awareness about the gravity of their condition and poverty. Herpes viruses are known to cause recurrent and devastating keratitis in developed countries. Limited data is available from African countries about herpes keratitis and diagnosis is often solely based on clinical presentation. In Africa, severe geographic or stromal ulceration presumed to be due to herpes simplex virus (HSV) on account of its morphological appearance and response to specific antiviral therapy, appears to be a common cause for ocular morbidity.

Limited data is available regarding the aetiology of infectious keratitis in South Africa as well as the rest of Africa.

Materials and methods

Patients who presented to the eye clinic at Tygerberg Hospital were prospectively included in the study if they met the...
inclusion criteria and provided informed consent. The inclusion criteria were: 1) corneal ulceration clinically considered to be infectious in origin; 2) epithelial defects measuring at least 1 mm at their greatest width; 3) some portion of the infiltrate involving the cornea; and 4) participants had to be 16 years or older. Clinical signs that were considered indicative of an infectious origin included large epithelial defects, stromal infiltrates, corneal thinning, anterior chamber reaction and hypopyon. Patients with clinically presumed isolated viral keratitis were not included in the study.

Clinical evaluation consisted of taking a complete history and slit-lamp evaluation which included measuring the size of both the epithelial defect and stromal infiltrate horizontally and vertically. Examination was followed by preliminary clinical classification of infectious keratitis as bacterial (Gram positive, Gram negative or mixed), viral, fungal or protozoan.

After instillation of topical anaesthetic (oxybuprocaine 0.4%), separate corneal scrape biopsies were placed on a glass slide for microscopy as well as on growth media including Saboraud, blood and chocolate agar plates. An additional scrape was performed and placed in a sterile saline specimen holder for herpes virus polymerase chain reaction (PCR) testing. Corneal scrapes were performed using a new calcium alginate swab for every scrape.

The slide and plates were evaluated in the laboratory and underwent microscopy, culture and sensitivity (MCS) testing as per routine investigation. PCR testing was carried out on all samples to evaluate for the presence of human herpes viruses 1–6. Samples were processed by the National Health Laboratory Service Medical Microbiology and Virology laboratories, Tygerberg Hospital. Herpes virus testing was performed by pulse vortexing corneal swabs in saline for 30 seconds, followed by nucleic acid extraction on the NucliSENS EasyMag platform (bioMérieux, Marcy l’Etoile, France) and multiplex PCR for six human herpes viruses (HSV-1, HSV-2, VZV, EBV, CMV and HHV-6) with the Seeplex Meningitis ACE Detection assay (Seegene Inc., Seoul, Korea).

Patient care followed our standard protocol including antimicrobial therapy modified according to response to therapy, clinical opinion and test results. Informed consent was obtained from all patients. The study adhered to the principles of the Declaration of Helsinki and was approved by the Health Research Ethics Committee (IRB0005239) at Stellenbosch University.

### Results

**Laboratory analyses**

A total of 57 patients with a clinical diagnosis of infectious keratitis were included in the trial, of which 37 were male (64.9%). The mean age at presentation was 44.4 years (range 17–79).

**MCS results**

Samples for MCS and PCR were collected from all 57 participants in the study. A positive culture was obtained in 24 cases (42.1%) while the remaining 33 cases (57.9%) were culture negative. In the 24 culture positive cases, a total of 27 organisms were cultured (Table I). *Pseudomonas* species (14.82%) and *Moraxella* species (14.82%) were the most frequently isolated Gram-negative organisms while *Staphylococcus aureus* (22.2%) was the most frequently isolated Gram-positive organism. *Candida albicans* and a *Penicillium* fungus were isolated in one case each. In three of the culture positive cases two different organisms were isolated as illustrated in Table II.

Seven of 24 culture-positive patients (29.2%) were found to have a herpes virus infection.

### Table I: Organisms isolated and relative frequencies

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of isolates (n=27)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-negative organism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas species</em></td>
<td>4</td>
<td>14.82</td>
</tr>
<tr>
<td><em>Moraxella species</em></td>
<td>4</td>
<td>14.82</td>
</tr>
<tr>
<td><em>Staphylococcus haemolyticus</em></td>
<td>2</td>
<td>7.41</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>2</td>
<td>7.41</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>1</td>
<td>3.70</td>
</tr>
<tr>
<td><strong>Gram-positive organism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>6</td>
<td>22.22</td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em></td>
<td>3</td>
<td>11.11</td>
</tr>
<tr>
<td><em>Corynebacterium species</em></td>
<td>2</td>
<td>7.41</td>
</tr>
<tr>
<td><em>Streptococcus group G</em></td>
<td>1</td>
<td>3.70</td>
</tr>
<tr>
<td><strong>Yeast</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>1</td>
<td>3.70</td>
</tr>
<tr>
<td><strong>Filaments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Penicillium species</em></td>
<td>1</td>
<td>3.70</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>27</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table II: Summary of patient characteristics and combination of organisms in the polymicrobial infection group

<table>
<thead>
<tr>
<th>Case</th>
<th>Age in years/Sex</th>
<th>Organisms cultured</th>
<th>HIV status</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39/F</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Negative</td>
<td>Contact lens wear</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Stenotrophomonas maltophilia</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18/M</td>
<td><em>Streptococcus group G</em></td>
<td>Negative</td>
<td>Allergic keratoconjunctivitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>49/F</td>
<td><em>Haemophilus influenzae</em></td>
<td>Negative</td>
<td>Entropion</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table III: Summary of patient characteristics and combination of organisms in the bacterial and viral co-infection group

<table>
<thead>
<tr>
<th>Case</th>
<th>Age in years/Sex</th>
<th>Organism cultured</th>
<th>Virus</th>
<th>HIV status</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53/M</td>
<td><em>Staphylococcus aureus</em></td>
<td>CMV</td>
<td>Positive</td>
<td>Previous HSV keratitis</td>
</tr>
<tr>
<td>2</td>
<td>18/M</td>
<td><em>Streptococcus group G</em></td>
<td>EBV</td>
<td>Negative</td>
<td>Allergic keratoconjunctivitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>26/M</td>
<td><em>Corynebacterium</em></td>
<td>EBV</td>
<td>Negative</td>
<td>Trauma</td>
</tr>
<tr>
<td>4</td>
<td>34/F</td>
<td><em>Corynebacterium</em></td>
<td>VZV</td>
<td>Positive</td>
<td>Previous herpes zoster opthalmicus</td>
</tr>
<tr>
<td>5</td>
<td>42/F</td>
<td><em>Staphylococcus aureus</em></td>
<td>VZV</td>
<td>Negative</td>
<td>Neurotrophic cornea</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>EBV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>74/M</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>CMV</td>
<td>Negative</td>
<td>Corneal exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>EBV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>36/M</td>
<td><em>Staphylococcus haemolyticus</em></td>
<td>HSV1</td>
<td>Positive</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Infectious keratitis
In our study, a positive bacterial culture for at least one organism occurred in 42.1% of corneal scrapes. Positive culture results have been reported in 38–86% of cases in similar studies. The most likely explanation for the lower positive culture rate in our study is that a large proportion of patients presenting to our tertiary facility are partially treated by the time they presented to our clinic. Antibiotic use prior to presentation to an ophthalmologist in developing countries has been reported in up to 58% of patients presenting to tertiary institutions.

Gram-negative organisms were slightly more prevalent than Gram-positive organisms as a cause of infectious keratitis accounting for 48.2% of positive cultures. Schaftenaar et al. reported predominantly Gram-positive organisms (68%) to be the causative organism in a similar study recently conducted elsewhere in South Africa.

*Stenotrophomonas maltophilia* is rarely implicated in microbial keratitis but has been reported to be the causative organism in 1.4% of cases presenting with microbial keratitis by Wu et al. A high rate (57%) of polymicrobial infection has been demonstrated in patients with *Stenotrophomonas maltophilia* keratitis, making it hard to determine the clinical significance of the organism. In our study, it was identified as the causative organism in two (8.3%) of 24 patients with a positive culture, one of which was a case of polymicrobial keratitis.

Fungi were responsible for 7.4% of all culture-proven samples, corresponding to findings from a similar study recently reported from South Africa that cultured fungi in 3.4% of cases. However, this is in sharp contrast to studies from Ghana and Tanzania that reported fungi as the causative pathogen in up to 50% of keratitis cases.

The most likely explanation for the markedly lower rate of fungal keratitis in South Africa compared to other regions in Africa is the difference in climate as it is well known that fungal keratitis is much more prevalent in tropical or subtropical areas.

More than one organism was isolated in 12.5% of culture-positive samples. Polymicrobial infection has been reported to occur in 33% of positive culture results in a similar study. Lim et al. found that older age and larger sized corneal infiltrates were commonly associated with polymicrobial keratitis. In our study, all three patients with polymicrobial infection were younger than 50 years of age and, contrary to what one would expect, also HIV negative. It was also found that polymicrobial keratitis more often has a prolonged course of disease and decreased antibiotic sensitivity. Combination therapy with fortified antibiotics covering both Gram-positive and Gram-negative organisms, which is the

### Viral PCR results

Sixteen patients (28.1%) had a positive herpes virus PCR result; the remaining 41 (71.9%) were PCR negative.

In total there were 21 viruses identified from the 16 samples. HSV1 accounted for almost half of the viruses identified as ten of 21 (47.6%) PCRs were HSV1 positive. VZV was only responsible for two (9.5%) of the positive PCR positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRS were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for ten of 21 (47.6%) PCRs were HSV1 positive. EBV accounted for six (28.6%) and CMV for two (9.5%) of the positive PCR positive. VZV was only responsible for seven of 21 (33.3%) PCRs were HSV1 positive. EBV accounted for five (23.8%) and CMV for two (9.5%) of the positive PCR positive.

### Table IV: Summary of patient characteristics and combination of herpes viruses positive on PCR

<table>
<thead>
<tr>
<th>Case</th>
<th>Age in years/Sex</th>
<th>Virus</th>
<th>HIV status</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46/F</td>
<td>HSV1</td>
<td>Negative</td>
<td>Previous HSV keratitis</td>
</tr>
<tr>
<td>2</td>
<td>39/M</td>
<td>VZV</td>
<td>Positive</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>53/M</td>
<td>HSV1</td>
<td>Positive</td>
<td>Foreign body</td>
</tr>
<tr>
<td>4</td>
<td>42/F</td>
<td>VZV</td>
<td>Negative</td>
<td>Neurotrophic cornea</td>
</tr>
<tr>
<td>5</td>
<td>74/M</td>
<td>CMV</td>
<td>Negative</td>
<td>Cornea exposure</td>
</tr>
</tbody>
</table>

### Discussion

In our study, a positive viral PCR test result (Table III). Of the 33 MCS-negative patients, nine (27.3%) had a positive PCR test for one or more of the herpes viruses. Epstein-Barr virus (EBV) was detected in four samples, Cytomegalovirus (CMV) and Varicella-Zoster virus (VZV) were each detected in two samples and herpes simplex virus 1 (HSV-1) was present in one sample.

