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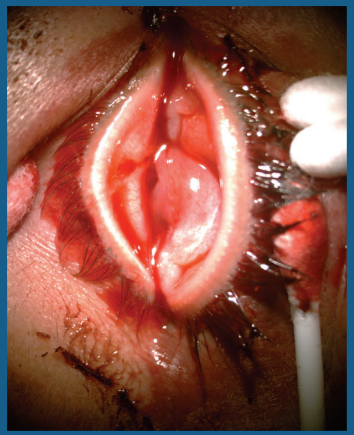

Missing globe from the orbit.

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Asian Journal of OPHTHALMOLOGY

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OPHTHALMOLOGY
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Focus and scope

As new technologies and therapeutic interventions are continually being developed, Ophthalmology has become a field of rapid change, particularly in the Asia-Pacific region, where disease patterns and health care delivery differ greatly from those seen in the West. Asian Journal of Ophthalmology was established in 1998 with the aim of disseminating information relevant to Ophthalmology and glaucoma throughout Asia and to interested groups worldwide.

The objectives of Asian Journal of Ophthalmology are as follows:

- To provide a platform for the publication of information with a focus on Ophthalmology in Asia.
- To disseminate information that will improve the care of patients with all types of ophthalmological disorders, with a special focus on glaucoma.
- To increase the understanding of such disorders through reporting of educational activities.
- To publish the results of research programmes to expand knowledge about the causes, prevention, and treatment of ophthalmological disorders.
- To work closely with Asian and international researchers to achieve these aims.
- To provide a forum for young and relatively inexperienced researchers to present their research results as Original Articles via an international platform.
- To maintain and promote relationships with any organization with similar goals.

Although the focus of Asian Journal of Ophthalmology mainly was on glaucoma with close ties to the South-East Asian Glaucoma Interest Group (SEAGIG) in the past, the journal now focuses on the entire spectrum of Ophthalmology.

The Asian Journal of Ophthalmology and Kugler Publications have started to collaborate since mid 2012 on the publication of the journal. A new website has been launched (www.asianjo.com), which facilitates all aspects of the peer-review and publication process, from manuscript submission to publication.

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Editorial
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Human research ethics in biomedical journals

Keith Ong
Asian JO Chief and Managing Editor

Human research involves research conducted on human subjects, their personal data, or tissue. This includes clinical trials involving testing and treatment, surveys which involve personal data, interviews, or observation, and blood or tissue specimens.

Looking through the history of research in medicine and science, we find that some experiments compromised the well-being of human research subjects. In World War II concentration camps, experiments were conducted without the consent of the subjects and involved extreme pain and suffering, many times ending in major disability and death of the research subjects. The Nuremberg Code and the related Declaration of Helsinki arose from the need for guidelines to protect the well-being of research subjects.

The World Medical Association (WMA) Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects was initially adopted by the 18th WMA General Assembly in Helsinki, Finland in June 1964.[1] It outlines the guidelines for physicians engaged in clinical research focusing on the responsibilities of researchers for the protection of research subjects.

The role of Human Research Ethics Committees (HREC) mainly involves protecting the welfare of human research subjects. This concern also extends to animals, included in item 21 of the Declaration of Helsinki: "Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected."[1] The same principles apply to animals as they do to human subjects, that is, the benefits should outweigh the harm.

Over the years, the Declaration of Helsinki has been further elaborated; it was last updated by the 64th WMA General Assembly in Fortaleza, Brazil in October 2013. While becoming more comprehensive, it has also become more difficult for researchers to understand. It may basically be summarized as follows: "To avoid or minimize harm to research subjects; where there is potential harm, it should

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be made clear to the research subjects and the benefits of the research should outweigh the potential harm."

When there is potential harm, a committee is then needed to decide if the benefits outweigh risks and harm to the subjects so that a comprehensive range of viewpoints has been evaluated, which is the reason why HREC are comprised of members from different vocations. The benefits of research include gains in knowledge, insight, and understanding to improve society and individual well-being as well as gains in expertise for researchers. Direct benefits to research participants include potential improvement in disease due to new treatments. The role of HREC is to protect potential participants involved in research. In doing so, they must take into account the potential risks and benefits for the community in which the research will be carried out. The ultimate goal is to promote high ethical standards in biomedical research.

Harm can be classified into physical, psychological, social, economic, and legal aspects. Discomfort, which can be physical (having blood pressure measured) or psychological (anxiety when being interviewed), is classified as less serious than harm. Less serious again is inconvenience, which may include the time taken to fill out a form or participate in research.

As guidelines become comprehensive, they have also become more complex to navigate. Asian JO would like to simplify and clarify these aspects, as follows:

1. All prospective studies require HREC or Institutional Review Board (IRB) approval; approval should identify the governing body issuing approval (or waiver of) and appropriate document numbers.
2. Retrospective studies do not need to apply for HREC approval if there is no contact (such as interviews) with the patients and/or when a researcher who is not part of the patients' treatment team is provided with de-identified data, ensuring there is no breach of privacy. Retrospective studies may be low/negligible risk (LNR). Low risk research is defined as research in which the only foreseeable risk is one discomfort. Negligible risk research is defined as research in which there is no foreseeable risk of harm or discomfort; and any foreseeable risk is no more than inconvenience. In LNR, if a researcher who is not part of the treatment team has to access a patient's medical records or contact a patient for clarification of medical details, there may be breach of privacy issues. In such instances, consent has to be given by the subject (patient) or guardian for release of information, otherwise there is a need to seek waiver of consent from HREC. Hence, the authors will make a statement that there was no breach of privacy issues or consent has been obtained or a waiver of consent has been approved by HREC. The authors will also make a statement that the study was retrospective in nature, did not alter the routine management of patients, and would not

alter the outcome of their procedures, which have already been performed prior to the study being conducted.

3. Manuscripts that include an individual patient's clinical information and/or images that may identify the individual, such as case reports and case series, require consent for publication from the subject. The authors are asked to keep this signed consent form in their records. Asian JO asks that authors complete a form declaring that informed consent has been obtained from study subjects.
4. Systematic review papers that review sources already published in journals or information available in the public domain do not need HREC application.

We hope that this editorial clarifies guidelines, interpretation and reasons regarding human research ethics requirements for Asian JO, which are also available online in our Ethics and Malpractice Policy. We would also like to inform prospective authors and other interested parties that our Author Guidelines have been updated and come into effect starting May 1, 2021.

Dr. Keith Ong
Chief and Managing Editor
Asian Journal of Ophthalmology

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1. World Medical Association. Declaration of Helsinki. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

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Original Article
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Prevalence of severe visual impairment and barriers to access eye care services in the Udupi district

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Abstract

Aim: *To assess the prevalence of severe visual impairment (SVI) and reasons for not accessing eye care services in a field practice area of a tertiary care hospital.*

Study design: *Cross-sectional observational study.*

Materials and methods: *Through a cross-sectional study using simple random sampling, a total of 1510, individuals above 18 years of age, from six rural and maternity welfare centers (RMCW) within a distance of 20 km from a tertiary hospital were approached. All participants underwent basic assessment of visual acuity, anterior segment evaluation using torch light, and answered a structured questionnaire on eye care.*

Results: *Of 1510 subjects, 267 had SVI (defined as visual acuity < 6/60 either in one or both eyes) with a prevalence of 17.7%. SVI was higher among men and those above 60 years of age (52.8%). Significant association was found between barriers to accessing eye care facilities and lack of knowledge to access health care (p = 0.004), lack of financial support (95% CI, p = 0.006), and social reasons (95% CI, p = 0.028). Prevalence of SVI among diabetics was 32.7% as compared to non-diabetics (OR: 2.630; 95% confidence interval: 1.864–3.712), and among hypertensives was 34.61% as compared to non-hypertensives (OR: 2.836; 95% confidence interval: 1.977–4.068).*

Conclusion: *In spite of being close to a tertiary care center, a prevalence of SVI in 17.7% of this population indicates a lack of knowledge regarding the importance of self-health care in subjects. This emphasizes the need to increase the awareness among the general public to access the ophthalmic health care facilities in order to improve the ocular health of the patients.*

Keywords: *barriers to access eye care services, house-to-house screening, lack of knowledge, severe visual impairment, social burden*

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Introduction

According to a 2010 World Health Organization report on visual impairment (VI) in India, approximately 62.6 million people are visually impaired, 8.01 million are blind, and 54.5 million have low vision.[1] A meta-analysis by Flaxman *et al.*,[2] as well as other studies,[3] have shown that, as the population increases and ages, common causes of VI are cataract and refractive errors, which are seen more in rural areas. Moreover, in India, more than 80% patients with cataract blindness who were advised surgery did not take the advice over a 2-year follow-up period because of economic or social constraints.[4,5]

In studies on the impact of successful cataract surgery on quality of life conducted in India, Shamanna *et al.*[6] and Finger *et al.*[7] found that overall quality of life improved for patients after cataract surgery. Despite the advantage of free health and eye care services, the majority of Indians living in rural areas are less likely to use eye care services and are more likely to suffer disability-adjusted life years and heavier economic loss.[6,8-10] The reasons for not accessing eye care services are good vision in the other eye, a feeling that there is no need for surgery, a belief that in older age VI is known to happen, fear of surgery, expenses, and lack of caretakers to accompany to the hospital.

VI is a significant public health problem in many parts of the world, including the Indian state of Karnataka.[11] To our knowledge, there has been no systematic study on the prevalence of VI and the perceived barriers to access eye care services in the rural areas of the Udupi district, in the state of Karnataka, India. In this study, we aim to provide a snapshot on the prevalence of VI and the reasons for not utilizing eye care services in the areas of six rural and maternity welfare centers (RMCW) attached to a tertiary care center by conducting a house-to-house survey.

Materials and methods

This is cross-sectional study included the rural population above 18 years of age living in the areas of RMCW centers attached to a tertiary care hospital situated in the Udupi district of the state of Karnataka. The study was approved by the Institutional Ethics Committee of Kasturba Medical College and followed the Declaration of Helsinki.

The population of the Udupi district is approximately 1.18 million.[11] The total population covered by the six RMCW centers is 46,856, with those above 18 years of age being 38,308. All the RMCW centers were located within 20 km from the base hospital. Based on a pilot study conducted by the principal investigator which anticipated a proportion of VI of 12.3% in the population, with a relative precision of 15 at 95% confidence, the calculated minimum sample size was 1,217 individuals. A total of 1,510 individuals above 18 years of age residing in homes in

the area covered by the RMCW centers were included in the study using a simple random sampling method.

The RMCW centers are managed by auxiliary nurse midwives (ANMs) who have close relationships with the population. The RMCW centers were established 40 years ago and the ANMs were employed to develop a positive interaction with the villagers. They act as a link between the tertiary care center and the villagers. ANMs have house lists of all village residents; all residents were enrolled in the ANMs' list. The villagers were informed well in advance to be at home on the given dates to take part in the study, which was a house-to-house survey. The principal investigator and assistants visited each house. The assistants were sixth semester medical students posted in the Department of Ophthalmology, Kasturba Medical College. After undergoing 2 weeks of training to assess visual acuity (VA), they were posted for the survey under the guidance of a final year postgraduate student. ANMs were recruited for help, as they were aware of the exact location and number of residents of each house.

The questionnaire on eye care services was prepared by the principal investigator (Annex 1). The contents were validated by three ophthalmologists and a statistician. The approved questionnaire was translated into the local language (Kannada) and the translation was validated by retranslation into English.

Written informed consent was obtained from all participants. All the subjects included in the study answered the questionnaire. The questionnaire probed into the reasons for not accessing eye care services, which were mainly lack of self-awareness of VI, lack of an accompanying person for medical visits, financial burden, and social burden.

All the participants underwent a brief ophthalmological examination. VA was checked using the Snellen chart (including the illiterate E cards whenever necessary) to evaluate whether participants were able to see the top letter on the chart at a distance of 6 meters in good day light. The aim was to identify individuals having SVI, defined as VA less than 6/60. In those who had spectacles, VA was assessed with the spectacles; in those who did not have spectacles, unaided VA was recorded. Whether with or without spectacles, the aim was to find out how many individuals were leading their lives with SVI. The data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 15. A *p*-value less than 0.05 was taken as significant.

Since our study focused on assessing the prevalence of SVI and the reasons for not accessing eye care facilities, the causes of SVI, pinhole test, and refraction were not examined. The subjects who were found to have SVI were later called to RMCW centers for complete evaluation. However, the results of those examinations are not a part of this present study. A further study to assess these items is planned and will be published later.