Figure I. Herpes viruses identified by PCR testing

![Figure I. Herpes viruses identified by PCR testing](image-url)

### Table IV: Summary of patient characteristics and combination of herpes viruses positive on PCR

<table>
<thead>
<tr>
<th>Case</th>
<th>Age in years/Sex</th>
<th>Virus</th>
<th>HIV status</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46/F</td>
<td>HSV1</td>
<td>Negative</td>
<td>Previous HSV keratitis</td>
</tr>
<tr>
<td>2</td>
<td>39/M</td>
<td>VZV</td>
<td>Positive</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>53/M</td>
<td>HSV1</td>
<td>Positive</td>
<td>Foreign body</td>
</tr>
<tr>
<td>4</td>
<td>42/F</td>
<td>VZV</td>
<td>Negative</td>
<td>Neurotrophic cornea</td>
</tr>
<tr>
<td>5</td>
<td>74/M</td>
<td>CMV</td>
<td>Negative</td>
<td>Cornea exposure</td>
</tr>
</tbody>
</table>
standard of treatment for corneal ulcers at our facility, covers a wide spectrum of organisms and should effectively treat a polymicrobial infection under most circumstances.

Our study focused on patients with presumed bacterial infection or suspected bacterial and viral co-infection. We therefore did not perform corneal scrapes when patients were clinically presumed to have isolated viral keratitis. Viral keratitis was proven by PCR testing in 29.2% of the 24 patients with proven microbial keratitis. Data on viral and bacterial co-infection in patients with infectious keratitis is limited. Twenty-eight per cent of the total sample size had a positive herpes viral PCR result, and 31.3% of these samples showed more than one herpes virus present on PCR testing. HSV keratitis occurs commonly with presumed microbial keratitis but either co-infection by different bacteria or co-infection by bacteria and herpes viruses and the latter has important implications for successful therapeutic outcomes.

Take-home messages
• Roughly 40% of corneal scrapes had positive culture results.
• Gram-positive and Gram-negative infections were evenly distributed.
• Fungi causes <10% of corneal infections.
• Polymicrobial infections may occur in HIV-negative patients.
• 29% of patients with culture-positive microbial keratitis had viral co-infection.

Availability of data and material
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References
Corneal grading system for post-operative assessment of manual small incision cataract surgery (MSICS)

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Abstract

Background: The post-operative assessment of corneal clarity is widely used to assess the quality of cataract surgical techniques. This is best done with a slit lamp, optical coherence tomography or endothelial photography. In settings where a slit lamp is not available, the assessment of corneal oedema still plays an important part of post-operative evaluation, particularly when teaching surgery.

Methods: We developed a system of corneal assessment, which could be used in the absence of a slit lamp to help in the evaluation of patients following manual small incision cataract surgery (MSICS). A hand-held white light source was used to grade corneal clarity from 0–4.

Results: A total of 74 patients were observed day 1 post-surgery. There were 49 women and 25 men, with an average age of 70.8 years (SD 10.7, 95% CI 2.4). Median pre-operative visual acuity was perception of light, improving to 6/36 one day post-surgery. Patients had an average corneal clarity grade of 1.04 (SD 1.02, 95% CI 0.23). Twenty-eight patients had no oedema, 30 had grade 1, nine had grade 2, seven had grade 3 and one had grade 4.

The observers agreed in 81% of readings, with a kappa linear weighting score of 0.85 (95% CI 0.75–0.92).

Conclusion: A rapid method of assessment of corneal clarity was found to be a reliable and consistent tool for the post-operative assessment of cataract surgery. The inter-observer agreement was high and could be used to monitor the quality of cataract surgery in a learning environment.

Keywords: cataract, MSICS, corneal clarity, corneal oedema

Funding: No funding was sought for this study.

Conflict of interest: The authors declare no conflicting interests with regard to this study.

Introduction

Manual small incision cataract surgery (MSICS) has been widely used since the 1990s as a safe, cost-effective method of cataract surgery. Several authors have highlighted the importance of good technique to achieve the best outcomes. MSICS is particularly effective for white, hyper mature, and brunescent cataracts, prevalent in the developing world context.

In the hands of the experienced surgeon, the incidence of complications is low, comparing well to phacoemulsification but with a slightly higher incidence of astigmatic errors which can be reduced with appropriate surgical technique and the potential for post-operative wound leak.

The importance of meticulous technique to reduce post-operative corneal oedema has been described. Several clinical grading systems have been developed to assess the cornea following cataract surgery. Some depend on simple clinical descriptions, others on a series of standard images, and some on imaging techniques such as optical coherence tomography (OCT) or performing endothelial cell counts. These techniques are often heavily dependent on equipment and skilled personnel, both of which may be lacking in a hospital with limited resources in the developing world.

To assess corneal clarity in a context where slit-lamp assessment was not available, we developed a system of grading corneal oedema for post-MSICS patients that was both clinically sensitive and rapid. The technique relies on hand-held ocular illumination to assess corneal oedema by assessing the clarity of the corneal and intraocular lens (IOL) Purkinje images. We felt it could be helpful in assessing our post-operative patients, and optimistic that it was a robust and consistent method of assessment, and therefore useful in training ophthalmic surgeons. This study was designed to assess the sensitivity and reproducibility of a unique grading technique to determine its usefulness for ophthalmic surgeon training.

Methods

Seventy-four patients were admitted to the Nelson Mandela Academic Hospital,
Mthatha, for cataract surgery during a training week for MSICS surgery. Patient demographics, age and sex were recorded. The median pre-operative and post-operative visual acuity were recorded. Ten surgeons performed the cataract surgery, including two visiting consultants, three permanent consultants and five registrars. Patients with pre-existing corneal disease were noted and excluded from the data set.

Visual acuity and corneal clarity were assessed. A handheld light-source (P5 Lensar, Solingen) emitting diode (95 lumens) was used to assess post-operative corneal clarity. The light was held 10 cm from the temporal limbus to assess corneal clarity (position 1) and then 10–20 cm in front of the patient (position 2) to assess the corneal and IOL Purkinje images and the clarity of iris detail.

Grade 0 corneal clarity was given if both the corneal and the IOL reflexes were bright and clear with absolutely no sign of haze or loss of clarity of the iris detail in both positions 1 and 2.

Grade 1 was given for a trace corneal haziness either focal or generalised in position 1 and/or trace reduction of the corneal light reflex in position 1.

Grade 2 was given if the cornea was clearly hazy or if any Descemet’s membrane (DM) folds were noted in position 1, or if the IOL reflex was dimmed with mild loss of iris features in position 2.

Grade 3 was given for severe corneal haze in position 1 and/or for poor corneal and IOL reflexes, definite DM folds/corneal striae, and loss of iris features in position 2.

Grade 4 corneal oedema was in very severe generalised corneal oedema in position 1 with little or no corneal or IOL reflexes visible. Little or no iris or anterior segment features were noted in position 2.

A summary description is presented in Table I.

### Table I: Grading for post-MSICS corneal oedema

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Clear cornea</td>
</tr>
<tr>
<td>1</td>
<td>Hazy cornea</td>
</tr>
<tr>
<td>2</td>
<td>Foggy cornea/DM folds/striae, poor IOL reflex</td>
</tr>
<tr>
<td>3</td>
<td>Cloudy cornea/DM folds/striae, poor IOL reflex, loss of iris detail</td>
</tr>
<tr>
<td>4</td>
<td>Opacified cornea/DM folds/striae, poor IOL reflex, no iris detail, poor pupillary detail</td>
</tr>
</tbody>
</table>

Statistical methods

The mean age (standard deviation/SD) was calculated for men and women, post-operative vision was recorded, and a weighted kappa statistic was calculated for agreement between two observers. The proportion of agreement between the two observers was also assessed for each grade of corneal oedema, and the grade was compared with the age of the patient using the unpaired one-tailed t-test.

**Results**

Demographic results showed the female to male ratio to be 2:1. The average age of patients was 69.2 years (SD 11.2) for men and 71.2 years (SD 10.3) for women. The median pre-operative visual acuity was perception of light (PL), and post-operatively the median visual acuity was 6/36. The vision improved in 95% of patients, with 42% achieving better than 6/24 vision on the first day (Figure 1).

**Corneal grading**

Of the total, 70.2% of patients scored between 0 and 1, 21% between 2 and 3, and one patient scored a grade of 4. The average score for corneal oedema was 1.04 (SD 1.02, 95% CI 0.23). Patients under 70 years were found to have less corneal oedema (0.79, SD 0.94, 95% CI 0.36) than those over 70 years (1.20, SD 1.02, 95% CI 0.29), p<0.05. This may relate to pre-operative endothelial cell counts.

The observers agreed in 81% of readings with a kappa linear weighting score of 0.85 (95% CI 0.75–0.92). Inter-observer agreement was calculated for

---

**Figure 1. Pre-operative Snellen visual acuity results one day post-surgery**
the different grades of corneal oedema. Excellent agreement was found for grade 0 and grade 3 corneas; the worst agreement was seen for grade 2 and grade 4 corneas (Table II).

Discussion

MSICS is rapidly becoming established as an efficient and safe method of removing cataracts in patients with mature cataracts. Several controlled trials have shown that the incidence of corneal oedema is similar to or lower than other techniques such as phacoemulsification or extra-capsular cataract surgery. There is little literature on techniques of grading corneal clarity in MSICS patients. The importance of rapid visual rehabilitation following surgery is vital in developing acceptance of cataract surgery among poorer socio-economic groups in developing nations, and assessment of individual surgeon outcomes is critical to continuously improve the quality of surgery. MSICS has the ability to deliver rapid visual rehabilitation for patients, if meticulous attention to detail is maintained. It is particularly important that good unaided vision is delivered rapidly to the majority of patients, as patient confidence is often low in rural communities and cataract surgery rates decline due to fears of complications.

The degree of post-surgery corneal oedema is an important indicator of endothelial stress post-surgery and as such is an important observation when changing or learning new cataract surgery techniques. We have found that audit of corneal clarity and measurement of visual acuity on day 1 post-operative patients provides a useful measurement of the overall safety and effectiveness of the cataract surgical system. In addition, specific problem areas may be identified such as the use of inappropriate techniques, medications or instruments based on patterns of complications in large numbers of patients.

This simple, unique method of grading of post-operative corneal oedema gives useful clinical information post-surgery with minimal (18%) inter-observer error. A high kappa score of 0.85 supports the possibility that this could be widely and consistently used. Most of the patients scored in the 0–1 grade with only 17 out of 74 patients having a grade of 2 or more. In our study, grade 3 and grade 4 outcomes were rare.

The use of a day 1 review may not be useful for routine surgery; giving early feedback to the trainee surgeon is important during the development of new techniques and skills. We hope that this will be a useful tool for future training, particularly in a low-tech, high-volume setting.

The incidence of post-surgery corneal oedema is strongly associated with surgical complications, and it has been shown that patients with severe post-operative corneal oedema have poorer long-term vision and a higher incidence of post-operative corneal grafting and macular oedema. Use of corneal clarity scores on day 1 post surgery reflects on the quality of the surgery and suggests the long-term prognosis for that patient, making it an important tool for assessing effectiveness of cataract surgery.

We selected routine uncomplicated cataract patients with no other associated conditions such as Fuch’s endothelial dystrophy or glaucoma.

Conclusion

Doing a day 1 post-operative ward round is useful for the assessment of surgical skills and the development of good practices in a cataract unit when learning new surgical techniques. We have shown that a rapid corneal assessment with a bright light source gives useful and consistent information regarding the corneal status following MSICS surgery. Comparison with corneal imaging, wavefront analysis, OCT and endothelial cell counting (specular microscopy) would also be helpful in correlating this with other more established methods.

References

Abstract

**Background:** The study was undertaken in order to determine in patients with large optic discs and large optic cups, the proportion with physiologic cupping (normal eyes) misdiagnosed as glaucomatous; and further, to evaluate the possible relationship between optic disc size and central corneal thickness.

**Method and design:** A case series of 69 Black African patients with large discs (vertical disc height measuring >1.8 mm) and large cups (vertical cup to disc ratio ≥0.6) was evaluated to determine what proportion had glaucoma. Patients categorised as normal were further evaluated to determine what proportion were previously misdiagnosed and treated for glaucoma.

**Results:** Sixty-nine Black African patients (138 eyes) with large discs and large cups were evaluated. Forty-one patients (59%) were females and 28 (41%) were males. The mean age was 56 years. Of the 69 patients, 51 (74%) had physiologic cupping (normal eyes) and 18 (26%) patients were glaucomatous. Of the group of 51 patients with physiologic cupping, there were nine patients who were previously misdiagnosed with glaucoma and who had received treatment.

**Conclusion:** Large CDR in relation to large disc size may be normal physiological cupping. It can be misdiagnosed as glaucomatous if objective RNFL analysis is not carried out. In this study, nine (18%) patients from a group of 51 patients with physiologic cupping were misdiagnosed as glaucomatous. There was no linear correlation between CCT and VDH in this study (Pearson’s correlation coefficient was 0.13). The majority of eyes (77.5%) had CCT<544 µm.

**Keywords:** large discs, large cups, physiologic cupping, central corneal thickness, glaucoma, Black African

**Introduction**

Glaumocatous optic nerve damage leads to visual field changes. In addition, retinal nerve fibre layer (RNFL) atrophy occurs in glaucoma. Diagnosing pathological changes based on CDR alone is of limited value. It is important to take into account the disc size.¹ There are different methods to measure disc size and each with its own strength and limitations. It is possible to measure the optic nerve head at the slit lamp with different types of lenses.² By using a slit lamp and a high magnification fundus lens (Volk 60D) a vertical slit is placed over the optic disc to measure the vertical disc diameter. Correction factors may be needed depending on the power of the lens used.³ A 60 dioptre Volk lens has a correction factor of 0.92.³

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Racial differences in optic disc size exist. Studies have shown that Black Africans have larger discs compared to Whites. Healey et al. showed in the Blue Mountain Eye Study that an increase in CDR occurs with an increased vertical disc size. This is significant enough to warrant measurement of optic disc size. Large discs are defined as optic discs measuring 1.8 mm or more. The importance of assessing CDR in relation to disc size was extensively studied by Jonas and co-workers as well as Garway-Heath and associates. They showed that the CDR for disc size has the highest diagnostic power compared to other optic disc parameters for separating normal subjects from pre-perimetric glaucoma patients.

It is clinically difficult to distinguish physiologic cupping from glaucomatous changes. Large CDR are sometimes misdiagnosed as glaucomatous. This can be prevented if disc size is measured because we know that large discs generally have large CDR. In this way, the distinction between physiologic cupping and glaucomatous cupping can be made with greater confidence.

There is controversy about whether there is a positive correlation between disc size and CCT in these patients. A cross-section study by Budenz et al. showed that for every mm² increase in cup disc area, the mean RNFL increased by 3.3 µm. Central corneal thickness (CCT) plays an important role in the diagnosis of glaucoma. CCT influences intraocular pressure (IOP). In a cross-section study by Brandt et al., a total of 1 301 patients with ocular hypertension were studied to determine if CCT influences IOP measurements and if CCT is related to race. They found that CCT for Black Africans was 555.7 µm and CCT for Whites was 573 µm. They showed that Black Africans had thinner corneas than Whites and concluded that CCT may influence the accuracy of IOP measurements. Thin corneas underestimate IOP measurements and thick corneas overestimate IOP measurements.

**Objectives**

The objectives of this study were to determine, in a cohort of 69 Black African patients with large optic discs and large optic cups, the proportion of patients with physiologic cupping misdiagnosed as glaucomatous; and secondarily to evaluate the possible relationship between optic disc size and CCT in these patients.

**Study design**

A case series consisting of 69 Black African patients with large optic discs and large optic cups was evaluated to determine what proportion had glaucoma and what proportion was normal. Patients categorised as normal were further evaluated to determine what proportion was misdiagnosed and treated as glaucoma. The relationship between disc size and CCT was also evaluated.

Glaucoma patients in this project are defined as patients who are diagnosed as glaucoma suspects, primary open angle glaucoma or normal tension glaucoma, and who attend the glaucoma clinic at St John’s Eye Hospital, Soweto, South Africa.

**Method**

This was a convenience sampling of glaucoma patients with large optic discs and large optic cups, attending the glaucoma clinic at St John’s Eye Hospital, who were invited to participate in the study. Informed consent was obtained from those patients willing to participate in the study and this research study was approved by the Human Research Ethics Committee (medical) at the University of the Witwatersrand, clearance certificate (M070435). Large discs were defined as optic discs having a corrected vertical disc height (VDH) measuring more than 1.8 mm. Large cups are defined as CDR≥0.6.

Clinical examination included history, slit-lamp biomicroscopy findings which included IOP, gonioscopy and fundus examination that concentrated on the qualitative and quantitative measurements of the optic nerve head.

A Haag Streit biomicroscope was used to examine the eye. A 60D lens was used to examine and measure the optic disc head. A vertical slit beam was placed over the optic disc and the beam was adjusted to measure the vertical disc diameter. The measurement was read off the calibrated knob on the biomicroscope. A correction factor was needed for the lens (+1.02 for the Nikon 60D lens). A calibrated Goldmann tonometer was used to measure the IOP.

Gonioscopy was performed using a Volk three-mirror lens. The Shaffer-Etienne classification system was used in this study, which defines the following grades:

- **Grade 0** - No structures are visible and represents a closed angle
- **Grade 1** - Schwalbe line is visible and represents possible angle closure
- **Grade 2** - Schwalbe line and trabecular meshwork are visible but scleral spur not visible in a narrow angle

**Grade 3** - Scleral spur is visible and angle closure is impossible

**Grade 4** - All structures are visible from Schwalbe line to the ciliary band

Special investigations included refraction, visual fields, CCT measurements and RNFL analysis.

Refraction was carried out with a Nikon handheld autorefractor and refined subjectively. Patients who were more myopic than −8 dioptres or more hyperopic than +4 dioptres were excluded from the study. Children were excluded from the study. High myopes were excluded because they have markedly different appearance of the optic nerve head in normal and glaucomatous patients. Also, the VDH is influenced by axial length (high myopia) and by the distance of the lens from the cornea or by the refractive errors up to −8 dioptres.

Four criteria were used to diagnose patients in the ‘glaucoma’ subgroup. A subgroup of patients with normal tension glaucoma was not included and remains a weakness in the study. The criteria were as follows:

1. A glaucoma suspect, defined as a patient with one of the following three features: an optic nerve or RNFL defect; or visual field abnormality consistent with glaucoma; or a consistently high IOP (>23 mmHg).

2. Primary open angle glaucoma, defined as a triad of increased IOP, optic nerve head changes and changes on the visual field or RNFL analysis.

3. Normal tension glaucoma, defined as IOP<21 mmHg with visual field defects and RNFL defects.

4. Ocular hypertension, defined as IOP>23 mmHg and no changes on visual fields or the RNFL analysis.

Visual fields were performed using the Oculus automated perimeter. This documented any functional loss or progression of function loss by the nerve over time. This was followed up for at least five years in order to exclude any progression to glaucoma in patients who were classified as having physiologic cupping.

The oculus automated perimeter was used to measure and document visual fields in all 138 eyes. Although the study was carried out over four months, visual fields done before the four months were also assessed and followed up for five years to ensure the absence of glaucomatous progression in patients diagnosed with physiologic cupping. The visual fields were compared to
ascertain if there were glaucomatos field losses or if there was any progression of field loss. Fields were categorised as having glaucomatos change, normal, unreliable or unsuccessful. In this study, fields with glaucomatos change were defined as one of the following: a glaucoma hemifield test outside normal limits on at least two consecutive occasions or a cluster of three or more non-edge points in a location typical for glaucoma or a corrected pattern standard deviation in less than 5% of normal individuals on two 26 consecutive fields. Normal fields were defined as visual fields with no glaucomatos changes. Unreliable fields were defined as visual fields where glaucomatos changes were difficult to assess. Unsuccessful visual fields were due to profound visual loss. If the visual field did not assist in making the diagnosis of glaucoma then the clinical picture with the RNFL thickness was used to determine the diagnosis, and vice versa.

CCT was measured using the Heidelberg Engineering IOPac Advanced Pachymeter. In this study, CCT<544 µm was defined as a thin cornea.

The GDxVCC (Carl Zeiss Meditec Inc., Dublin CA, USA) is an RNFL analyser that uses scanning laser polarimetry to quantify nerve fibre layer thickness in order to detect early glaucomatos changes. A retinal nerve fibre analysis was done with a scanning laser polarimeter to confirm the presence or absence of glaucomatos RNFL defect. This was based on the nerve fibre index TSNIT (temporal, superior, nasal, inferior, temporal) graph and parameters, and the deviation map.

The parameters that were considered for the diagnosis of glaucoma or unclear were based on:

1. The nerve fibre index (NFI). This is the best parameter to differentiate glaucomatos and healthy eyes. The NFI ranges from 0 to 100. The more advanced the glaucoma, the higher the NFI. Glaucoma eyes have NFI values of 35 and above and healthy eyes have NFI values of 44 and below. An NFI value of between 35 and 44 is considered borderline and therefore other data in the GDxVCC printout may be used to make the diagnosis of glaucoma.
2. The TSNIT graph. This shows RNFL values of each of the eyes on the expected age-related normal range.
3. The deviation map. This map plots the RNFL values that deviate from the normal range. The colour-coded p-values indicate the extent of the deviation.