Results

A total of 1,510 individuals who were above 18 years of age were approached from six RMCW center areas. Of the 1,510 subjects examined, 43% of the subjects were 18–44 years of age, 28.2% were 45–60 years of age, and 28.8% were over 60 years of age. Among the total subjects examined, 63.18% were females and 36.82% were males. The majority (41.4%) of subjects had academic qualifications between grades 5–10. The demographic characteristics of the population are summarized in Table 1.

Table 1. Sociodemographic characteristics of the subjects

Variables	*n* (%)
Age group (years)	
18–44	650 (43%)
45–60	425 (28.2%)
> 60	435 (28.8%)
Gender	
Female	954 (63.2%)
Male	556 (36.8%)
Education	
Illiterate	96 (6.4%)
Grades 1–5	202 (13.4%)
Grades 5–10	625 (41.4%)
Grades 11–12	277 (18.3%)
Higher education	310 (20.5%)

Prevalence of SVI

SVI, *i.e.*, visual acuity less than 6/60 either in one or both eyes was noted in 267 (17.7%) subjects. Monocular SVI was found in 8.8% of subjects and binocular SVI was found in 8.9% of subjects.

Correlation of SVI with gender and age

Among 267 subjects who had SVI, 159 (59.55%) were females. By taking the gender proportion of the specified population into consideration, approximately 16.6% of women and 19.4% of men suffered SVI. The prevalence of SVI was greater in

individuals above 60 years of age (52.81%) when compared to the 18–44 (14.23%) and 45–60 age groups (32.96%).

Correlation of SVI with education level and employment status

Details about the education level of all participant subjects and presence or absence of SVI are shown in Table 2. There was greater prevalence of SVI among the group with less than 10 years of schooling (79%) when compared to the group with more than 10 years of schooling (21%); this was statistically significant $p = 0.000$ (Table 3).

There was no statistically significant association between the presence of SVI and level of employment. Of 654 subjects in the employed group, SVI was noted in 66; of the 589 subjects in the unemployed group subjects, SVI was noted in 67.

Table 2. Education level of all participant subjects versus presence or absence of severe visual impairmentt

Academic qualifications	No SVI*	Monocular SVI*	Binocular SVI*	Total
Illiterate	62	20	14	96
Grades 1–5	154	18	30	202
Grades 5–10	496	56	73	625
Grades 11–12	246	21	10	277
Higher education	285	18	7	310
Total	1,243	133	134	1,510

SVI defined as visual acuity < 6/60
SVI: severe visual impairment

Table 3. Severe visual impairment versus years of schooling (n = 267)

Years of schooling	Monocular SVI*	Binocular SVI*	Chi-square test
> 10 years of schooling	39 (14.6%)	17 (6.4%)	0.0000
< 10 years of schooling	94 (35.2%)	117 (43.8%)	

SVI defined as visual acuity < 6/60
SVI: severe visual impairment

Self-awareness about SVI

Of the 267 subjects with SVI, 61.04% were aware of their SVI. However, they did not seek any treatment or ocular examination.

SVI and systemic disease association

Of 1,510 subjects examined, 180 (11.92%) were diabetic. Of the 267 subjects with SVI, 59 (22.1%) were diabetic. Prevalence of SVI among diabetics was 32.7%, while in non-diabetics it was 15.6%. This was statistically significant (odd ratio: 2.630; 95% confidence interval: 1.864–3.712).

Similarly, of the 1,510 subjects examined 156 (10.33%) were hypertensive. Of the 267 subjects having SVI, 22.2% were hypertensives. The prevalence of SVI among hypertensives was found to be 34.61%, while among non-hypertensives it was 15.73%, which was also statistically significant (odd ratio: 2.836; 95% confidence interval: 1.977–4.068).

Reasons for not accessing of eye care services

Among the 267 subjects who were found to have SVI, the main reasons given for not accessing eye care services were: lack of knowledge to access health care (50.19%, $n = 134$), lack of accompanying person (34.83%, $n = 93$), lack of financial support (8.61%, $n = 23$), and lack of social support (6.37%, $n = 17$). (Table 4).

When analyzing non-utilization of eye care services in relation to education status, we found that there was a significant association between less than 10 years of schooling and lack of knowledge to access health care ($p = 0.004$), lack of social support ($p = 0.028$), and lack of financial support ($p = 0.006$) (Table 5).

Discussion

Approximately 285 million people are visually impaired worldwide: 90% of the visually impaired live in developing countries.[1] Even though 80% of all VI can be avoided or cured, the prevalence of blindness in the population aged 50 years and above is 8.5%. The top two causes of VI impairment worldwide are uncorrected refractive errors and unoperated cataract.[12] Cataract surgery has a positive impact on the quality of life and income of the patients.[13,14,] In India, the prevalence of blindness in the general population is 1.1%.[15]

Table 4. Reasons for not accessing eye care services among subjects with severe visual impairment

Reasons	*N* (%)
Lack of knowledge to avail health care facility	134 (50.19%)
Lack of accompanying person	93 (34.83%)
Financial burden	23 (8.61%)
Social burden	17 (6.37%)
Total	267

SVI: severe visual impairment

Table 5. Association between barriers for eye care versus years of schooling

Reasons	> 10 years of schooling	< 10 years of schooling	OR (CI)	*P*-value
Financial burden	0	23	1.122 (1.072–1.177)	0.006
Lack of accompanying person	18	75	0.904 (0.593–1.379)	0.753
Social burden	0	17	1.082 (1.041–1.125)	0.028
Lack of knowledge to avail health care facility	38	96	1.491 (1.181–1.883)	0.004

$p < 0.05$ is considered significant
CI: confidence interval; OR: odds ratio; SVI: severe visual impairment

Our study found that, in spite of being close to a tertiary care hospital, availability of primary and secondary level of care nearby, and many awareness programs being conducted in this area, 17.7% of subjects were found to have SVI, i.*e.*, visual acuity less than 6/60 or inability to count fingers at 6 meters in one or both eyes. Other studies in comparable populations, such as by Zhang *et al.*[16] and Srinivisan *et al.*[17] found much lower prevalence of SVI at 0.9% and 0.8%, respectively.

Our study showed that SVI was more prevalent among males and those aged 60 years or more. A study conducted by Singh *et al.* showed similar results, [18] as did Zhang *et al,* who also found a higher prevalence of SVI in individuals above 50 years of age, but contrary to our study, found higher SVI prevalence among females.[16]

In this study, the single most important reason for not accessing eye care was lack of knowledge to avail health care facility among those who had SVI (50.19%), followed by 34.83% who had no accompanying person, lack of financial support (8.6%), and lack of social support/social reasons (5.9%) such as taking care of grandchildren and other social responsibilities like attending functions and performing other household activities, etc.).

In our study, of the 267 subjects with SVI, 61.04% were aware of their SVI. However, they did not seek any treatment or ocular examination. Of these, almost 50.19% did not have the knowledge to access ophthalmic health care facilities.

Lack of knowledge included the following misconceptions: poor vision is a part of ageing and so individuals are expected to live with it; in case they opt for eye checkup, fear that their visual complaints will be revealed to others; lack of knowledge about whom to approach for their visual complaints, which also

included fear of losing existing vision if they opt for surgical treatment for their ocular condition.

Another compelling reason for not accessing health care service was lack of accompanying person. Most of the families are working couples, so elderly individuals do not have someone to bring them to the hospitals on weekdays. Hence, most of them postponed their eye checkup. Lack of joint family system and young family members working in distant places (away from home) are some of the reasons for the above problem.

Although the district's blindness control society and a non-governmental organization run camps accommodate the accompanying person and reduce the financial burden on the patients, our study showed that 8.61% informed that they did not avail the free treatment due to the financial burden. On questioning, they explained that they have to spend on the accompanying person's food, the accompanying person loses their pay during the hospital stay as most of them are daily wagers, and other family members need to take time off from their duties to take care of the children at home. All these together cause a significant financial burden on the family.

Lastly, around 5.9% did not avail the health care facility due to social reasons. For example, many elderly individuals had to take care of pregnant or postpartum women and children whose parents were away for work. Some also have the misconception that locking the house is a bad omen: some houses have daily deity worship, which goes against locking and leaving the house.

We find it notable that, even with available primary, secondary, and tertiary health services in the vicinity that may be accessed for free, almost 61.4% of the participants who were aware of their SVI had not sought treatment, which is similar to the reported urban data of Andra Pradesh Eye Disease Study (APEDS).[19] This might be due to the health-seeking priorities in relation to age in rural areas, as many believe that visual impairment is a part of aging and nothing can be done about it. However, our study uncovers that, in addition to the idea that VI is to be accepted as a normal part of aging, there are other powerful factors at play. A similar study by Srinivasan *et al.* showed that person-related barriers to undergo cataract surgeries were lack of perceived need (for reasons such as old age, good vision in other eye) and lack of accompanying person. The service-related barriers were lack of affordability and accessibility.[17]

Our analysis also clearly shows that the majority of the rural population under study with less than 10 years of schooling did not seek eye care mainly due to lack of knowledge about availing health care facility, as well as the economic and social burden of accessing ophthalmic care. Less than 10 years of schooling had a statistically significant association with the prevalence of SVI.

Strengths and limitations

The main strength of our study lies in providing a snapshot of SVI prevalence for certain areas of the Udupi district as well as outlining key factors that prevent individuals with SVI from accessing eye care. The main limitation is that the study sample covered various RMCW centers, and therefore is not representative of the whole district. In addition, we did not examine the causes of SVI, which will be outlined in further planned studies. However, we believe the data presented in this study may provide a foothold for a larger cluster-sampled data collection, which is required to plan future public health interventions.

To conclude, our study captured a snapshot of SVI prevalence of visual impairment in the Udupi district of southern India and identified the factors preventing individuals from accessing ophthalmic care. The observation that economic and social reasons are important for not seeking treatment for the subjects included in the study leads us to conclude that, in order to increase the uptake of services, there is a need to understand the link between social and economic factors and impact of direct and indirect costs on seeking treatment in the social context of rural people. Hence, it is recommended that, a comprehensive framework be evolved to provide health care facility in rural areas, which should include community education regarding eye check-ups and a well-established referral system.

Declarations

Competing interests

None to declare.

Funding

None to declare.

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Annex 1. Questionnaire used in the study.

Prevalence of severe visual impairment in age group > 18 years and barriers to access eye care services in a field practice area of KMC, Manipal in Udupi District of Karnataka. A survey by the Department of Ophthalmology, KMC Manipal.

PART A

NAME: ADDRESS:
AGE: CONTACT NO:
SEX: DIETARY HABITS: Vegetarian/Non-vegetarian
CASTE: ACADEMIC QUALIFICATIONS:
OCCUPATION: ECONIMIC STATUS:

PART B

1. Which statement best describes your vision?
(a) Excellent (b) Good (c) Fair (d) Poor (e) Unable to see

2. Do you use eyeglasses/contact lenses?
(a) Yes (b) No

3. Do you have a history of any of the following eye problems?
(a) Cataract (b) Glaucoma (c) Color blindness (d) No

4. Have you noticed any decrease in vision in the last 5 years?
(a) Yes (b) No

5. Are you of the opinion that decreased vision is natural with old age?
(a) Yes (b) No

6. If yes, do you think treatment is not REQUIRED in such instances?
(a) Yes (b) No

7. Are you worried that seeing someone for an eye check-up would reveal vision loss?
(a) Yes (b) No

8. Do you know where and to whom to approach for eye check-ups?
(a) Yes (b) No

9. Do you have to travel far for an eye check-up?
(a) Yes (b) No

10. Do you feel that an eye check-up is not a priority because of other serious medical problems?
(a) Yes (b) No

11. Do you feel that you would like you have an eye check-up, but other medical problems prevent you from going for an eye check-up?
(a) Yes (b) No

12. Are you afraid of surgery?
(a) Yes (b) No

13. Is lack of finance the reason for not going for eye check-up?
(a) Yes (b) No

14. Is lack of an accompanying person preventing you from getting an eye check-up?
(a) Yes (b) No

15. Are family/business /other commitments reasons that prevent you from having an eye check-up?
(a) Yes (b) No

16. Is it because the dominant family member does not feel there is a need for an eye check-up for other family members, especially elderly members?
(a) Yes (b) No

17. Do you feel that a lot of time is taken in tertiary eye care hospital for eye check-ups?
(a) Yes (b) No

18. Do you feel that students perform the examination rather than consultants?
(a) Yes (b) No

19. Do you have any significant systemic illness?
(a) Yes (b) No

20. If YES, then specify the type of illness and duration:
    - Diabetes
    - Hypertension
    - Anemia
    - Others

21. If YES to any of the above illness, have you undergone an eye check-up in:
    - The last two years
    - The last five years
    - Never had a check-up
    - Don't think it is required to do so

PART C

Vision: (RE) (LE)

For those who have severe visual impairment in any eye:
- Visual axis:
- Extraocular movements:
- Anterior segment (torch light examination)

IMPRESSION: (CAUSE OF VISUAL IMPAIRMENT):
- Cataract
- Corneal blindness
- Others:

ADVICE TO PATIENT:

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Profile of fungal keratitis in a Sub-Himalayan territory of north India

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Abstract

Aim: *To study the microbiological and epidemiological profile of patients with suppurative corneal ulcer presenting in a rural referral center situated in a Sub-Himalayan territory of north India. The study was conducted to evaluate the epidemiology and frequency of mycotic keratitis among the patients of suppurative corneal ulcer and to identify various fungal species as etiological agents.*

Methods: *Corneal scrapings from 56 patients of suppurative corneal ulcers were subjected to direct microscopy and culture.*

Results: *Of the 56 cases of suppurative corneal ulcer investigated, fungal etiology was identified in 18 (32%) cases. Most of the patients (82.1%) worked in agriculture. Trivial trauma with vegetative matter was the most common predisposing factor. Fusarium and Acremonium species were the most common fungi isolated, followed by Aspergillus. Four cases of rare mycotic keratitis caused by Paecilomyces lilacinus, Scedosporium apiospermum, Monilia sitophila, and Ulocladium species were detected. Four cases were smear positive (10% KOH wet mount) but culture negative. Analysis of KOH wet mount was done using culture as gold standard. The sensitivity and specificity of KOH wet mount was 71.43% and 90.48%, respectively.*

Conclusion: *Direct microscopy and culture has a greater diagnostic value in the management of suppurative corneal ulcer. The authors have observed changes in the pattern of organisms identified as cause of fungal keratitis in the region. Rare species of fungi may also be detected if corneal scrapings are collected for direct microscopy and culture from all the cases of suppurative corneal ulcers greater than 2 mm.*

Keywords: *corneal ulcer, fungal keratitis, north India, rare fungi, Sub-Himalayan*

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Introduction

Fungal infections of the eye are recognized as an important cause of morbidity and blindness worldwide. The prevalence of individual pathogens largely depends on geographical and climatic factors. Due to a large agrarian population and environmental factors, mycotic keratitis is common in India. Direct microscopy, a simple and widely available laboratory technique, is of greater diagnostic value in the management of suppurative corneal ulcers. The diversity of clinical presentations observed in each case and also new emerging cases each year pose a diagnostic and therapeutic challenge to the ophthalmologist. It shows greater morbidity than bacterial keratitis because of delayed diagnosis and available drugs that may not be effective. Newer and rare fungi are being reported all over the globe. More than 70 genera of filamentous fungi and yeasts have been identified as the etiological agents of mycotic keratitis.[1-4]

This study was undertaken to evaluate the frequency of positive fungal cultures in suppurative corneal ulcers and of various fungal species identified as etiological agents in the patients attending a rural referral centre in a Sub-Himalayan territory of north India.

Material and methods

A total of 56 cases of suppurative corneal ulcer were studied. These patients presented during a 2-year period. Patients with suspected or confirmed viral keratitis, healing corneal ulcers, neuroparalytic keratitis, interstitial keratitis, ulcers associated with autoimmune conditions, cornea at risk of perforation, small ulcers (less than 2 mm size), and patients who refused to participate were excluded from the study. Patients were examined using standardized protocols and proforma. A detailed ocular examination was performed. To determine the causative organism, corneal scrapings were taken under magnification of slit-lamp biomicroscope for direct microcopy and culture. After topical anesthesia with xylocaine 4%, the base and the leading edge of the ulcers were scraped from periphery to centre with the blunt edge of no. 15 disposable blades. The material was smeared on two slides, *i.e.*, wet mount KOH 10% and Gram staining. It was smeared thinly with a marked area on the glass slides for Gram staining. For KOH 10% preparation, scrapings were placed within a marked area on glass slide and then covered with one drop of KOH 10%, followed by placement of cover slip. The material was then inoculated onto blood agar and Sabouraud's dextrose agar (SDA) with and without antibiotic, followed by subculture on solid medium. Two sets of SDA with and without antibiotic were maintained at 25°C and 37°C separately over a period of 4 weeks. The inoculated SDA was examined daily and discarded at 3 weeks if no growth was seen. If fungal hyphae were seen on KOH smear, but failed to grow in culture, the causative organism was reported as fungi.

A treatment protocol was followed. After taking the corneal scrapings for direct microcopy and culture, the patient was put on empirical treatment consisting of fortified cefazoline 5%, fortified tobramycin 1.3%, atropine eye drops 1%, tablet acetazolamide 15mg/kg/day. If KOH wet mount was positive, natamycin 5% drops were added to the treatment regime. Oral dose of itraconazole 100 mg was given BID in non-responding cases.

Results

A total of 56 patients met the inclusion criteria of this study. Thirty (53.6%) patients were male and 26 (46.4%) were female. All cases lived in rural areas. The most common affected age group was 41–60 years (37.6%). The mean age was 52.7 years (range 22–95 years). Forty-one cases (73.2%) worked in agriculture (Table 1). Corneal injury (44 cases, 78.6%) was the most common predisposing factor (Table 2). Trivial trauma with vegetative matter (35 cases, 62.5%) was the most common mode of injury (Table 3). The majority of patients (38 cases, 67.9%) had consulted health care providers of some kind before presenting to our referral rural center and had used topical medications such as antibiotics, antifungals, and steroids, or traditional medicines such as ayurvedic eye drops, plant juice, etc.

Table 1. Occupation distribution of subjects

Occupation	Agriculture	Laborer	Mechanic	Driver	Other	Total
Cases (%)	41 (73.2%)	6 (10.7%)	3 (5.3%)	2 (3.7%)	4 (7.1%)	56

Table 2. Distribution of subjects according to their predisposing factors

Ocular factors	No. of cases
Corneal injury	44
Lagophthalmos*	3
Chronic dacryocystitis*	3
Trichiasis	2
Use of topical steroids	5
Ectropion	1
Entropion	1
Systemic factors	
Diabetes mellitus*	4
None	5

***Some patients had more than one predisposing factor**

Table 3. Distribution of subjects according to mode of injury (*n* = 44)

Traumatic agents	Vegetative matter	Dust	Stone	Metal	Toothbrush	Total
No. of cases	35	3	3	2	1	44

Table 4. Distribution of subjects according to fungal isolates detected from culture (*n* = 14)

Fungi	Pure isolates	Mixed with bacteria	Total
Acremonium	4		4
Aspergillus flavus	1	1	2
Fusarium	4		4
Peacilomyces lilacinus	1		1
Monilia sitophila	1		1
Scedosporium apiospermum	1		1
Ulocladium	1		1
Total	**13**	**1**	**14**

Most patients were from low socioeconomic status (41 cases, 73.2%). A significant increase in the number of cases was observed during the harvesting seasons between March and April (19 cases, 33.9%) and November and December (14 cases, 25%). Thirty-one cases had an associated hypopyon. Site of the ulcer was central in 38 cases and paracentral in 18 cases. Forty-nine cases (87.5%) were treated as inpatients and seven cases (12.5%) were treated as outpatients. Mean duration of inpatient treatment was 13.46 days (range 3–29 days).

Of 56 cases of suppurative keratitis, a fungal etiology was identified in 18 cases. Of these, 11 were male and 7 were female. All cases were of unilateral mycotic keratitis. Among 18 cases of fungal keratitis 10 cases were both culture- and smear-positive, 4 cases were culture-positive and smear-negative, and 4 cases were smear-positive and culture-negative. Among 14 culture-positive cases, the most frequent agents isolated were *Fusarium* (4 cases) and *Acremonium* species (4 cases), followed by *Aspergillus flavus* (2 cases). One case each of *Paecilomyces lilacinus*, *Scedosporium apiospermum*, *Monilia sitophila*, and *Ulocladium* species were detected (Table 4). Analysis of KOH wet mount was done using culture as gold standard. The sensitivity and specificity of KOH wet mount was 71.43% and 90.48%, respectively. The positive predictive value and negative predictive value of KOH wet mount was 71.42% and 90.47%, respectively (Table 5).

Table 5. KOH wet mount using culture as gold standard (*n* = 56)

KOH Wet mount culture		Total
Positive	**Negative**	
10	4	**14**
4	38	**42**
14	**42**	**56**

Sensitivity: 71.43%
Specificity: 90.48%
Positive predictive value: 71.42%
Negative predictive value: 90.47%

Discussion

Corneal infections are known to be the second most significant cause of monocular blindness rated after unoperated cataract in some developing nations in particular and in the tropics in general. Limited technical and infrastructural capability for diagnosis and research as well as inaccessible treatment pose considerable challenges in the management of fungal keratitis in developing countries. The etiological and epidemiological patterns of corneal ulceration have been found to vary with the patient population, health of the cornea, geographic location and climate, and time. Hence, an understanding of the epidemiological and etiological features as well as the risk factors that occur in a specific region are important in rapid recognition, timely institution of therapy, optimal management, and prevention of this disease. In order to start specific therapy, it is necessary to conduct meticulous laboratory investigations which include microscopy and culture of corneal scrapings for identification of the microbial agent.[5-8]

In this Sub-Himalayan territory of north India, suppurative corneal ulcer continues to be a cause of concern; the predominance of agricultural activity is the principal causative factor. Most of these ulcers follow minor agricultural injuries. Corneal ulcers and ocular trauma are the commonest cause of corneal blindness, defined as "visual acuity less than 20/400 in one eye caused by corneal disease".[9-11]

In the present study, all patients (100%) were from a rural background. We observed that illiterate individuals were more prone to corneal ulceration. Song *et al.*[9] and Gupta *et al.*[12] also observed that rural populations with low education levels, little or no access to health care, from lower socioeconomic status, with poor knowledge about proper eye care, and little awareness regarding preventive measures were more prone to develop suppurative corneal ulcers following trivial trauma.

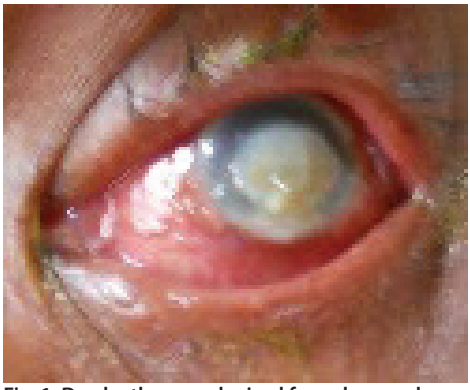

Fig. 1. Dry, leathery, and raised fungal corneal ulcer with thick hypopyon.

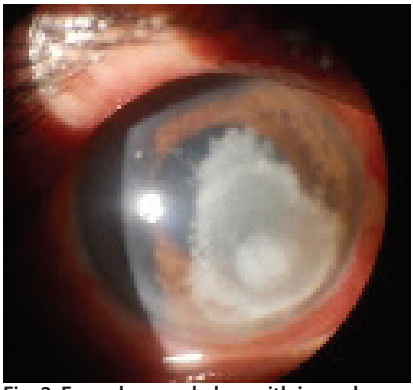

Fig. 2. Fungal corneal ulcer with irregular and feathery margins.

Most patients presented during the harvesting season, when agricultural activities are more intensive, due to which individuals are more prone to trivial corneal injuries with vegetative matter. Taylor *et al.*[13] and Bharati *et al.*[14] found a very high prevalence of fungal keratitis in rural India and China; furthermore, the incidence of keratitis was greater at the times of the year when agricultural work intensified.

It was observed that corneal injury was the most common predisposing factor causing suppurative keratitis. Vegetative matter was observed to be the most common traumatic agent. Titiyal[15] and Srinivasan *et al.*[16] also reported agricultural products as the main agents responsible for trauma.

Forty-five patients had consulted health care providers before presenting to our institute, having used some kind of topical medication including antibiotics, antifungals, ayurvedic eye drops, topical steroids, plant juice, seeds etc. Five patients had visited traditional healers before presentation. In their study of infectious keratitis in Delhi, Saha *et al.* found that 3.5% patients gave history of use of topical herbal medicine before presentation.[1] They further stated that the topical use of breast milk, castor oil, onion extract, flower extracts, honey, steam, and even chicken blood has been reported in south India.