**Outcome measures**
- Central corneal thickness (CCT)
- Intraocular pressure (IOP)
- Corrected vertical disc height (VDH)
- Vertical cup to disc ratio (CDR)
- Relationship between VDH and vertical cup height
- Relationship between VDH and CCT
- Retinal nerve fibre layer (RNFL) analysis
- Visual fields

The Excel database was used for data summary. Statistics were performed using the statistical software Stata version 14 (Stata Corporation, College station, Texas, USA).

**Results**
A total of 138 eyes of 69 Black African patients were evaluated. Forty-one (59%) were females and 28 (41%) were males. Patient ages ranged between 18 and 87 years with a mean of 56 years. Visual acuity ranged from 6/6 to light perception.

Refractive errors extended from myopia of −6.5 D to hyperopia of +4 D. Of the 69 patients with large discs and large cups, 51/69 (74%) had normal eyes and 18/69 (26%) had pathologic cupping. The group of 51 patients with normal eyes was further evaluated and 9/51 (18%) were previously misdiagnosed and treated with anti-glaucoma medications. The main reason for the misdiagnosis was an increased CDR in the presence of a large disc.

**Central corneal thickness (CCT)**
CCT ranged between 534 µm and 618 µm. The mean CCT was 516 µm±37.5 µm. (Figure 1). Out of a total of 138 eyes, 107 eyes (77.5%) had CCT<544 µm (thin corneas).

**Intraocular pressure (IOP)**
The IOPs measured with the Goldmann applanation tonometer ranged between 6 mmHg and 23 mmHg, and the mean IOP was 13±3.5 mmHg.

**Corrected vertical disc height (VDH)**
Vertical and horizontal disc diameters were measured. The VDH ranged between 1.9 mm and 3.2 mm (mean±SD, 2.3±0.26 mm). The horizontal disc diameters (HDD) ranged between 1.7 mm and 2.9 mm (mean±SD, 2.1 mm±0.21 mm) (Figure 2).

**Vertical cup to disc ratio (CDR)**
The vertical CDR was measured relative to VDH. CDR ranged from 0.6 to 1 (mean±SD, 0.7±0.08).

**Relationship between VDH and vertical cup height**
The vertical cup height was calculated by taking the CDR and multiplying it by the
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(61%) were correctly diagnosed as having glaucoma at their initial diagnosis. Forty-two patients did not have RNFL thickness done and were misdiagnosed as glaucoma. The misdiagnosis was made because these patients had physiologic cupping of the optic discs and had normal visual fields over a period of five years.

Relationship between VDH and CCT

VDH ranged between 1.9 mm and 3.2 mm. The CCT ranged from 454 μm to 618 μm. There was no linear correlation between VDH and CCT. The Pearson correlation co-efficient was 0.13.

Retinal nerve fibre layer (RNFL) analysis

The nerve fibre index (NFI) for normal eyes ranged between 3 and 44. The mean NFI for all normal eyes was 3.8. The NFI for glaucoma eyes ranged between 35 and 98. The mean NFI for glaucoma eyes was 49.6. In eyes that had borderline NFI values, i.e. NFI values between 35 and 44, other parameters on the GDxVCC together with the visual fields were used to determine if the eye had glaucoma. The GDxVCC evaluation was unsuccessful in eight eyes because of poor visualisation of the fundus due to cataract formation.

Visual fields

Of the 69 patients, 51 patients had physiologic cupping and 18 patients had pathologic cupping based on clinical examination and visual fields alone. In the group with physiologic cupping, nine patients (13%) had unreliable visual fields and were misdiagnosed as glaucoma. The misdiagnosis was made because these patients did not have RNFL thickness done at their initial diagnosis. Forty-two patients (61%) were correctly diagnosed as having physiologic cupping of the optic discs and had normal visual fields over a period of five years.

Discussion

Examination of the optic nerve head in glaucoma commonly involves the evaluation of the optic cup, the neuroretinal rim contour and the RNFL. An important but overlooked component of the optic nerve head evaluation is measurement of the optic disc size.

In healthy subjects, small discs can have small cups and large discs can have large cups. Large discs with large cups can therefore be misdiagnosed as glaucoma. Sometimes the visual fields obtained may be unreliable and therefore the diagnosis of glaucoma becomes a challenge to the ophthalmologist.

This study was limited to Black African patients. There were several reasons for this. First, there is an increased prevalence of glaucoma in Black African patients. This was shown in the Baltimore Eye Study which showed that African-Americans have a higher prevalence of glaucoma across all age groups when compared to Whites in the same city. A study done by Rotchford et al. also showed that glaucoma was one of the leading causes of blindness in people of Black African origin in rural Zululand (South Africa). Secondly, the optic disc head characteristics in Black African patients differ from their White counterparts. Black African patients have larger optic disc sizes when compared to their White counterparts. Thirdly, Black African patients have thin CCT when compared to their White counterparts. By limiting the data to Black African patients, it was hoped that consistent results, not confounded by findings from other racial groups, would be obtained.

Optic disc size is influenced by a number of demographic factors that include race, age and sex. In addition, variation in anatomic structures of the optic nerve head and the RNFL is associated with variation in disc size. Due to the small number of cases, a limitation of this study is that no comparisons could be drawn about disc size related to age and sex.

Black Africans have larger discs when compared to their White counterparts. The mean vertical and HDDs as measured by Quigley et al. for the disc of a normal human eye is a vertical disc diameter of 1.88 mm and a horizontal diameter of 1.77 mm. In this study, large discs were defined as discs with a vertical height measuring more than 1.8 mm. The VDH ranged between 1.9 and 3.2 mm (mean±SD, 2.3±0.26) and the HDD ranged from 1.7 to 2.9 mm (mean±SD, 2.1±0.22). Studies conducted by Quigley et al. also demonstrated large VDH in Black Africans (1.96±0.16) compared to the VDH of Whites (1.82±0.15). This study showed much larger disc sizes, possibly due to genetic variation. There was a normal Gaussian distribution for VDH (Figure 2). Large cups were defined as a cup-disc ratio greater than 0.6. The Blue Mountains Eye Study showed that that for each 0.1 mm increase in disc diameter there was an increase in CDR of 0.27. Beck et al. reported that large discs have proportionately large CDRs in the normal eyes of Black African subjects. The data from our study showed that there was a direct linear relationship between VDH and vertical cup height (Figure 3).

CCT influences IOP measurements. The mean CCT in the normal human eye is 545 μm. In this study, the CCT ranged from 457 μm to 616 μm (mean±SD, 516±37 μm) and 77.5% of patients had thin corneas (CCT<544 μm). Thick corneas overestimate actual IOP measurements and thin corneas underestimate IOP measurements. In this study, no correlation could be found between disc size and CCT. The Pearson correlation co-efficient was 0.12667.

Pakravan et al. showed that there was an inverse relationship between disc size and CCT in African-American patients, but that this was not statistically significant. To diagnose glaucoma, the following criteria were used: an increased IOP; structural changes of the optic nerve head; visual field changes and corresponding RNFL damage on the scanning laser polarimeter (GDxVCC). In this study, unreliable visual...
fields sometimes made it difficult to make a diagnosis of glaucoma and the researchers therefore had to rely on the RNFL analysis to assist with the diagnosis. It is important to bear in mind that during early glaucoma, there may not be visual field defects and patients therefore needed to be followed up for at least five years to ensure that patients categorised as having physiologic cupping did not progress to glaucoma.

Of the 69 patients studied, 51 patients (74%) had physiologic cupping and 18 patients (26%) had pathologic cupping. Of the 51 patients with physiologic cupping, nine (18%) were previously misdiagnosed as glaucoma and had received unnecessary treatment while the other 42 (82%) patients were correctly diagnosed as having physiologic cupping. The researchers concluded that large discs that have large discs, large discs on their own are not a risk factor for the development of glaucoma. The researchers further concluded that large discs that have proportionately larger cups are more likely to be misdiagnosed as glaucoma than be diagnosed as physiologic cupping.

A significant number of patients in the group of patients with large discs (51/69) had physiological cupping. The researchers concluded that although Black Africans are more susceptible to glaucoma and have large discs, large discs on their own are not a risk factor for the development of glaucoma. The researchers further concluded that large discs that have proportionately larger cups are more likely to be misdiagnosed as glaucoma than be diagnosed as physiologic cupping. Nine of the 51 patients were erroneously misdiagnosed as having glaucoma. The main reason for misdiagnosis was a large cup in relation to a large disc. Measuring these parameters may aid in preventing the misdiagnosis of glaucoma, unnecessary treatment and morbidity to these patients.

Black Africans have thin corneas and may have large discs. The CCT may influence IOP. In this study, 77.5% of patients had thin corneas (CCT>544 μm) but the researchers found no inverse correlation between CCT and disc size.

References
Optimal time for OCT-guided laser treatment following a single bevacizumab intravitreal injection in patients with macular oedema

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Abstract

Background: The aim of the study was to ascertain the ideal time to commence adjunctive focal or grid laser photocoagulation therapy in macular oedema based on optical coherence tomography (OCT)-guided maximum macular dryness.

Methods: A prospective observational study was undertaken of patients treated with a single intravitreal bevacizumab injection for persistent or resistant macular oedema secondary to either retinal vein occlusion (RVO) or diabetes mellitus. Patients were followed up weekly for six weeks, repeating visual acuity and measuring central macular thickness (CMT) using spectral domain OCT. The study was conducted over a year extending from 1 November 2017 to 31 October 2018.

Results: A total of 23 eyes of 21 patients who fulfilled the minimum eligibility criteria were included in the study. The mean age of the subjects was 65.24±11.36 years; 52% were females and 48% males, with an average baseline CMT of 528±158.6 µ. The minimum CMT corresponding to the maximum macular dryness was achieved by week 3 following intravitreal bevacizumab injection, with an average thickness of 338.6±123.8 µ (p-value=0.0001). However, during week 1, the CMT was 391.5±156.8 µ, showing a reduction in the excess macular thickness by 136.5 µ constituting approximately a 51% reduction in the excess CMT from baseline, which was statistically significant (p<0.0058).

Conclusion: Maximum macular dryness was attained at week 3 following a single intravitreal injection of bevacizumab in patients with macular oedema secondary to either RVO or diabetes. These results suggest that the ideal time to perform adjunctive laser for macular oedema following intravitreal injection of anti-VEGF (vascular endothelial growth factor), such as bevacizumab, would be at week 3.

Keywords: macular oedema, retinal vein occlusion, diabetes mellitus, laser, anti-VEGF

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Conflict of interest: None of the authors have any conflicts of interest to declare with regard to this study.

Introduction

Macular oedema is a leading cause of central visual acuity impairment in patients with diabetic retinopathy1 causing poor quality of life. It has become a global epidemic and represents a public health problem.2

Retinal vein occlusion (RVO) is the second most common sight-threatening vascular disorder following diabetic retinopathy3 and is also an important cause of macular oedema. Although most RVOs occur in patients older than 50 years, they are reported in almost all age groups.4-5 The correlation between elevated levels of vitreous vascular endothelium growth factor (VEGF) and diabetic macular oedema (DMO)/macular oedema secondary to RVO is well established.5-7 These increased levels contribute to the breakdown of the blood retinal barrier and formation of macular oedema.