Among 14 fungal culture-positive cases, *Fusarium* and *Acremonium* species were detected in four cases each, *Aspergillus flavus* was detected in two cases, and *Scedosporium apiospermum*, *Monilia sitophila*, *Paecilomyces lilacinus*, and *Ulocladium* were detected in one case each (Table 4). Analysis using culture as the gold standard revealed sensitivity and specificity of KOH wet mount as 71.43 % and 90.48%, respectively. Ong *et al.*[17] also observed the altered pattern of fungal keratitis at a London ophthalmic referral hospital. Ansari *et al.*[18] found that although *Fusarium* and *Aspergillus* were most commonly associated with fungal keratitis, many other species such as *Scedosporium apiospermum*, *Culvaria*, and

Fig. 3. Fungal corneal ulcer with pseudodendrites.

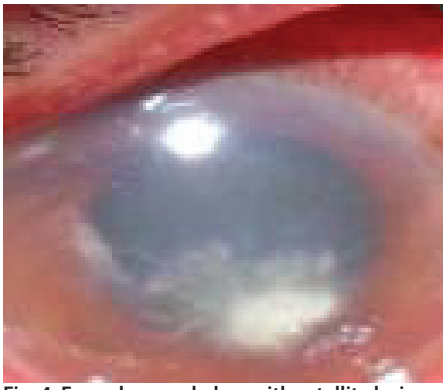

Fig. 4. Fungal corneal ulcer with satellite lesions.

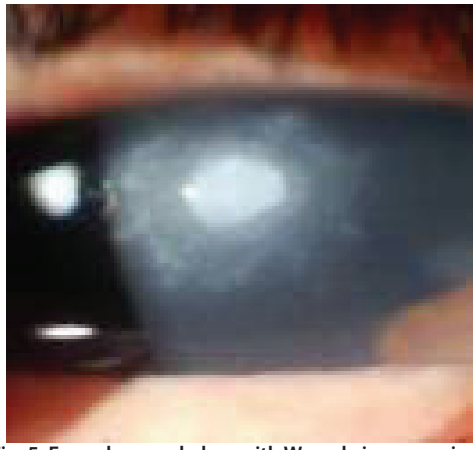

Fig. 5. Fungal corneal ulcer with Wessely immune ring.

Peacilomyces have also been robustly reported. It was observed that among 18 cases (14 culture-positive and 4 smear-positive but culture-negative) of fungal keratitis, 5 patients improved with topical natamycin alone, 9 patients improved with a combination of topical natamycin and oral itraconazole, and 3 patients were refractory to treatment and had the affected eye eviscerated. One subject with *Scedosporium apiospermum* keratitis was refractory to the above regime and responded only with topical voriconazole. On average, it took 6 weeks to 6 months to treat a case of fungal keratitis. Our observation did not match the study by Rajaram *et al.*[19] which found that oral antifungal therapy did not add significant benefit to topical natamycin therapy in treating deep fungal keratitis.

The diagnostic validity of traditional clinical features such as dry, raised, leathery ulcers with thick and immobile hypopyon (Fig. 1), pseudodendrites or feathery borders (Figs. 2 and 3), satellite lesions (Fig. 4), and Wessely immune rings (Fig. 5) has been challenged in recent years. However, we did observe these clinical features in our cases. That said, the utility of clinical diagnosis alone can be unreliable.[18]

Of 56 cases of suppurative keratitis, surgical procedures or other interventions were performed in 12 cases (25.8%). Three cases with associated lagophthalmos were operated for lateral tarsorrhaphy, five cases which developed endophthalmitis due to perforation were eviscerated, two cases with descematocele were applied bandage contact lens, and two cases associated with chronic dacryocystitis were operated for dacryocystorrhinostomy. Extracorneal factors such as entropion, trichiasis, lagophthalmos, chronic dacryocystitis, and dry eye that directly or indirectly initiate or enhance keratitis should be treated meticulously. Despite advances in diagnosis and medical treatment of keratomycosis, 15–27% of patients require surgical intervention such as keratoplasty, enucleation, or evisceration due to either failed treatment or advanced disease at presentation.[20,21]

We conclude that suppurative corneal ulcer is a major cause of preventable monocular blindness and educational strategies can reduce avoidable risk such as trauma, but treatment protocols are required to manage established disease**.** Direct microscopy and culture are of greater diagnostic value than traditional clinical features in the management of infective keratitis. The authors have observed changes in the pattern of organisms identified as cause of fungal keratitis. Rare mycotic keratitis may not be so uncommon if corneal scrapings are taken in all cases of suppurative corneal ulcers greater than 2 mm for direct microscopy and culture.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Dr. Rajendra Prasad Government Medical College Kangra Tanda (India).

Competing interests

None to declare.

Funding

None to declare.

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Wick technique in subscleral and subconjunctival Ologen™ implantation with trabeculectomy in patients with high risk of failure

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Abstract

Introduction: *Ologen™ is traditionally placed subconjunctivally during trabeculectomy, which limits its area of action. Subscleral implantation of Ologen has been described involving fashioning a gutter beneath the scleral flap. This, however, would not prevent fibrosis at the margins of the scleral flap. We describe a modified technique of Ologen® placement that has the potential to prevent scarring at the margins of the flap without the need to fashion a gutter.*

Materials and methods: *The study involved a retrospective review of patients who had undergone trabeculectomy with Ologen implantation by the wick technique between January 2015 and August 2016. Patients judged to be at high risk of trabeculectomy failure were operated with this technique.*

Results: *A total of six patients with median age of 38.5 years were included in the study. The mean preoperative intraocular pressure (IOP) was 30.8 ± 7.3 mmHg, which reduced to 10.6 ± 2.2 mmHg 18 months after surgery. By 18 months postoperative, all patients had IOP in the low teens (two patients required additional topical medication). One patient had two episodes of hypotony that responded to steroids and cycloplegics. Another patient required two needlings to bring IOP under control. No other complications were noted. Ultrasound biomicroscopy done 3 months after surgery showed two pieces of Ologen in one patient.*

Conclusions: *The results of our study show that this technique may be used effectively in patients at high risk of trabeculectomy failure. Further studies in a larger number of patients with diverse high-risk conditions are required before this technique is recommended for general use.*

Keywords: *subscleral Ologen, trabeculectomy, wick technique*

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Introduction

Long-term success of conventional glaucoma filtering procedures is limited by scarring at various places, including the sclera-sclera interface, episclera-sclera interface, conjunctiva-Tenon episclera interface, and at the internal ostium. Ologen™ (Aeon Astron, Leiden, Netherlands) is a bioengineered collagen matrix that causes fibroblasts to grow through it in a random fashion resulting in a loose scar tissue matrix. Traditionally it is placed subconjuctivally.[1,2,3] Subscleral Ologen implantation has been described with an aim to limit subscleral fibrosis. The technique of implanting subscleral Ologen has been described elsewhere. Briefly, after placing a corneal traction suture, peritomy, and fashioning a rectangular scleral flap, mitomycin C (MMC)-soaked sponges are applied over a wide area for one minute. After removing the sponges, the area is washed off thoroughly with balanced salt solution. A rectangle of deep sclera is dissected 2 mm away from the limbus under the scleral flap to fashion a scleral gutter and place a small piece of subscleral Ologen. The remaining Ologen is placed over the scleral flap after placing the releasable sutures.[1,4] However, as only a small piece is placed subsclerally, the area wherein fibrosis may be limited is also restricted. This may be particularly true at the margins of the scleral flap. Additionally, a gutter needs to be fashioned in the scleral bed to position the implant. There is limited experience with the use of subscleral Ologen, with only three studies having been published so far by a single group.[1,4,5] We describe a novel method in which Ologen is placed subsclerally without the need to fashion a gutter beneath the sclera. After making a scleral flap and punching the ostium as in a routine trabeculectomy, one-fourth of the Ologen is simply tucked under the apex of the scleral flap, with a small portion protruding on either side resembling a "wick", and the apical suture tightly placed. The remaining Ologen is placed on the top of the scleral flap and trabeculectomy completed. This technique offers the potential to limit fibrosis at the margins of the flap in addition to the scleral bed. If the use of subscleral Ologen by the wick technique is proven to be effective, there is an opportunity to enhance the efficacy of trabeculectomy with Ologen implantation and low concentration MMC in high-risk situations.

Materials and methods

Study protocol

Institutional review board approval was obtained for a retrospective review of records of patients who had undergone trabeculectomy along with subscleral implantation of Ologen by the wick technique between January 2015 and August 2016. The study adhered to the tenets of the Declaration of Helsinki.

Data with regards to previous intraocular surgery, baseline intraocular pressure (IOP), antiglaucoma medications, anterior segment fundus findings, visual fields, complications, postoperative IOP, antiglaucoma medications and bleb morphology were collected.

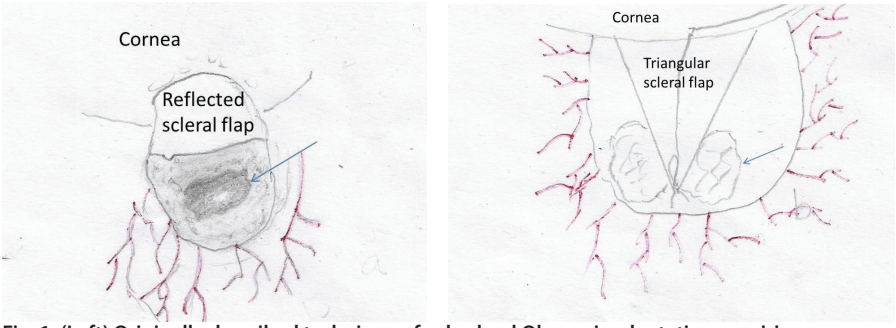

Fig. 1. (Left) Originally described technique of subscleral Ologen implantation requiring fashioning of gutter for Ologen placement (arrow). (Right) Technique used in the present study. A piece of Ologen is simply tucked at the apex of the scleral flap (arrow) and the releasable suture tied tightly. The piece juts out on either side, resembling a "wick".

Video 1. The video shows the steps in the technique from punching the ostium onwards. A 5 x 5 mm triangular scleral flap is made. A Kelly Descemet's punch is used to make the ostium and a peripheral iridectomy is done. The iris is swept off the ostium through the side port with a spatula. A releasable suture is placed at the apex of the scleral flap following Cohen and Osher's technique. One-fourth of the Ologen is positioned under the apex of the scleral flap and the releasable suture tightly tied. Note that the Ologen gets compressed in the process. A second releasable suture is placed at the temporal border of the scleral flap. Viscoelastic is washed off from the anterior chamber with a Symcoe cannula and air injected into the anterior chamber. In view of an air leak from the nasal margin of the scleral flap, an additional releasable suture is placed in the nasal border of the flap. No further air leaks are noted on injecting air into the anterior chamber. The remainder of the Ologen is placed over the scleral flap. The conjunctiva is closed over the Ologen implant with 8-0 vicryl sutures.

Table 2. Postoperative findings of six patients who underwent trabeculectomy with Ologen implantation by wick technique

Patient	Age (years)	Ocular risk factors	Gonioscopy	Antiglaucoma medications	BCVA	IOP (mmHg)
1	27	PK	Closed angles	3T + 1S	20/32	36
2	8	Developmental cataract surgery	NA (Child did not cooperate for gonioscopy)	3T	20/40	24
3	37	Failed trabeculectomy	180° closed angles	4T	20/60	23
4	44	Failed trabeculectomy in fellow eye	Open angles	3T + 1S	20/20	36
5	67	PK	Closed angles	3T + 2S	20/200	40
6	40	None	Narrow angles	3T + 1S	20/20	26

BCVA: best corrected visual acuity; IOP: intraocular pressure; NA: not available; PK: penetrating keratoplasty; S: systemic antiglaucoma medication; T: topical antiglaucoma medication

Surgical technique

Patients judged to be at high risk of failure (risk factors mentioned in Table 1) with conventional trabeculectomy were offered subscleral Ologen implantation (in addition to subconjunctival Ologen placement). Written informed consent was obtained from the patient/legal guardian. All surgeries were performed by a single surgeon (MR) under peribulbar anesthesia. Under surgical asepsis, trabeculectomy was performed using a standard technique. Multiple pledgets (approximately 2 x 1 mm) soaked in 0.1 mg/ml MMC were placed in the subconjunctival space for 1 minute over 4 clock hours. The area was washed with 30 ml of saline. A triangular scleral flap with base 5 mm and height 5 mm was made. Viscoelastic was injected into the anterior chamber after entering with a 15° side port blade. Kelly Descemet's punch (Indo-German Surgical Corporation, Mumbai, India) was used to make the ostium after entering the anterior chamber. A peripheral iridectomy was done. A 6 x 2 mm Ologen implant was inserted for all cases. It was cut into two pieces: three-fourths for subconjunctival placement and one-fourth for subscleral placement (Video 1). The smaller implant was positioned at the apex of the scleral bed and an apical releasable suture tightly placed using the technique described by Cohen and Osher.[5] This resulted in the Ologen showing up on either side of the apex of the scleral flap resembling a wick (Video 1, Fig. 1). An additional releasable suture was placed on the temporal border of the scleral flap. Viscoelastic was washed off from the anterior chamber and air was injected into the anterior chamber. A suture was placed on the nasal border of the scleral flap if air leaks were noted. The conjunctiva was then closed with 8-0 vicryl.