Several studies point to the fact that upregulation of VEGF-A (isoform) may act by increasing vesicular transport and decrease the availability of tight-junction proteins among the endothelial cells, leading ultimately to capillary hyperpermeability.8-10 It therefore seems rational to inhibit VEGF-A with the intention of restoring the inner blood–retinal barrier, minimising the leakage and macular oedema, and improving visual function. In addition, it should aid in reducing the macular thickness for more effective argon laser treatment as numerous studies have shown the benefit of this laser treatment in eyes
with DMO as well as macular oedema secondary to perfused branch retinal vein occlusion (BRVO).

Several retrospective case series have shown the benefit of treatment with intravitreal bevacizumab (a recombinant monoclonal antibody binding to all isoforms of VEGF) in patients with macular oedema secondary to central retinal vein occlusion (CRVO) and diabetes mellitus, with an improvement in visual acuity and a decrease of central retinal thickness. Management of DMO and RVO macular oedema can be challenging using monotherapy and several studies have shown benefit from combination treatment using both anti-VEGF and laser to treat macular oedema and improve visual function in diabetes and vein occlusion. Reported in 2010, DRCR.net (diabetic retinopathy clinical research network) protocol I stated that intravitreal anti-VEGF with prompt or deferred (≥24 weeks) focal/grid laser is more effective over laser alone in treatment of DMO involving central macula. In 2014, Barteselli et al. reported that standardised combination therapy using bevacizumab injections followed by navigated laser treatment for DMO demonstrated significant visual gain. Further advantages were central macular thickness (CMT) reduction after bevacizumab injections and stabilisation after navigated laser treatment. The number of injections was eventually reduced over 12 months.

Furthermore, Barteselli et al. also reported that laser monotherapy demonstrated to be as effective as anti-VEGF monotherapy in the case of retinal thickness of 300 µ or less as measured by the StratusOCT. Therefore, laser alone seems to have a role in the treatment of DMO in the case of not too thick retina, which can be achieved following intravitreal anti-VEGF injections.

Shalaby et al. revealed that combined bevacizumab injections and prompt macular laser treatment at two weeks post injection led to more stable improvement in the treatment of eyes with DMO. In this prospective observational clinical study, we evaluated the effect of a single intravitreal bevacizumab injection on the optical coherence tomography-measured central macular thickness (OCT-CMT) in the eyes of patients with macular oedema secondary to diabetes mellitus and RVOs of all types. The RVOs included BRVO, hemi-retinal vein occlusion (HRVO) and CRVO. The purpose was to establish the time point of maximum decrease in the CMT as this would help with the timing of the laser treatment for the macular oedema.

The aim of the study was to determine the ideal time to initiate focal or grid laser photocoagulation therapy in macular oedema based on optical coherence tomography (OCT)-guided maximum dryness. The main objective of the study was the establishment of time to maximal macular dryness following a single bevacizumab intravitreal injection in order to guide the optimal timing for macular laser therapy for macular oedema secondary to diabetes or RVO. Secondary objectives included a comparison of the response to a single bevacizumab intravitreal injection, in terms of reduction of CMT, in macular oedema secondary to diabetes mellitus versus macular oedema secondary to vein occlusion, and a comparison of the response between different ethnic groups. We finally also wanted to assess the change (gain, loss or no change) in visual acuity from baseline following a single bevacizumab intravitreal injection in the study population.

**Materials and methods**

This was a prospective, observational study of patients treated with a single intravitreal bevacizumab injection for persistent or resistant macular oedema secondary to either RVO or diabetes mellitus at the eye clinic of Inkosi Albert Luthuli Central Hospital. The study was conducted over a year extending from 1 November 2017 to 31 October 2018. The study included adult patients (>18 years) with non-ischaemic macular oedema (evidenced by fundus fluorescein angiogram) secondary to RVO of all types including BRVO, HRVO and CRVO and diabetes mellitus with CMT greater than 250 µ measured by spectral domain OCT (Zeiss Cirrus HD-OCT). This, as according to Grover et al., the average normal SD-OCT central macular thickness is between 227.3 µ and 270.2 µ. In our practice at Inkosi Albert Luthuli Central Hospital we use the average OCT-CMT of 250 µ.

The study excluded patients with active proliferative diabetic retinopathy, age-related macular degeneration, previous intravitreal injections of anti-VEGF, previous intraocular or periocular steroids in the study eye within 90 days of enrolment, SD-OCT proven vitreomacular tractions or epiretinal membranes, patients on systemic immunosuppression, patients who had undergone chemotherapy or radiotherapy for malignancies, pars plana vitrectomy in the study eye, previous intraocular surgery in the study eye within 90 days of enrolment, laser photocoagulation (pan-retinal or macular) treatment within 90 days of enrolment or more than two previous macular laser treatments in the study eye.

Subjects were assigned to the study based on their clinical eligibility above to meet the tight study criteria and their willingness to enrol. There was no random sampling or blinding.

All enrolled patients underwent a complete ophthalmologic examination before intravitreal injection, including measurement of best-corrected visual acuity using an electronic ETDRS chart, slit-lamp examination, fundoscopy using a 90 D lens, intraocular pressure measurement using applanation tonometry, and dilated fundus examination with an indirect ophthalmoscope. Colour fundus photography, fundus fluorescein angiography and spectral domain optical coherence tomography (SD-OCT), looking at the CMT using Zeiss Cirrus HD-OCT were also performed.

The intravitreal injection of off-label bevacizumab (1.25 mg in 0.05 ml) was given according to a standard protocol in the special procedure room under complete aseptic conditions. The protocol includes obtaining informed consent, applying topical 0.4% oxybuprocaine hydrochloride minims eye drops to the ocular surface followed by scrubbing of the eye lids and lashes with 10% povidone iodine and instillation of 5% povidone iodine into the conjunctival fornices several minutes prior to the actual injection. The injection is then given in the superotemporal quadrant, 3.5–4.0 mm posterior to the surgical limbus, using a 30-gauge needle. Post-injection, a sterile cotton swab is placed at the site of injection to prevent reflux of vitreous or drug, and light perception is assessed. Patients are informed of the symptoms and signs of endophthalmitis and asked to return immediately should they experience any of these.

Patients were followed up at week 1 and thereafter weekly for a further five weeks, repeating visual acuity using electronic ETDRS chart; and CMT was measured using SD-OCT. Patients were also assessed for adverse events including elevated intraocular pressure, cataract progression, retinal detachment and post-injection inflammation.
The study was approved by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal, with BREC number BE026/16, and adhered to the tenets of the declaration of Helsinki. Written informed consent was taken from every patient in the study.

**Statistical analysis**

All statistical analyses were performed using IBM SPSS for Windows 25 (SPSS Inc, Chicago, IL, USA). Continuous variables such as patient ages were summarised as mean±SD and compared using the Student’s t-test. Categorical variables such as patient sex and race were summarised using proportions and compared using the chi-squared test or Fisher’s exact test as appropriate. The assumption of data normality was checked using Kolmogorov-Smirnov test.

Each variable was first analysed using a univariate model. The coefficient of determination (R²) in the linear regression was reported, and p-values <0.05 were considered statistically significant.

**Results**

A total of 22 patients fulfilled the minimum eligibility criteria at the beginning of the study and were enrolled after obtaining the informed consent representing 24 eyes. One patient unfortunately had a complication of traumatic cataract after bevacizumab intravitreal injection and was excluded from the study, leaving a total of 23 eyes of 21 patients enrolled in the study. Two patients missed subsequent follow-up visits in weeks 1 and 2 respectively, but were analysed based on the subsequent visits they attended. This meant eventually a total of 23 eyes of 21 patients were enrolled in the study. The mean age of the subjects was 65.24±11.36 years, with an age range of 34 to 91 years. A total of 11 females and 10 males were included in the study. Demographic and clinical data of patients are summarised in Table I.

Of the total number of patients (n=21), 15 (71%) were both hypertensive and diabetic, only two (10%) were hypertensive and non-diabetic and four (19%) were neither hypertensive nor diabetic.

Seven (30%) of the affected eyes presented with DMO and 16 (70%) presented with RVOs of different levels comprising seven (44%) BRVOs, four (25%) HRVOs and five (31%) CRVOs as shown in Table I.

Table II and Figure 1 show weekly changes in OCT-CMT, following intravitreal injection of bevacizumab. In this current study the average baseline CMT was 528.3 µ (SD 158.5). Therefore, our average baseline CMT was 278 µ in excess of the prescribed normal (250 µ). During week 1, following intravitreal injection of bevacizumab, there was a reduction in the excess macular thickness by 136.5 µ, constituting approximately a 51% reduction in the excess CMT from baseline, which was statistically significant (p=0.0058).

### Table I: Baseline demographics and clinical characteristics

<table>
<thead>
<tr>
<th>Subject factors</th>
<th>Variables</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (years) mean±SD: 66.33±11.5 (median age: 67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Females</td>
<td>11 (52%)</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Race</td>
<td>Black African</td>
<td>7 (33%)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>1 (5%)</td>
</tr>
<tr>
<td></td>
<td>Indian</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>HPT</td>
<td>2 (10%)</td>
</tr>
<tr>
<td></td>
<td>DM, HPT</td>
<td>15 (71%)</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>4 (19%)</td>
</tr>
</tbody>
</table>

### Table II: Changes in OCT-CMT from baseline to week 6 following single intravitreal bevacizumab injection

<table>
<thead>
<tr>
<th>Week</th>
<th>OCT (µ)</th>
<th>Difference (µ)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>528±158.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>391.5±156.8</td>
<td>136.5</td>
<td>0.0058</td>
</tr>
<tr>
<td>2</td>
<td>379.5±152.6</td>
<td>148.5</td>
<td>0.0033</td>
</tr>
<tr>
<td>3</td>
<td>338.6±123.8</td>
<td>189.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>4</td>
<td>344.7±136.1</td>
<td>183.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>5</td>
<td>353±135.3</td>
<td>175</td>
<td>0.0004</td>
</tr>
<tr>
<td>6</td>
<td>363.2±146.8</td>
<td>164.8</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

*p-value* Comparison between weekly OCT readings and baseline.
weeks, OCT-CMT was observed to increase again, with final thickness of 363.2±146.8 µ at week 6 as shown in Table II and Figure 1.

Figure 2(A) shows an example of a patient in our study that presented with a significant macular oedema (OCT-CMT: 638 µ) secondary to CRVO. Figure 2(B) demonstrates a significant reduction of this macular oedema to a near normal (OCT-CMT: 268 µ) at week 1 following a single intravitreal bevacizumab injection.