Postoperatively, the patients were treated with topical prednisolone acetate 1% 8 times a day tapered over 3 months, topical homatropine twice a day for 3 weeks, and topical gatifloxacin 0.3% QID for 6 weeks. Patients were reviewed weekly for the first 3 weeks, once every 10 days for the next 2 weeks, and every 3 months thereafter for 18 months. All releasable sutures were removed between 3 and 6 weeks. At each visit, IOP as well as anterior and posterior segment findings were recorded.

Outcome measures

IOP was the primary outcome measure. Absolute success was defined as IOP < 15 mmHg without antiglaucoma medications and qualified success as IOP < 15 mmHg with a maximum of two topical antiglaucoma medications at 18 months. Failure was defined as IOP > 15mmHg with topical antiglaucoma medications or < 6 mmHg with hypotony maculopathy. Secondary outcome measures included best-corrected visual acuity (BCVA), number of antiglaucoma medications used, and bleb morphology.

Table 2. **Postoperative findings of six patients who underwent trabeculectomy with Ologen implantation by wick technique**

Patient	Complications/ additional interventions	IOP 6 weeks	IOP 3 months	IOP 12 months	IOP 18 months	BCVA 18 months	Bleb morphology (MBGS) 18 months	Antiglaucoma medications 18 months
1	Underwent cataract surgery a year after trabeculectomy	11	7	10	11	20/32	CA: 1; PA: 2; H: 1; V: 3	0
2	None	10	11	13	12	20/40	CA: 1; H: 3; V: 2	0
3	None	12	10	12	14	20/60	CA: 2; PA: 3; H: 1; V: 2	0
4	Two episodes of hypotony with shallow AC and SCE at month 7 and 11	18	18	12	10	20/20	CA: 2; PA: 2; H: 1; V: 1	1T
5	Required two needle revisions	8	8	14	9	20/200	CA: 2; PA: 3; H: 3; V: 2	2T
6	None	10	10	6	8	20/20	CA: 2; PA: 2; H: 2; V: 2	0

AC: anterior chamber; BCVA: best corrected visual acuity; CA: central area; H: height; IOP (mmHg): intraocular pressure; MBGS: Moorfields Bleb Grading System; PA: peripheral area; PK: penetrating keratoplasty; S: systemic antiglaucoma medication; SCE: serous choroidal effusions; T: topical antiglaucoma medication; V: vascularity

Results

A total of six patients were included in the study. Preoperative patient data is summarized in Table 1; postoperative patient data is summarized in Table 2. The median age was 38.5 years. All patients had advanced glaucomatous field loss and optic nerve cupping at presentation. Mean preoperative IOP was 30.8 ± 7.3 mmHg. The mean number of antiglaucoma medications (topical and systemic) prior to surgery was four. Four patients (Patients 2, 3, 4, and 6) were deemed to be at high risk of failure on account of young age. Two patients (Patients 1 and 5) had previous penetrating keratoplasty, one (Patient 3) had a failed trabeculectomy, and one (Patient 4) had a failed trabeculectomy in the fellow eye. No intraoperative complications were noted. Median IOP at week 1 postoperative was 11 mm Hg. Mean IOP at week 6 postoperative was 12 ± 3.4 mmHg. All releasable sutures were removed in the postoperative period in all patients by week 6 postoperative. Patient No. 4 developed two episodes of shallow anterior chamber with hypotony and serous choroidal effusions that responded to topical steroids and cycloplegics. Patient No. 5 required two needle revisions to keep the IOP low. IOP reduction at 3 months postoperative was 20.2 ± 8.3 mmHg. At 12 months postoperative, mean IOP was 12.2 ± 1.5 mmHg. Patient 1 underwent uneventful cataract surgery a year after trabeculectomy; no substantial change in IOP was noted after the cataract surgery. At 18 months postoperative, mean IOP was 10.7

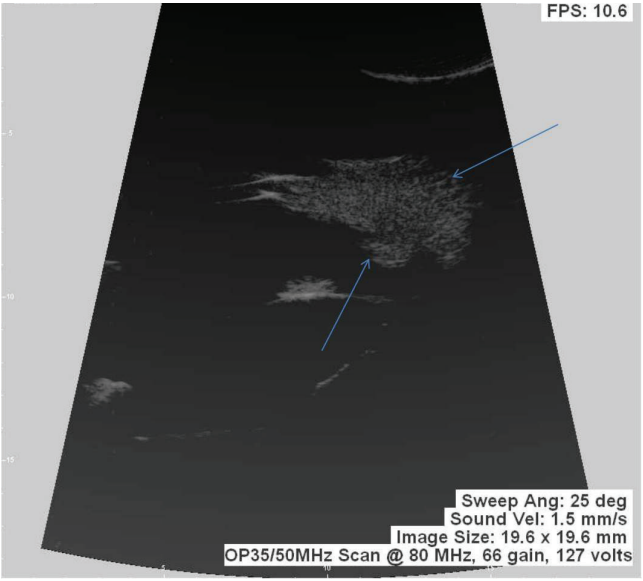

Fig. 2. Ultrasound biomicroscopy of Patient 1 performed 3 months after surgery showing two pieces of Ologen.

± 2.2 mmHg. Two patients were on topical antiglaucoma medications. Thus, four out of six patients met the criteria for absolute success and the remaining two had qualified success. None of the patients had a reduction in BCVA. At 18 months, the bleb area had vascularity similar to the adjacent conjunctiva and all patients had elevated, diffuse blebs. Ultrasound biomicroscopy conducted at 3 months postoperative in Patient 1 showed two pieces of Ologen (Fig. 2).

Discussion

Trabeculectomy with adjunctive MMC is currently the gold standard for lowering IOP in patients with advanced glaucoma. The use of MMC is however associated with a number of complications such as late hypotony, scleral melts, bleb leaks, and blebitis, to name a few. Biodegradable collagen implants such as Ologen were introduced to avoid the complications of MMC. Ologen causes the fibroblasts to grow in a random fashion, thereby reducing scar formation. It also acts as a spacer between the sclera and conjunctiva, preventing adhesions. However, Ologen can only act over a small area 6 mm in diameter and may not be effective in preventing fibrosis in the surrounding areas. Some studies have shown that the use of Ologen with trabeculectomy gives lower success rates than trabeculectomy with MMC. Combining Ologen implantation with a low concentration of mitomycin application has been shown to give higher success rates without any vision-threatening complications.[1-5]

Failure of trabeculectomy over the long term may occur because of scarring at the conjunctiva-sclera interface, sclera-sclera interface and at the internal ostium.[6] Subscleral implantation of Ologen has been described after making a gutter under the scleral flap.[1] However, as mentioned earlier, this may not be effective in preventing scarring at the margins of the flap. We have also noted that it is very difficult to make a deep gutter without risking perforation. Our technique of implantation may be easier and allows for the implant to be in position at the margins and under the scleral flap. Our study shows that trabeculectomy with Ologen implantation by the wick technique may be effective in lowering IOP in these high-risk cases. As MMC was used in a very low concentration for one minute (as is recommended for use with Ologen implantation),[1,4,6] it is unlikely that this alone may have been the only reason for success. Only one patient had a late hypotony. The presence of subscleral Ologen on UBM (Fig. 2) after releasable suture removal may be proof of efficacy. The releasable sutures were tightly placed across the Ologen implant. We have noted that Ologen becomes very soft and compressible once it comes in contact with saline. All releasable sutures were removed in the postoperative period to facilitate Ologen expansion at the margins and under the scleral flap. Patients with higher baseline IOP had a greater drop in IOP.

The limitations of our study include a small number of patients, its retrospective nature, and the lack of a control group. This technique has not been studied in other high-risk conditions, such as neovascular glaucoma. We recommend further studies on a larger number of patients before this technique can be recommended for general use.

Declarations

Competing interests
None to declare..

Funding
None to declare.

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None to declare.

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Tocotrienol-rich vitamin E from palm oil (Tocovid) and its effects in diabetes and diabetic retinopathy: a pilot phase II clinical trial

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Abstract

Aim: *To identify the effects of tocotrienol-rich vitamin E from palm oil (Tocovid) on diabetic retinopathy (DR) in patients with type 2 diabetes.*

Materials and methods: *The intervention group (n = 21) received 200 mg Tocovid twice daily while the control group (n = 22) received placebo twice daily for 8 weeks. Changes in retinal photography by conventional grading and novel quantification of retinal hemorrhage were assessed. Changes in serum biomarkers advanced glycation end products (AGE) general, sRAGE (soluble receptor of AGE), Nε-CML (specific type of AGE), and cystatin C were evaluated.*

Results: *A novel technique to quantify retinal hemorrhage had a strong positive correlation with conventional grading of DR in both eyes at baseline and at the end of the study. Eight-week supplementation of Tocovid resulted in significant reduction in retinal hemorrhage in the right eye. Liver enzymes and ALT significantly reduced. No significant changes in grade of DR, serum biomarkers, HbA1c, blood pressure, renal profile, and lipid profile were observed.*

Conclusions: *Tocovid is a potential adjunct to current treatment of DR and fatty liver disease. A novel method of quantifying retinal hemorrhage is a potential technique for assessing disease severity of DR, particularly the early changes.*

Keywords: *advanced glycation end products, carboxymethyl-lysine, diabetic retinopathy, palm oil, tocotrienol, vitamin E*

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Introduction

Diabetes mellitus (DM) is an alarming public health concern that is approaching epidemic proportions on a global scale. Diabetic retinopathy (DR), one of the main microvascular complications of diabetes, affects 34.6% of the diabetic cohort.[1] It is a leading cause of new onset blindness among individuals aged 20 to 64 years old and accounts for 2.6% of global blindness.[2,3] Effective treatment strategies to prevent onset and progression of DR are needed.

Vitamin E has been touted as a potent antioxidant capable of attenuating oxidative and inflammatory stressors involved in the pathogenesis of diabetes and its related complications. It exists in two major forms, tocopherol and tocotrienol. Its therapeutic role in diabetes, however, remains largely controversial.[4-6] The bulk of the studies done on vitamin E, however, is on the more common tocopherol. Tocotrienol on the other hand, only contributes to less than 3% of the entire literature on vitamin E. Interestingly, growing evidence has demonstrated that tocotrienols possess antioxidant properties that are 40–60 times greater than tocopherols and is more capable of ameliorating diabetic-related complications.[7] A study by Nazaimoon *et al.* demonstrated that tocotrienol was able to reduce lipid peroxidation within 2 months in patients with type 2 DM (T2DM).[8] Other animal studies further endorse the antioxidative properties of tocotrienol in diabetic rat models.[9-12] Among the many sources of tocotrienols, vitamin E extracted from palm oil (*Elaeis guineensis*) contains the most concentrated form of tocotrienols.[13,14]

In addition, animal studies have shown that tocotrienols possess antiangiogenetic abilities and confers significant protection in the retina.[15,16] However, literature on the effects of tocotrienol in attenuating DR is limited. Nevertheless, tocotrienol has also been shown to reduce advanced glycation end products (AGE), a key component in the pathogenesis of DR.[9,17] AGE constitute a group of inflammatory biomarkers formed from reactions between reducing sugars and free amino acids, nucleic acids, and lipids.[18] AGE react with its receptor, RAGE, to produce oxidative stress and activate proinflammatory cytokines including RAGE itself, thus forming a vicious cycle. This ultimately results in DR and other diabetic-related complications.[18,19] On the same note, the landmark Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Trial (DCCT/EDIC) and United Kingdom Prospective Diabetic Study (UKPDS) also demonstrate that it is not HbA1c, which lasts only 3 months, but AGE, which last a lifetime, that are better predictors of DR.[20-25] As the current treatment for DR, which is tight glycemic control, does not address the AGE pathway, tocotrienol is proposed as an adjunct to the treatment regime of DR.