Figure 3 illustrates the comparison between DMO and RVO patients with respect to OCT-CMT following intravitreal bevacizumab injection over a period of six weeks. The average baseline OCT-CMT was higher for RVO patients (581.7 µ) compared to DMO patients (413 µ).

In RVO patients, a decrease of 187.4 µ (32%) from average baseline OCT-CMT was observed, compared to a decrease of 27.9 µ (6.8%) in the DMO patients during the first week. However, as the average baseline in RVO patients was 331.7 µ in excess of normal OCT-CMT compared to 168 µ for DMO patients, the corresponding decrease in excess of normal OCT-CMT was 56.5% and 17% for RVO and DMO patients respectively during week 1.

In both groups maximum macular dryness was achieved by week 3, but interestingly in DMO patients, after six weeks follow-up, the OCT-CMT increased by 41 µ (10%) above the average baseline thickness while in RVO patients it remained 256.5 µ (44%) below average baseline.

Following intravitreal injection with bevacizumab, a decrease in OCT-CMT is associated with a corresponding increase in VA (Figure 4).

The mean baseline BCVA was 20/100 (LogMAR=0.7) and subsequently after injection it showed an improvement by gaining 10±5 ETDRS letters throughout the follow-up visits. Eventually in the last week of follow-up, the mean BCVA was 20/80 (LogMAR = 0.6) gaining five ETDRS letters compared to baseline. This was demonstrated in Figure 4 as an inverse relation between the mean change in BCVA and the mean change in CMT.

Comparing the response to a single bevacizumab injection between Black African and Indian subgroups, some differences were noted. Black African RVO patients had a baseline OCT-CMT of 634.4 µ, which was 384.4 µ (154%) in excess of normal OCT-CMT of 250 µ, and Indian RVO patients had a baseline OCT-CMT of 563.4 µ, which was 313.4 µ (125%) in excess of normal OCT-CMT. During the first week
following the intravitreal bevacizumab injection, a 198.6 µ decrease in OCT-CMT was observed among Black African RVO patients, which is equivalent to 52% of the total excess thickness at baseline, compared with an 182.3 µ decrease in OCT-CMT among Indian patients which is equivalent to 58% of the total excess thickness at baseline. However, Black African RVO patients showed a marked further decrease in excess to a maximum dryness at three weeks (246.5 µ), contrary to an observed lack of decrease in excess oedema after the first week among Indian patients (Figure 5).

Comparing Black African DMO and Indian DMO patients, we observed a 34% and 3.25% decrease in the excess CMT, respectively (Figure 5).

Discussion
In this study we observed that maximum macular dryness based on SD-OCT following a single intravitreal bevacizumab injection was at week 3, after which there was a gradual increase of OCT-CMT. However, the greatest weekly decrease in macular oedema was observed during week 1 and this was found to be statistically significant (p<0.05).

Perhaps to further understand the OCT-guided optimal time to commence macular laser treatment, a multi-centre controlled trial can be conducted comprising two comparative groups, one in which laser treatment occurs after one week and the other in which laser treatment occurs after three weeks.

This study is of importance in low- and middle-income countries where bevacizumab is generally not readily available or affordable and human resources are scarce. By commencing laser treatment either at week 1 or week 3 after a single bevacizumab intravitreal injection, one might be able to reduce the number of further injections, which would be an advantage.

Our study also revealed that RVO patients in general have a baseline higher excess oedema than DMO patients. They, however, respond better to a single intravitreal anti-VEGF (bevacizumab) injection, with the final OCT-CMT at week 6 significantly lower than baseline. Even though DMO patients have much less macular oedema at baseline and show a modest decrease in OCT-CMT at week 1, this gradually increases to a level even above the baseline at week 6, indicating a worsening in macular oedema. This was previously reported by Sonoda et al., and
might indicate that VEGF plays a pivotal role in the pathogenesis of macular oedema in RVO more profoundly than DMO. This fact may support the theory that DMO is not driven only by VEGF but also has an inflammatory component suggesting that blocking VEGF alone would not necessarily be sufficient to reduce macular oedema; alternative medication, such as intravitreal steroids, might be needed as an initial treatment instead of anti-VEGF medication.

This study also showed differences in response to bevacizumab injections between Black African and Indian subjects; however, this analysis has some limitations owing to the nature of the data. A univariate analysis was used to analyse the difference in response between racial groups, and it was not possible to perform a multivariate analysis at the patient level which perhaps might arrive at a different conclusion.

Finally, when analysing changes in visual acuity following a single intravitreal bevacizumab injection, it was found to be inversely proportionate to the changes in OCT-CMT.

Conclusion

This prospective study conclusively showed that maximum macular dryness was attained at week 3 following a single intravitreal injection of bevacizumab in patients with macular oedema secondary to either RVO or diabetes. It further showed that the greatest reduction in oedema occurred during the first week following the injection. These results suggest that the ideal time to perform adjunctive laser for macular oedema following intravitreal anti-VEGF injections would be at week 3.

Acknowledgment

We would like to thank Mrs Rajeshree Budhoo, optometrist at Inkosi Albert Luthuli Central Hospital, for her contribution and assistance in data collection.

References

Why hindsight is 2020

Twenty-twenty was always going to be a significant year for ophthalmology. Even greater for South African ophthalmology – the WOC was coming to town! Who could have predicted that a tiny virus, invisible to the eye, would bring everything crashing down.

Covid-19 has come to town instead. A global pandemic on a scale not witnessed since the Spanish Flu pandemic of 1918. Panic and fear spread quickly as we witnessed thousands dying elsewhere – Bergamo, a small village in northern Italy, the worst hit. Who will forget the patients lined up in the streets or the coffins lined up in churches. Scientists, governments and NGOs working together to find a way through.

Based on information available, governments called for national lockdowns to ‘flatten the curve’ and prevent another Bergamo, their economies spiralling down.

With too much time on our hands, everyone turned to social media and anyone with an opinion became an overnight expert. Fake news abounded – rumours of biological warfare, a complicit WHO, the rich orchestrating it to become even richer.

As I pen this, South Africa is about to come out of level 5 lockdown. Our numbers manageable (only linear increase, not exponential), we’ve bought time to better prepare. Our President has urged us to continue being responsible and protect the vulnerable as we expect our peak in the next two months. With everyone playing their part, we should make it through without too many casualties, though it might take longer than anticipated.

Our world will never return to the ‘normal’ of pre-2c2c, but maybe our new normal will turn out to be better. Maybe we have learnt a few uncomfortable truths about ourselves and realised what really is important. Tomos Roberts’ poem ‘The Great Realisation’ (@probablytomfoolery), where a father tells his son a bedtime story, gives us food for thought. Do yourself a favour and watch the video on YouTube.

Son: Tell me the one about the virus again. Then, I’ll go to bed.
Father: But, my boy, you’re growing weary, sleepy thoughts about your head.
Please! That one’s my favourite. I promise, just once more ...
Okay, snuggle down my boy, though I know, you know full well, this story starts before then in a world I once would dwell. It was a world of waste and wonder. Of poverty and plenty. Back before we understood why hindsight’s 2c2c.
You see, the people came up with companies to trade across all lands. But they swelled and got much bigger than we ever could have planned.
We’d always had our wants, but now, it got so quick. You could have anything you dreamed of in a day and with a click. We noticed families had stopped talking. That’s not to say they never spoke. But the meaning must have melted and the work–life balance broke.
And the children’s eyes grew squarer and every toddler had a phone. They filtered out the imperfections but amidst the noise, they felt alone.
And every day, the skies grew thicker, till you couldn’t see the stars. So we flew in planes to find them, while down below, we filled our cars.
We’d drive around all day in circles. We’d forgotten how to run. We swapped the grass for tarmacs, shrunk the parks, till there were none.
We filled the sea with plastic, because our waste was never capped. Until, each day, when you went fishing, you’d pull them out already wrapped.

And while we drank and smoked and gambled, our leaders taught us why, it’s best to not upset the lobbies, more convenient to die. But, then, in 2c2c, a new virus came our way. The governments reacted and told us all to hide away. But while we all were hidden, amidst the fear and all the while, the people dusted off their instincts. They remembered how to smile.
They started clapping to say thank you. And calling up their mums. And while the car keys gathered dust, they would look forward to their runs. And with the skies less full of voyagers, the earth began to breathe. And the beaches bore new wildlife that scuttled off into the seas. Some people started dancing, some were singing, some were baking.
We’d grown so used to bad news but some good news was in the making.
And so when we found the cure, and were allowed to go outside, we all preferred the world we found to the one we’d left behind. Old habits became extinct and they made way for the new. And every simple act of kindness was now given its due.

But why did it take a virus to bring the people back together?
Well sometimes you’ve got to get sick, my boy, before you start feeling better.
Now, lie down and dream of tomorrow, and all the things that we can do. And, who knows, if you dream hard enough, maybe some of them will come true.
We now call it The Great Realisation and yes, since then there have been many.
But that’s the story of how it started, and why hindsight’s 2c2c. ☺

Message from the President

Roberts’ poem ‘The Great Realisation’

Tomos Roberts’ poem ‘The Great Realisation’ (@probablytomfoolery), where a father tells his son a bedtime story, gives us food for thought. Do yourself a favour and watch the video on YouTube.

The Great Realisation

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But that’s the story of how it started, and why hindsight’s 2c2c. ☺
Many years ago, I was taught that there were three O’s involved in eye care: Ophthalmologists, Optometrists and Orthoptists. This is still the international standard in many countries. But not anymore in this country, South Africa has only nine orthoptists left. And these nine fine ladies are not getting any younger!

The first orthoptist in the world was trained in the early 1900s. She was the daughter of an ophthalmologist. Her father trained her to work with children mainly to save him time in his busy practice.

What is Orthoptics?
The name derives from the Greek word *orthos* which means straight. So, it literally means straight eyes. But there is far more to it than that.

What is an orthoptist?
An orthoptist diagnoses and treats disorders involving eye movements and binocular vision both in adults and children. They usually work as part of a multi-disciplinary team consisting mainly of ophthalmologists but also sometimes optometrists, paediatricians, neurologists, occupational therapists, remedial teachers and educational psychologists. Together with ophthalmologists, orthoptists often help with other activities such as fluorescein angiograms, OCTs, tonography, biometry and IOL calculations, visual field testing, contact lens fitting, fundus photos, patient explanations and instructions, etc.

School screening of young children is also a large part of the orthoptist’s activities. Many optometrists were critical of this in the past because they accused orthoptists of being unable to refract. Missing a significant refractive error in a young child is a serious offence. But nowadays, there are easy-to-use paediatric visual screening devices which screen for refractive errors, meaning this criticism is usually no longer valid.

Besides, most orthoptists are trained in basic refraction techniques including retinoscopy. They are not allowed to perform cycloplegic refractions as cycloplegic drops are scheduled medications. But then neither are optometrists unless they have passed recent stringent courses and exams.