Among the AGE, N-epsilon-carboxymethyl lysine (Nε-CML) has been shown to be the most promising biomarker for predicting the presence and

progressive severity of DR.[20,26-28] Another potential biomarker for DR is soluble RAGE (sRAGE).[29,30] sRAGE isoforms sequester AGE and therefore ameliorate against AGE-RAGE mediated complications of diabetes.[31] On the other hand, cystatin C is a novel biomarker which has been shown to be superior to serum creatinine in detecting the early stages of diabetic nephropathy, another microvascular complication of diabetes.[32]

Therefore, the primary aim of this pilot study is to investigate the effect of tocotrienol-rich palm oil (Tocovid) compared with placebo on inflammatory biomarkers AGE, sRAGE, Nε-CML, and cystatin C and on the disease severity of DR as assessed by retinal photography. The secondary aim of this pilot study is to investigate the effect of Tocovid on other glycemic and metabolic parameters in T2DM.

Materials and methods

Study design

This study was designed as a prospective, randomized, double-blinded, placebo-controlled clinical trial to compare the effect of Tocovid *versus* placebo in adult T2DM patients with DR. This study consisted of 8 weeks of screening and 8 weeks supplementation with either Tocovid or placebo. The overall study design is shown in Figure 1. Ethical approval was obtained from the Monash University Human Research Ethics Committee (Project number: 12091) and the study complied with the principles of the Declaration of Helsinki. Informed written consent was obtained from all participants prior to commencement of screening. The sample size was set at 52 participants based on previous literature.[33] This was based on power calculations demonstrating a difference of 30% ± 5% SD in primary outcome between the intervention and control group. However, due to financial constraints, only 43 participants were recruited.

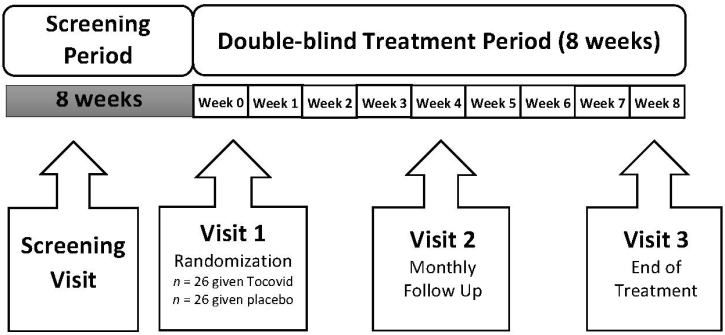


Fig. 1. Overall study design.

Participants and study enrolment

Participants were recruited from the existing pool of patients at the Monash University Clinical Research Center (CRC) in Johor Bahru and in Bandar Sunway, Malaysia. Patients with T2DM were invited to attend the screening visit. Patients were reminded to observe an 8 h fasting period, as per routine diabetes follow-ups, to miss their morning dose of diabetic medication, not to wear contact lenses, and bring their prescribed visual aids.

During the screening visit, complete history-taking and physical examination was obtained. Further screening tests including fasting blood glucose, HbA1c, and digital retinal photography were obtained. Safety tests including electrocardiogram, renal profile, liver function test, lipid profile, and urine dipstick were conducted to confirm the participants' fitness to participate in the study. Serum biomarkers AGE, sRAGE, Nε-CML and cystatin C were tested only on patients who met the inclusion and exclusion criteria.

Participants with the following criteria were included:

1. Participants aged 18–80 years old at the time informed consent was provided.
2. Participants who had T2DM with stable glucose control (not more than 10% change in HbA1c levels over the last 2 months) and HbA1c range within 6.5–14%.
3. If the participant had hypertension, they must have had stable blood pressure control (not more than 10% change in blood pressure over the last 2 months) and blood pressure range of less than 160/100 mmHg.
4. Participants who had stable DR in at least one eye as assessed by retinal photography with no laser, intraocular injections, or other invasive treatment in the last 3 months.

Participants with the following criteria were excluded from the study:

1. Participants who had severe media opacity (*i.e.*, corneal opacities, dense cataracts, and vitreous hemorrhage).
2. Participants who had acute or severe eye diseases (*i.e.*, retinal detachment, periorbital cellulitis, and angle-closure glaucoma).
3. Participants who had acute or severe chronic diseases (*i.e.*, acute coronary syndrome, active tuberculosis, active cancer, end-stage kidney failure, liver or inflammatory diseases).
4. Participants who were pregnant or hoped to become pregnant during the trial.
5. Participants who took water-soluble antioxidants (*i.e.*, vitamins B or C, polyphenols, glutathione) during the past 2 weeks or fat-soluble

antioxidants (*i.e.*, vitamins A, D, E and K) during the past 4 weeks.
6. Participants who were heavy smokers (≥ 20 sticks/day) or had stopped smoking for less than 1 month.

Randomization, study groups, and supplement formulation

Participants who met the inclusion and exclusion criteria were randomized into double-blind treatment period for 8 weeks. Randomization was done by an independent operator by using computer-generated permuted blocks of size 4 in a 1:1 ratio for intervention or control, stratified for patient's age, gender, and duration of DM. Allocation concealment was done by sequentially numbered opaque sealed envelopes.

Both Tocovid and placebo capsules were of similar shape, size, taste, and excipients. The study drugs were labelled as Drug A and Drug B and their identity was kept confidential by ExcelVite (Hovid Berhad, Ipoh, Malaysia). Allocation was concealed until the end of the study. The intervention group received 200 mg twice a day tocotrienol-rich vitamin E (Tocovid Suprabio™), while the control group received placebo twice a day for 8 weeks. EVNol SupraBio, the active ingredient of Tocovid Suprabio™ was manufactured by ExcelVite, Malaysia.

Follow-up visits

Follow-up visits every 4 weeks were conducted to monitor for adverse drug events and participant's compliance to treatment via capsule count. Anthropometric measurements, blood pressure, fasting blood glucose, and urine dipstick were routinely carried out during follow-up visits. In the final visit, HbA1c, retinal photographs and biomarkers AGE, sRAGE, Nε-CML and cystatin C were obtained. Baseline safety tests including ECG, renal profile, liver function test, and lipid profile were repeated to ensure the study drugs had no adverse effect to the participant.

Evaluation of outcomes

The primary outcomes were biomarkers AGE, sRAGE, Nε-CML, and cystatin C and the disease severity of DR as assessed by retinal photography. The secondary outcomes were HbA1c, blood pressure, and other safety tests including renal, lipid, and liver profile.

Retinal photographs

Retinal photographs were taken using a fully automated, non-mydriatic digital retinal imager (Digital Retinography System (DRS), CenterVue, Padova, Italy). Seven different 45° fields were taken for both eyes using this retinal camera at baseline and after 8 weeks. Thereafter, high quality multi-image mosaics (retinal maps) were constructed from the 7-field retinal photographs using an

advanced image registration and montage software i2k Retina® software (Dual Align LLC, Clifton Park, NY, USA) to obtain a more complete and accurate view of the patient's retina.[34] The retinal mosaics or maps were then graded for DR based on the Early Treatment Diabetic Retinopathy Study (ETDRS) grading[35] by an ophthalmologist who was double-blinded. Participants were allocated one of five retinopathy grades: no DR (NDR), mild non-proliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR).

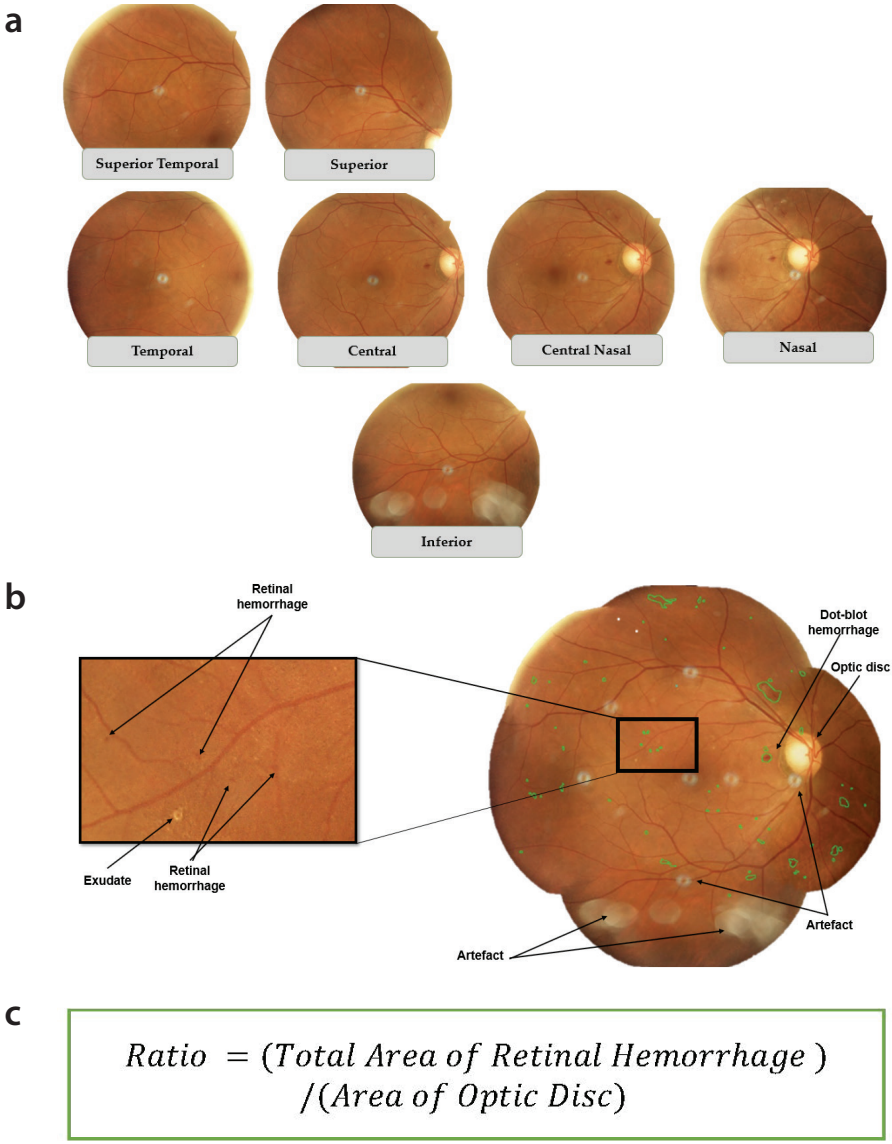
Additionally, the retinal maps were quantified manually by the investigator and vetted by two coinvestigators for retinal hemorrhage by an open-source image processing software, Fiji (National Institutes of Health, USA).[36] The parameters measured were surface area of retinal hemorrhage in the unit measurement of pixels at 100% image zoom. The ratio of total surface area of retinal hemorrhage to surface area of optic disc was then obtained to minimize variances from the retinal photographs pertaining to different zooms, patient position, dimension of eyeball, and refractive errors. The overall process quantifying the retinal hemorrhage is shown in Figure 2.

The specifications of the DRS used to capture the retinal photographs were:
1. Field of view: 45° x 40°.
2. Non-mydriatic operation: minimum 3.8 mm pupil size.
3. Fixation target: 7 internal LEDs.
4. Operating distance: 37 mm.
5. Sensor size: 5 MP (2592 x 1944).
6. Sensor resolution: 48 pixels/degree.

The specifications of the computer monitor used during the quantification of retinal hemorrhage were:
1. Dimensions: 21.5′ (height 10.4″, width 18.7′).
2. Display: 100% brightness, 100% contrast.
3. Resolution: 1920 x 1080.
4. Orientation: Landscape Display HP P22va.
5. Environment: completely dark room.

Biomarkers AGE, sRAGE, Nε-CML, and cystatin C

The serum samples of participants for biomarkers AGE, sRAGE, Nε-CML and cystatin C were stored in a -80°C laboratory freezer. Biomarker processing was conducted by a qualified biochemist on a batch-to-batch basis at the end of the study to avoid inter-assay variation. Serum AGE, sRAGE, Nε-CML, and cystatin C concentrations were measured in duplicates and quantified by calorimetric method using Enzyme-linked Immunosorbent Assay (ELISA) (TECANInfinite 200 PRO, Männedorf, Zürich, Switzerland). The ELISA kit for



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$$Ratio = (Total\ Area\ of\ Retinal\ Hemorrhage) / (Area\ of\ Optic\ Disc)$$

Fig. 2. Overall process to quantify retinal hemorrhages: (a) Seven 45° retinal image fields taken for the right eye. (b) Retinal map constructed from the 7 individual retinal photographs using i2k Retina® software. Areas of retinal hemorrhage manually quantified (circled in green) with Fiji software. Zoomed-in picture showing small areas of retinal hemorrhage which are difficult to see with the naked eye. (c) Ratio of total area of retinal hemorrhage and area of optic disc obtained to minimize errors pertaining to variance of retinal photographs.