My personal experience with orthoptists has been very positive. As a general ophthalmologist and cataract surgeon, I have little time for paediatric ophthalmology and strabismology. My receptionists are trained to send all paediatric cases with binocular vision issues straight to my itinerant orthoptist, Kate Houslay, who visits my practice once per month. She is excellent with these children and with their management, be it surgical referral, patching, vision therapy or prisms. Sometimes I think that she knows more about strabismus and amblyopia than most ophthalmologists. I mean when last did you use a synoptophore?

In preparation of this article I performed an informal survey by asking various optometrists and ophthalmologists what they thought about orthoptists. I received a few neutral comments but all the rest were overwhelmingly positive. Here are some examples:

- **Strabismologist, Nilesh Dahya:** ‘Orthoptists are an integral, essential and indispensable part of a strabismus unit. It is an absolute shame that the HPCSA has stopped the training and registration of orthoptists in SA.’
- **Strabismologist, Claire Cullen:** ‘Absolutely a dire need for them.’
- **Senior academic ophthalmologist, Nicky Welsh:** ‘Orthoptists play a vital role…’
- **Past chairman of OMG, William Earl:** ‘It has been a disappointment that orthoptists have struggled to have their specialisation continually recognised by the HPCSA, and that they are unable to have potential new students study and qualify. As a result, there will gradually be fewer and fewer of them over time, which will be a loss to the public and all ophthalmologists that have patients with eye movement disorders, especially children.’
- **Professor of Optometry, Alan Rubin:** ‘I have a positive attitude towards them.’
- **Senior optometrist, Sheila Thomas:** ‘I strongly believe there is still a role for orthoptists and I value their input.’
- **Senior optometrist, Christine Croker:** ‘Definitely a place for orthoptists. Many optometrists don’t do a complete binocular work-up.’
- **Senior orthoptist who qualified cum laude:** ‘I wouldn’t even know where to start if my patient was bi-ocular.’
- **Senior paediatric optometrist, Larry Berman:** ‘There could definitely be a role for orthoptists.’
- **Past President of SA Optometric Society, Zena Jacobson:** ‘I am useless with strabismus therapies and prism prescriptions. So, if I need a measurement, I send to Mignon Klugman to help me. I would have thought that orthoptists play a valuable role for ophthalmology.’

Over the years I have spoken to many optometrists about this issue. I can safely say that the majority of optometrists that I have spoken to and had dealings with are not interested in this field. They do not claim expertise in this field and are positively disposed towards orthoptists.

Here is a list of the nine orthoptists presently practising in SA together with their contact details (published with their permission):

**Johannesburg area:**

1. Linda Malan. Johannesburg. +27 82 873 1626
2. Kate Houslay. Johannesburg and East Rand. +27 83 229 4578.

**KwaZulu-Natal:**

4. Diane van Damm. Qualified at Wits 1976. Prof Phillip Tobias and Prof Anthony...
Murray were among her lecturers.

Western Cape:
5. Moira Pewsy, Belville and Tygerberg. 084 512 5994.

Current challenges
There are two main issues affecting the orthoptics profession in SA today:

1. There is no longer a school of orthoptics.
   The last orthoptist qualified from the Wits School of Orthoptics in 1998 before it was closed down. Linda Malan and Mignon Milwid have been trying for years to establish another school but have met with barriers at the HPCSA.

2. Recently all SA orthoptists have been deregistered and have therefore lost their practice numbers! This means that they are no longer able to claim from medical aids. This is a severe blow and needs urgent reversal if these colleagues are to remain in practice.

I would like to end off with a message I received from one of the orthoptists on behalf of all of them:

“We desperately need all ophthalmologists to support us in our attempts to be re-classified and to start a training facility.”

Dr Clive Novis
Dip Optom, MBBCh(Wits), MMed(Wits), FCS(Ophth)
clivenovis@mweb.co.za

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I write this review under lockdown – practising social distancing and self-isolation against the coronavirus and Covid-19! And as if we were not stressed enough here in SA, I have just heard that we are now fully into ‘junk status’ after the inevitable Moody’s downgrade. This is more than enough to cause another epidemic here in SA: anxiety and depression! So, I thought it appropriate now to re-read and review this classic book.

Peter D. Kramer was born in New York in 1948. He obtained his MD degree from Harvard and then became Professor of Psychiatry at Brown University.

Fluoxetine hydrochloride was the first SSRI (selective serotonin re-uptake inhibitor) and was discovered in the early 1970s but only launched by Eli Lily in 1987 as Prozac. This book tells us about the history of this game-changing drug. But this book is much more than that. It is a revision of basic psychological and psychiatric principles. It is also the story about the development of psychopharmacology.

Dr Kramer states that anxiety is at the heart of the psychological understanding of man. The ‘dynamic’ in psychodynamic psychotherapy is anxiety. And it is anxiety that is the motor force behind psychoanalysis.

There is so much anxiety about this novel coronavirus and the infectious disease that it causes (Covid-19) in the world at present. It would obviously be great to have a cure for Covid-19, but we already have some very promising treatments for anxiety. Prozac being one of them. Prozac and other SSRIs are known as anti-depressants, but they have other major therapeutic benefits too such as anti-anxiety, mood-stabilising, anger-controlling, OCD-ameliorating, ADD-improving, sleep-improving, anti-migraine, and many others. They are literally capable of bringing about major personality changes in a person (and even in animals). Before Prozac, personality and its disorders were classically in the arena of psychotherapy and were a contraindication for treatment with medication.

Dr Kramer emphasises that depression is a relapsing and recurring illness and the key to treatment is thoroughness. If a patient can be put into remission for a period of about six months, then the odds are good for a sustained remission. Early and prolonged intervention is crucial in the management of depression. In the mid-1960s it was thought that low noradrenaline levels cause depression. But by the mid-1970s it was realised that serotonin levels also play a role (the biogenic amine theory of depression).

Similar to ophthalmology (and most areas of medicine), the way a psychiatrist diagnoses a disease or disorder depends to a large extent on what treatment is available. Therefore, a major shift occurred in the ideology of psychiatry in 1957. Before that, other anti-depressants were available but their effectiveness was not very good and side-effects limited their use. Of course, psychotherapy was (and still is) widely practised to reduce ‘intrapsychic conflict’, which was considered to be the main cause of anxiety. An example of the shift in ideology and diagnosis is the distinction between manic-depressive illness (now known as bipolar disorder) and schizophrenia (and other psychoses), which in the past were considered to be all part of a single spectrum of disorders. Once lithium treatment had been discovered to be effective for manic depression in 1949, diagnostic distinction between this neurosis and schizophrenia became important. Many examples also occurred in ophthalmology.

Before lithium were discovered, the distinction between viral and bacterial conjunctivitis was not important. Before anti-VEGFs were discovered, the diagnostic distinction between wet and dry ARMD was not as important as it is today. The treatment of schizophrenia was revolutionised in 1952 with the introduction of chlorpromazine (Largactil) which became known as the drug that emptied the state mental hospitals. Before this the distinction between psychosis and neurosis was not as important.

Dr Kramer ends off by warning that Prozac and other drugs should not be abused by insurance companies and third-party payers. This is because they have discovered that treatment with these drugs (especially the generics that are now widely available) is much cheaper than psychotherapy. Psychotherapy, he says, is still the most helpful treatment for minor depression and anxiety.
Another local innovation stands out on South African Mint’s newest collectable coin

The South African Mint, a wholly owned subsidiary of the South African Reserve Bank (SARB), continues to unearth virtuous examples of South African ingenuity and innovation to further enrich the coin-collecting experience. The retinal cryoprobe, invented and commercialised by South African ophthalmologist and biomedical engineer, Dr Selig Percy Amoils, is the subject of the new 2½c tickey and R2 crown series.

The ‘South African Inventions’ theme was introduced on the crown and tickey coin series in 2016 to highlight globally relevant inventions and firsts by South Africans. In 2019 it recognised Pratley Putty, the world’s first epoxy adhesive invented by South African engineer George Pratley, and used by NASA aboard its Ranger moon-landing craft over 50 years back. This year the series features the retinal cryoprobe, invented in 1965 at Baragwanath Hospital, Africa’s largest hospital located in Soweto, Johannesburg.

The cryoprobe is a large, pen-like instrument commonly used in cryosurgery, a technique that uses extreme cold to remove abnormal or diseased tissue. The retinal cryoprobe emits analgesic nitrous oxide, at below freezing temperatures of –80 °C. When inserted into a cut in the eye it freezes the cataract, which is then removed effortlessly. The procedure only targets damaged tissues without

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NEW!
as well as those whose lives have been changed due to this extraordinary invention. This is an everlasting way in which one can cherish the wonderful contributions made by South Africans,’ says Ms Honey Mamabolo, Managing Director, South African Mint.

The crown coin features the anatomy of an eye on the reverse, the years ‘1965’ and ‘2020’, the words ‘RETINAL CRYOPROBE’, and the denomination ‘R2’. On the obverse, the national coat of arms, the words ‘South Africa’ in all the official languages, and the year of issue, ‘2020’, are featured. The reverse of the much smaller tickey coin depicts a gloved hand holding the retinal cryoprobe, the letters ‘SPA’ for ‘Selig Percy Amoils’, and the denomination 2½c. The obverse shows a king protea, the words ‘SOUTH AFRICA’, and the year ‘2020’. When the tickey is placed on top of the crown in the designated area, the surgical procedure is recreated.

Only 1 000 of the 2020 South African Inventions sterling silver R2 crown coins and the single 2½ c sterling silver tickey coins will be produced individually, and 700 in a set including a sterling silver miniature sculpture of the eye. The sets are packaged in a beautiful piano finish varnished walnut wood box. The range also includes the Krugerrand and Crown Launch set which consists of a proof sterling silver R2 crown and a proof fine silver Krugerrand with a privy mark. Only 500 of these sets will be produced.

These coins and sets can be purchased from the Mint’s retail store in Centurion, as well as at Elegance Jewellers in Melrose Arch, True Story Stores at the OR Tambo Airport or Sandton City, as well as the African Medallion Group in Sandton. You can also place an order online at https://www.samint.co.za/order-form/ (correct at the time of writing on 3 March 2020, prior to lockdown).
The International Council of Ophthalmology is honoured to host delegates from every part of the world to WOC2020 Virtual® from 26–29 June 2020. This unique 37th World Ophthalmology Congress will be a virtual experience that showcases the latest developments in all fields of ophthalmology. Join in for an unforgettable personalised learning journey and learn from world-class experts, network with colleagues, visit the virtual exhibition, and access content for three months.

During these extraordinary times, WOC2020 Virtual® brings to you an exciting educational opportunity – all in one place, at your own pace, and keeping you safe.