AGE (Cell Biolabs STA-317, San Diego, CA, USA), N"-CML (Cell Biolabs STA-816, San Diego, CA, USA), sRAGE (Elabscience E-EL-H0295, Houston, TX, USA), and cystatin C (Elabscience E-EL-H0055, Houston, TX, USA) had intra-assay coefficient variances of 4% and inter-assay coefficient variances of 8%.

HbA1c, BUSE creatinine, liver enzymes, and lipid profile

A capillary blood sample of 1.5 µL was used to measure HbA1c. HbA1c kits (Alere Afinion, Waltham, MA, USA) had a measuring range of 4–15% with coefficient variances (CV) < 3%. Serum was procured from participants at baseline and after 8 weeks of supplementation and sent to a national certified pathology lab for general biochemical examination of blood including serum creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine transaminase (ALT), total cholesterol (TC), and high-density lipoproteins (HDL) (ARCHITECT, Abbott Diagnostics, Abbot Park, IL, USA) on the same working day. Coefficient variances for the tests were approximately < 6%.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25 (IBM SPSS Inc, Chicago, IL, USA). All data were analyzed by intention-to-treat basis. Each eye was analyzed separately. Probabilities less than 5% were deemed statistically significant. Baseline characteristics between Tocovid and placebo group were measured using chi-square test for gender; Fisher's exact test for race, smoking status, and grade of DR; Mann-Whitney test for compliance; independent *t*-test for age, duration of T2DM, retinal hemorrhage, glycemic and metabolic parameters, as well as safety tests. ANCOVA, adjusting for baseline values, was used to analyze treatment changes at the end of the study between the intervention and control groups. Odds ratio was calculated for improvement and deterioration in grade of DR for the Tocovid and placebo groups. Correlation between grade of DR with serum biomarkers, retinal hemorrhage, and HbA1c was analyzed by Spearman's rank correlation.

Results

Patient characteristics

Of 118 participants, a total of 43 participants (83 eyes identified with DR) fulfilled the study inclusion and exclusion criteria and were included into the clinical trial. Of these, 21 participants (41 eyes identified with DR) were randomized to the Tocovid group and 22 participants (42 eyes identified with DR) to the placebo group. All participants completed the study duration with no dropouts recorded. All participants and eyes were included for analysis. The flow diagram of participants is shown in Figure 3.

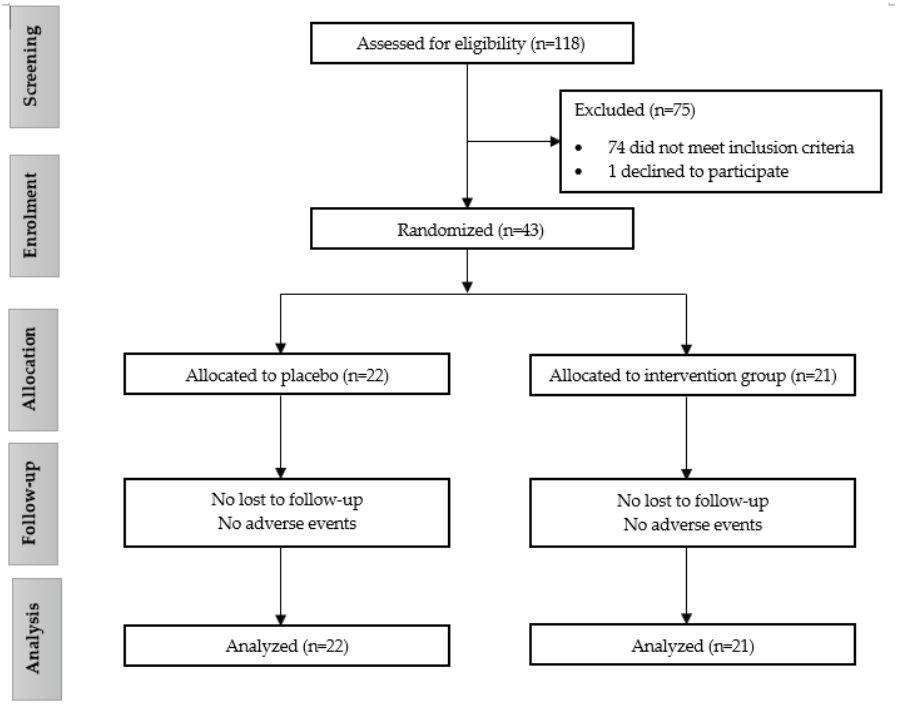

Fig. 3. Flow diagram of participants.

The baseline characteristics of the participants are illustrated in Table 1. The mean participant age was 61.51 ± 1.25 years; 74.4% were male. In terms of ethnicity, 53.5% of the subjects were Malay, 14% were Chinese, and 32.6% were Indian. Both the intervention and control group had statistically similar distributions in age, gender, and ethnicity ($p > 0.05$). The mean duration of T2DM was 18.28 ± 8.28 years and there was no significant difference ($p = 0.694$) between intervention and control group. Both groups also had statistically similar prevalence ($p = 0.057$) of smoking status. The median (interquartile range, IQR) compliance was 0.98 (0.06) and 0.95 (0.18) in the placebo and Tocovid group, respectively, with no statistical differences between both groups ($p = 0.123$).

Baseline ophthalmic parameters and analytes

The baseline ophthalmic parameters and analytes of the participants are illustrated in Tables 2 and 3, respectively. There were no significant differences in baseline ophthalmic parameters including retinal hemorrhage and grade of DR between intervention and control groups. No statistically significant

Table 1. Baseline characteristics of the study population

	All participants (*n* = 43)	Control (*n* = 22)	Intervention (*n* = 21)	*p*-Value
Gender (n, %): Male Female	 32 (74.4) 11 (25.6)	 15 (68.2) 7 (31.8)	 17 (81) 4 (19)	0.337
Race (n, %): Malay Chinese Indian	 23 (53.5) 6 (14) 14 (32.6)	 12 (54.5) 5 (22.7) 5 (22.7)	 11 (52.4) 1 (4.8) 9 (42.9)	0.165
Smoking status (n, %) Non-smoker Current smoker Ex-smoker	 23 (54.8) 6 (14.3) 13 (31)	 11 (50) 1 (4.5) 10 (45.5)	 12 (60) 5 (25) 3 (15)	0.057
Age (years)*	61.51 ± 1.25	63.14 ± 8.59	59.81 ± 7.60	0.187
Duration of T2DM (years)*	18.28 ± 8.28	18.77 ± 7.20	17.76 ± 9.44	0.694
Compliance**	0.96 (0.11)	0.98 (0.06)	0.95 (0.18)	0.123

T2DM: type 2 diabetes mellitus
***Data presented as mean ± standard deviations.**
****Data presented as median (interquartile range).**
Data not significant at p > 0.05.

Table 2. Baseline ophthalmic parameters of Tocovid and placebo groups

	Right eye (*n* = 41)			Left eye (*n* = 42)		
	Placebo (*n* = 21)	Tocovid (*n* = 20)	*p*-Value	Placebo (*n* = 22)	Tocovid (*n* = 20)	*p*-Value
Grade of DR (*n*, %)			0.662			0.637
NDR	3 (14.3)	4 (9.8)		3 (13.6)	1 (5.0)	
Mild NPDR	10 (47.6)	5 (12.2)		10 (45.5)	8 (40.0)	
Moderate NPDR	6 (28.6)	8 (19.5)		6 (27.3)	7 (35.0)	
Severe NPDR	1 (4.8)	1 (2.4)		2 (9.1)	1 (5.0)	
PDR	1 (4.8)	2 (4.9)		1 (4.5)	3 (15.0)	
Retinal hemorrhage (DA)*	0.74 ± 0.84	1.01 ± 1.10	0.398	0.78 ± 0.94	0.99 ± 1.16	0.532

DA: disc area; NDR: no diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy
***Data presented as mean ± standard deviations.**
Data not significant at p > 0.05.

Table 3. Baseline analytes of Tocovid and placebo groups

	Placebo (*n* = 22)	Tocovid (*n* = 21)	*p*-Value
HbA1c (%)	8.69 ± 1.74	9.38 ± 2.05	0.240
Blood pressure			
SBP (mmHg)	136.84 ± 13.85	134.75 ± 18.06	0.671
DBP (mmHg)	77.09 ± 8.71	75.38 ± 8.67	0.522
BMI (kg/m2)	27.58 ± 4.23	28.11 ± 4.19	0.677
Safety tests			
Urea (mmol/L)	6.10 ± 4.53	6.14 ± 3.62	0.372
Creatinine (µmol/L)	108.05 ± 52.52	111.28 ± 51.23	0.839
eGFR (ml/min/1.73m2)	68.23 ± 26.68	67.81 ± 22.98	0.956
Total chol (mmol/L)	4.49 ± 1.11	4.62 ± 0.94	0.675
HDL (mmol/L)	1.18 ± 0.21	1.18 ± 0.25	0.972
AST (IU/L)	20.27 ± 12.31	25.48 ± 10.70	0.148
ALT (IU/L)	21.50 ± 14.68	27.95 ± 14.86	0.160
Serum biomarkers			
AGE (µg/mL)	109.50 ± 140.02	117.06 ± 167.85	0.874
sRAGE (pg/mL)	978.82 ± 516.85	1261.53 ± 869.54	0.199
Nε-CML (µg/mL)	1.91 ± 2.38	2.04 ± 2.41	0.859
Cystatin C (ng/mL)	1835.25 ± 958.60	2113.26 ± 897.79	0.333

AGE: advanced glycation end product; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; DA: disc area; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; HDL: high density lipoprotein; NDR: no diabetic retinopathy; Nε-CML: N-epsilon carboxymethyl lysine; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; SBP: systolic blood pressure; sRAGE: soluble receptor for AGE; Total chol: total cholesterol
All values are presented as means ± standard deviations.
Data not significant at $p > 0.05$.

differences were observed for baseline analytes such as HbA1c, blood pressure, BMI, biomarkers AGE, sRAGE, Nε-CML, and cystatin C. In addition, there were no significant differences in baseline safety tests, including renal profile, lipid profile, and liver enzymes between both groups.

Changes in metabolic, ophthalmic, biomarkers, and safety test parameters after 8 weeks of placebo and Tocovid

Table 4 compares the treatment changes between placebo and Tocovid group at the end of 8 weeks while controlling for the respective baseline values. Tocovid significantly reduced retinal hemorrhage in the right eye (-0.24 DA ± 0.11, p = 0.038). While there was reduction in intraretinal hemorrhage in the left eye in both groups, the mean difference was not significant (p = 0.498) between both groups. However, the improvement in retinal hemorrhage did not correspond to significant changes (p = 0.05) in level of ETDRS grading of DR between both groups (Table 5).

For liver enzymes, Tocovid significantly improved AST compared to placebo (-8.01 IU/L ± 2.56, p = 0.003). In addition, ALT was significantly reduced in Tocovid compared to placebo (-6.01 IU/L ± 2.00, p = 0.005). There was, however, no significant difference in biomarkers AGE, sRAGE, Nε-CML, and cystatin C between the Tocovid and placebo groups. In addition, no significant differences (p > 0.05) were found in HbA1c, mean blood pressure, BMI, and safety tests including renal and lipid profile between both groups after 8 weeks of supplementation with either Tocovid or placebo.

Correlation between grade of DR with retinal hemorrhage and serum biomarkers

Correlation analysis between grade of DR with retinal hemorrhage and serum biomarkers are presented in Tables 6 and 7. At baseline, there was a highly significant, strong positive correlation between grade of DR and retinal hemorrhage in both eyes (right eye: r = 0.676, p < 0.001; left eye: r = 0.772, p < 0.001). The same finding was found at the end of the study. At the 8-week trial period, there was still a highly significant, strong positive correlation between grade of DR and retinal hemorrhage in both eyes (right eye: r = 0.773, p < 0.001; left eye: r = 0.708, p < 0.001). These highly significant results indicated that the area of retinal hemorrhage was significantly higher in subjects with increasing severity of DR, as assessed by ETDRS grading.

In addition, at baseline and at the end of the study there was a significant, weak positive correlation between grade of DR in the right eye and serum Nε-CML (baseline: r = 0.342, p = 0.028; end of study: r = 0.379, p = 0.015). However, this correlation was not seen in the left eye. In addition, no significant differences between biomarkers AGE, RAGE, and cystatin C and grades of DR were found.