This innovative online learning experience will enable you to access:
- Live keynote sessions
- Online question and answers
- Over 2,000 talks from world experts
- Virtual industry exhibition
- All sessions for up to three months

Benefits of the online experience
- Latest knowledge from world experts – receive the latest developments in clinical care, surgical techniques, innovation and equipment
- Personalised on-demand content – never miss out on a parallel session and get customised learning suggestions
- CME points – claim Continuing Medical Education Credits from home
- Three-month access to programme – registration offers you an opportunity to review material for three months at your own pace
- Over 2,000 presentations from world experts, for up to three months (until 30 September 2020)
- Access to +100 live sessions, including live question and answers and interactivity features
- Satellite symposia
- Virtual industry exhibition
- Abstract e-book
- Discussion forums

Registration payments
All registrations must be made online. The WOC2020 Virtual® will not process registrations that do not include payment information, and receipt of partial registration does not guarantee the registration rate.

The ICO reserves the right to review each registration for the appropriateness of the selected registration category and make any necessary corrections. For example, a full-time faculty member of ophthalmology that chooses the Accompanying Person or Medical Student rate will be corrected upon review. The ICO reserves the right to charge his/her credit card the difference in registration fees.

By registering for the WOC2020 Virtual®, you are providing us with permission to include your name, organisation, and country for the list of attendees shared with select exhibitors.

Contact details for registration
Email: woc@icowoc.org
Telephone: +31 20 575 4220
Operating hours: Monday to Friday, 09:00–17:30 (Central European Summer Time GMT +2)

Visit https://icowoc.org for all the information.
Sessions by topic
The topics are colour-coded on the website, https://icowoc.org/program/sessions/, for ease of use, and the same colours are used in the list below. Topic sessions include subspecialty day sessions, free paper sessions, symposiums, instruction courses and presentations by various ICO member societies. Please refer to the website for the details.

Cataract and Lens Surgery
Contact Lens and Refraction
Cornea, External Eye Diseases, and Eye Banking
Cutting Edge Ophthalmology
Evidence-Based Medicine

Eye Care Delivery
Glaucoma
Interdisciplinary
International Eye Care
Medical Retina
Neuro-Ophthalmology
Ocular Imaging/Artificial Intelligence
Ocular Trauma
Ophthalmic Education
Ophthalmic Epidemiology
Ophthalmic Oncology
Ophthalmic Pathology and Microbiology
Ophthalmic Pharmacology
Orbital, Oculoplastic, and Lacrimal Diseases
Pediatric Ophthalmology and Strabismus
Refractive Surgery
Surgical Retina
Uveitis
Vision Rehabilitation

**Prolong corneal contact time with DexaGel1,2

◊ For greater anti-inflammatory effect vs dexamethasone solution1,2
◊ Equivalent efficacy and safety compared to prednisolone1


More potent1
More bioavailability2
More effect2

BAUSCH+LOMB

**Prolong corneal contact time with DexaGel1,2

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Besides benefiting from reduced registration fees for their members, ICO Member Societies have the possibility to present their latest research over the course of the Congress, by taking part in the Worldwide Program Contributions.

The International Council of Ophthalmology is proud to list its participating Member Societies:

- Academia Ophthalmologica Belica (AOB)
- Academia Ophthalmologica Internationalis
- Afghanistan Eye Doctors Society
- African Ophthalmology Council (AOC)
- Albanian Ophthalmological Society
- Algerian Ophthalmological Society
- American Academy of Ophthalmology (AAO)
- American Association for Pediatric Ophthalmology and Strabismus (AAPOS)
- American Association of Ophthalmic Oncologists and Pathologists (AAOOP)
- American Glaucoma Society (AGS)
- American Ophthalmological Society (AOS)
- American Society of Ophthalmic Pathologists (AOS)
- American Society of Pediatric Ophthalmology and Strabismus (ASOPS)
- Argentinian Society of Ophthalmology
- Argentinian Council of Ophthalmology
- Argentinian Society of Ophthalmology
- Asia Pacific Glaucoma Society (APSS)
- Asia Pacific Society of Eye Genetics
- Asian Society of Ophthalmic Plastic and Reconstructive Surgery
- Argentine Council of Ophthalmology
- Argentine Ophthalmological Society
- Association for Research in Vision and Ophthalmology (ARVO)
- Association of Ophthalmologists of Latin America
- Australia and New Zealand Glaucoma Society (ANZGS)
- Austrian Ophthalmological Society
- Bahrian Ophthalmological Association
- Bahrain Society of Ophthalmology
- Black Sea Ophthalmological Society
- Bulgarian Society of Ophthalmology
- Brazilian Council of Ophthalmology
- Bulgarian Society of Ophthalmology
- Burkina Faso Society of Ophthalmology
- Burundi Ophthalmological Society
- Cambodian Ophthalmology Society
- Cameroonian Society of Ophthalmology
- Canadian Ophthalmology Society
- Canadian Society of Ophthalmology
- Catalan Ophthalmological Society
- Ceylon Ophthalmological Society
- Chinese Ophthalmological Society
- College of Ophthalmologists of Sri Lanka
- Colombian Society of Ophthalmology
- Complexes of Ophthalmology
- Contact Lens Association of Ophthalmologists, Inc. (CLAO)
- Corner Society
- Croatian Ophthalmological Society
- Cuban Society of Ophthalmology
- Cyprus Ophthalmological Society
- Czech Ophthalmological Society
- Danish Ophthalmological Society
- Dominican Society of Ophthalmology
- Ecuadorian Society of Ophthalmology
- Egyptian Ophthalmological Society
- Emirates Ophthalmic Society
- Estonian Ophthalmological Society
- EURETINA – European Society of Retina Specialists
- EuroLim Retina
- European Association for Vision and Eye Research (EVER)
- European Board of Ophthalmology (EBO)
- European Dry Eye Society
- European Pediatric Ophthalmological Society
- European Society of Cataract and Refractive Surgeons (ESCRS)
- European Society of Ophthalmic Plastic and Reconstructive Surgery (ESPORS)
- European Strabismological Association (ESA)
- Finnish Ophthalmological Society
- French Society of Ophthalmology
- Gabonese Society of Ophthalmology
- Georgain National Ophthalmology Society
- German Ophthalmological Society (DOG)
- Global Alliance Eye Bank Association (GABA)
- Global Eye Genetics Consortium
- Haitian Society of Ophthalmology
- Haitian Ophthalmological Society
- Honduran Ophthalmology Society
- Hong Kong Ophthalmology Society
- Hungarian Ophthalmological Society
- Icelandic Ophthalmological Society
- Indonesian Ophthalmological Society
- International Joint Commission for Allied Health Personnel in Ophthalmology (IJCAHP)
- International Medical Contact Lens Council (IMCLC)
- International Ocular Inflammation Society (IOIS)
- International Pediatric Ophthalmology and Strabismus Council (IPOSC)
- International Society for Genetic Eye Diseases & Retinaldegeneration (ISGERD)
- International Society for Ophthalmic Pathology (ISOP)
- International Society of Geographical and Epidemiologic Ophthalmology (ISGEO)
- International Society of Ocular Oncology (ISO)
- International Society of Oculoplastic and Reconstructive Surgeons (ISOPRS)
- International Strabismological Association (ISA)
- International Uveitis Study Group (IUS)
- Iranian Society of Ophthalmology
- Iraq Ophthalmology Society
- Irish College of Ophthalmologists
- Israeli Ophthalmology Society
- Italian Society of Ophthalmology
- Ivory Coast Society of Ophthalmology
- Japanese Ophthalmological Society
- Jordanian Ophthalmological Society
- Korean Ophthalmological Society
- Kuwaiti Ophthalmological Society
- Korean Association of Ophthalmologists
- Lao Society of Ophthalmology
- Lebanese Ophthalmological Society
- Lithuanian Ophthalmological Society
- Madagascan Society of Ophthalmology
- Malaysian Ophthalmological Society
- Malawi Ophthalmological Society
- Malaysian Society of Ophthalmology
- Mall Ophthalmology Society
- Mauritian Society of Ophthalmology
- Mexican Society of Ophthalmology
- Middle East Africa Cataract and Refractive Surgery Society (MEACRS)
- Middle East African Council of Ophthalmology (MEACO)
- Middle East African Pediatric Ophthalmology and Strabismus Society (MAEAPSS)
- Middle East Society of Ophthalmic Plastic and Reconstructive Surgery (MEAPSSR)
- Middle East Ocular & Torticollis Society (MEO&TS)
- Mongolian Ophthalmological Society
- Moroccan Ophthalmology Society
- Mozambican College of Ophthalmologists
- Nepal Ophthalmic Society
- Netherlands Ophthalmological Society
- Nigerian Ophthalmological Society
- Norwegian Ophthalmological Society
- Oman Ophthalmic Society
- Ophthalmic Oncology Group (OOG)
- Ophthalmological Society of Bangladesh
- Ophthalmological Society of Ethiopia
- Ophthalmological Society of Ghana
- Ophthalmological Society of Jamaica
- Ophthalmological Society of Malaysia
- Ophthalmological Society of Nigeria
- Ophthalmological Society of Pakistan
- Ophthalmological Society of South Africa
- Ophthalmological Society of Taiwan
- Ophthalmological Society of the West Indies
- Ophthalmologists of Southern Africa (OSA)
- Pacific Eye Care Society (PaeCEYES)
- Palestinian Ophthalmological Society
- Panamanian Ophthalmology Society
- Pan-American Retina & Vitreous Society (PVRVS)
- Paraguayan Society of Ophthalmology
- Palestinian Society of Ophthalmology
- Philippine Academy of Ophthalmology
- Polish Ophthalmological Society
- Portuguese Society of Ophthalmology
- Refractive Surgery Alliance (RSA)
- Romanian Society of Ophthalmology
- Royal Australian and New Zealand College of Ophthalmologists (RANZCO)
- Royal College of Ophthalmologists of Thailand
- Royal College of Ophthalmologists of the UK
- Russian Society of Ophthalmologists
- Rwanda Ophthalmological Society
- SAARC Academy of Ophthalmology
- Salvadorian Association of Ophthalmologists
- Saudi Ophthalmological Society
- Serbian Association of Ophthalmologists
- Serbian Association of Ophthalmologists
- Singapore Society of Ophthalmology
- Slovak Ophthalmological Society
- Slovenian Society of Ophthalmology
- South African Society of Oculoplastic Surgeons (SASOPS)
- South East European Ophthalmology Society
- Spanish Society of Ophthalmology
- Swedish Ophthalmological Society
- Swiss Society of Ophthalmology
- Syrian Ophthalmological Society
- Tanzania Ophthalmology Society
- The Macau Society
- The Latina Society
- The Ocularists Society
- Topso Society of Ophthalmology
- Tunisian Ophthalmological Society
- Turkish Ophthalmological Society
- Turkish Republics Ophthalmology Society
- Uganda Ophthalmology Society
- Ukrainian Society of Ophthalmologists
- Uruguayan Association of Ophthalmologists
- Uzbek Scientific Ophthalmic Society
- Vietnamese Ophthalmological Society
- Women in Ophthalmology (WIO)
- World Glaucoma Association (WGA)
- Yemeni Ophthalmological Society
- Zambia Ophthalmological Society