Table 4. Adjusted changes in metabolic, ophthalmic, biomarkers, and safety test parameters after 8 weeks of placebo and Tocovid

Parameters	Placebo (*n* = 22)	Tocovid (*n* = 21)	Mean difference (95% CI)	*p*-Value
Retinal hemorrhage (DA)				
Right eye	0.61 ± 0.08	0.37 ± 0.08	-0.24 ± 0.11	0.038*
Left eye	0.50 ± 0.08	0.58 ± 0.09	0.09 ± 0.12	0.498
HbA1c (%)	8.80 ± 0.17	8.67 ± 0.18	-0.13 ± 0.25	0.605
Blood pressure (mmHg)				
SBP	131.65 ± 2.08	133.48 ± 2.12	1.83 ± 2.97	0.542
DBP	74.78 ± 1.98	76.37 ± 2.02	1.59 ± 2.83	0.578
BMI (kg/m^2)	27.67 ± 0.24	28.17 ± 0.24	0.50 ± 0.34	0.150
Serum biomarkers				
AGE (µg/mL)	92.47 ± 27.76	79.09 ± 29.18	-13.53 ± 40.28	0.739
sRAGE (pg/mL)	1293.27 ± 152.87	1247.49 ± 156.54	-45.78 ± 221.01	0.837
Nε-CML (µg/mL)	1.53 ± 0.40	1.64 ± 0.41	0.11 ± 0.57	0.850
Cystatin C (ng/mL)	2019.80 ± 172.16	2156.09 ± 176.26	136.29 ± 247.81	0.585
Safety tests				
Urea (mmol/L)	6.44 ± 0.29	6.45 ± 0.30	0.00 ± 0.42	0.997
Creatinine (µmol/L)	108.45 ± 2.43	107.69 ± 2.50	-0.77 ± 3.48	0.827
eGFR (ml/min/1.73m2)	68.86 ± 1.66	69.34 ± 1.70	0.49 ± 2.38	0.839
Total chol (mmol/L)	4.47 ± 0.13	4.59 ± 0.13	0.12 ± 0.18	0.515
HDL (mmol/L)	1.12 ± 0.03	1.13 ± 0.03	-0.043 ± 0.04	0.239
AST (IU/L)	25.96 ± 1.77	17.95 ± 1.81	-8.01 ± 2.56	0.003*
ALT (IU/L)	27.47 ± 1.38	21.46 ± 1.41	-6.01 ± 2.00	0.005*

AGE: advanced glycation end product; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; DA: disc area; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; HDL: high density lipoprotein; NDR: no diabetic retinopathy; Nε-CML: N-epsilon carboxymethyl lysine; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; SBP: systolic blood pressure; sRAGE: soluble receptor for AGE; Total chol: total cholesterol
All values are presented as means ± standard errors of mean.
Data adjusted for baseline values.
***Significant at $p < 0.05$.**

Table 5. Progression and regression of diabetic retinopathy after 8 weeks of placebo and Tocovid

	Right eye (*n* = 41)				Left eye (*n* = 42)			
	Placebo (*n* = 21)	Tocovid (*n*=20)	OR (95% CI)	*p*-Value	Placebo (*n* = 22)	Tocovid (*n* = 20)	OR (95% CI)	*p*-Value
Improvement in grade (*n*, %)								
1 level	4 (19)	1 (5)	0.22 (0.02, 2.20)	0.343	8 (36.4)	6 (30)	0.75 (0.21, 2.73)	0.750
2 levels	0	1 (5)	-	0.476	0	0	-	-
Deterioration in grade (*n*, %)								
1 level	1 (4.8)	3 (15)	3.53 (0.34, 37.15)	0.343	2 (9.1)	1 (5)	0.526 (0.04, 6.3)	1.000
2 level	0	1 (5)	-	0.488	0	0	-	0

Data not significant at $p > 0.05$.

Table 6. Correlation between grade of DR with retinal hemorrhage and serum biomarkers at baseline

Baseline parameters	Right eye, Grade of DR		Left eye, Grade of DR		HbA1c	
	Correlation, *r*	*p*-Value	Correlation, *r*	*p*-Value	Correlation, *r*	*p*-Value
Retinal hemorrhage (DA)	0.676	0.000**	0.772	0.000**		
HbA1c	0.309	0.049*	0.283	0.073	-	-
Serum biomarkers						
AGE (µg/mL)	0.148	0.361	0.153	0.339	0.246	0.117
sRAGE (pg/mL)	0.123	0.444	0.173	0.274	0.361	0.017*
Nε-CML (µg/mL)	0.342	0.028*	0.232	0.139	0.055	0.780
Cystatin C (ng/mL)	0.064	0.693	0.132	0.406	0.078	0.617

AGE: advanced glycation end product; DA: disc area; HbA1c: hemoglobin A1c; Nε-CML: N-epsilon carboxymethyl lysine; sRAGE: soluble receptor for AGE

***Significant at $p < 0.05$.**

****Significant at $p < 0.001$.**

Table 7. Correlation between grade of DR with retinal hemorrhage and serum biomarkers at the end of the study

End of study parameters	Right eye, Grade of DR		Left eye, Grade of DR		HbA1c	
	Correlation, *r*	*p*-Value	Correlation, *r*	*p*-Value	Correlation, *r*	*p*-Value
Retinal hemorrhage (DA)	0.773	0.000**	0.708	0.000**	-	-
HbA1c	0.283	0.073	0.313	0.044	-	-
Serum biomarkers						
AGE (μg/mL)	0.179	0.276	0.204	0.207	-0.201	0.207
sRAGE (pg/mL)	-0.017	0.915	-0.092	0.563	0.214	0.167
Nε-CML (μg/mL)	0.379	0.015*	0.252	0.108	0.113	0.472
Cystatin C (ng/mL)	-0.140	0.383	-0.004	0.978	0.142	0.362

AGE: advanced glycation end product; DA: disc area; HbA1c: hemoglobin A1c; Nε-CML: N-epsilon carboxymethyl lysine; sRAGE: soluble receptor for AGE

***Significant at $p < 0.05$.**

****Significant at $p < 0.001$.**

Lastly, there was a borderline significant, weak positive correlation between grade of DR in the right eye and HbA1c at baseline ($r = 0.309$, $p = 0.049$). However, the correlation between grade of DR and HbA1c was neither seen at the end of the study or in the left eye. At baseline, biomarker sRAGE also showed a significant weak positive correlation with HbA1c ($r = 0.361$; $p = 0.017$). However, this same correlation was not seen at the end of the 8-week trial period. Otherwise, our findings showed no significant correlation between biomarkers and HbA1c.

Discussion

This clinical study shows that 8-week supplementation with Tocovid compared to placebo significantly improved the area of retinal hemorrhage in the right eye in patients with DR (Table 2). To the best of our knowledge, this is a new finding, as there are articles describing the benefits of tocotrienol in improving oxidative stress and other metabolic parameters, but literature on its role in DR is limited. In fact, only two animal studies suggest tocotrienol as a potential retinoprotective agent and an inhibitor of angiogenesis.[15,16] This finding suggests the potential role of tocotrienol as a safe and non-invasive adjunct to the current management of DR. This is particularly important because, other than good glycemic control, treatment options for DR, which include photocoagulation, intraocular injections with antivascular endothelial growth factor, and surgery, are quite limited, costly, and can be debilitating.[37,38]

The novel technique to quantify area of retinal hemorrhage from digital retinal photographs was developed and performed to assess the disease severity of DR in addition to the established conventional ETDRS grading. This is because the natural history and progression of DR spans many years and by reverse inference, any changes in the grade of DR by Tocovid may only become apparent after a considerable amount of time.[39,40] Hence, with the help of modern technology and high-resolution displays, this new technique was developed to accurately identify and quantify areas of retinal hemorrhage on the digital retinal photographs at zoomed-in views. This includes very early changes in the retina including small areas of hemorrhage which would normally remain unnoticed to the naked eye of the assessor (Fig. 2b). In order to establish the validity of this technique, correlation analysis between the area of retinal hemorrhage and gold-standard ETDRS grading of DR was performed. There was a highly significant ($p < 0.001$) strong positive correlation between area of retinal hemorrhage and grade of DR in both right and left eyes at baseline and at 8 weeks post-intervention (Tables 6 and 7). This strong correlation endorses the validity of this new technique as an alternative method of assessing disease severity of DR.

However, if retinal hemorrhage strongly correlated with the grade of DR and if Tocovid was able to significantly reduce retinal hemorrhage, why was Tocovid not

able to cause a corresponding change to the grade of DR? This is because, other than retinal hemorrhage, there are other components such as exudates, venous beading, and neovascularization involved in the ETDRS grading of DR.[35] As previously mentioned, the pathogenesis of DR spans years. Thus, a longer treatment period with Tocovid would likely be needed for an effect to these other components to occur, thereby allowing a change to the ETDRS grade of DR. On the same account, a longer treatment duration is likely required for a significant improvement in retinal hemorrhage to occur in both eyes due to the protracted nature of DR. Therefore, while the findings of this study report a potential breakthrough in the treatment of DR, more extensive and lengthy research should be conducted to affirm this finding.

In addition, the results of this study demonstrate that 8 weeks of Tocovid supplementation compared to placebo caused a significant improvement in liver enzymes AST and ALT (Table 4). A literature review on this subject matter reveals an increasing interest in tocotrienol and its role as a hepatoprotective agent. Animal studies have shown that tocotrienols are preferentially distributed to the liver.[41] Here, it acts as an antioxidant by reducing lipid peroxidation as well as an anti-inflammatory agent by the inhibition of the NF-kB pathway, thereby attenuating steatosis in the liver.[41] Further clinical studies demonstrate the role of tocotrienol in improving liver conditions, including reduced liver echogenicity[42] and liver stiffness[43] in patients with non-alcoholic fatty liver disease (NAFLD). NAFLD is associated with metabolic syndrome, which includes DM, hypertension, and obesity, which are very relevant in our patient cohort.[44] Other than controlling for risk factors, there is no specific pharmacologic treatment available for NAFLD.[44] Hence, it would be worthwhile for further investigation to be conducted to verify the benefits of tocotrienol on the liver and if it would be a suitable pharmacological treatment for NAFLD.

However, the results of this trial report no significant improvement in serum biomarkers AGE, sRAGE, Nε-CML, and cystatin C as well other parameters including HbA1c, blood pressure, BMI, total cholesterol, and HDL-cholesterol despite 8-weeks of high-dose Tocovid (Table 4). This is in contrast to previous studies that reported an improvement in AGE and oxidative stress as well as glycemic and metabolic parameters as early as 2 months.[9-12,17] The lack of effect of Tocovid may be attributed to our study criterion, which required T2DM patients with DR, a complication which conventionally takes years of poor glycemic control to develop. The mean duration of T2DM of our participant pool at 18.28 years ± 8.28 years was significantly longer than previous studies which recruited participants or animal models with newly diagnosed DM. Studies report that tissues glycated during chronic hyperglycemia can persist in diabetic organs and cause harm for a protracted duration of time.[45,46]

The DCCT and UKPDS trials, which showed the importance of tight glycemic control in reducing diabetic-related complications, had recruited patients with newly diagnosed DM. When both trials ended, the patients were followed up for another 10 years. The post-trials showed that, despite achieving similar glycemic control for the next 10 years, patients who were formerly in the control group still had significantly higher rates of diabetic-related complications.[20-25] Interestingly, the Action in Diabetes and Vascular Disease (ADVANCE), Veteran Administrations Diabetes Trial (VADT), and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials also reported that intensive glycemic control had minimal effect in preventing diabetes complications. These three trials had recruited patients with long-standing DM at 8, 10, and 11.5 years respectively.[47-49] Hence, it can be inferred that chronic hyperglycemia had caused sustained harm or a bad "metabolic memory". In other words, even after glucose normalization, there was persistent diabetic vascular stress which led to complications and caused the patients to be refractory to treatment.[50,51] Thus, the previous studies were able to show improvement in AGE and metabolic parameters of DM because metabolic memory had yet to develop and the effects of chronic hyperglycemia could still be reversed. In our study, chronic exposure to hyperglycemia had led to formation of metabolic memory, causing the lack of treatment effect of tocotrienol.

However, tocotrienol had nonetheless, significantly improved retinal hemorrhage and liver enzymes. This suggests an alternate pathway used by tocotrienol to improve these parameters. More extensive research is warranted to investigate this pathway.

On another note, the results of our trial show that serum levels of biomarker Nε-CML significantly correlates with the presence and progressive severity of DR of the right eye at baseline and at the end of the 8-week treatment period. In addition, the levels of Nε-CML did not correlate with HbA1c, indicating that it is an independent predictor of DR. This positive correlation between Nε-CML and DR is congruent with other similar cross-sectional studies.[20,26-28] This finding is potentially important as current diagnosis of DR is conducted by either of two techniques: traditional ophthalmoscopic examination, which has a wide sensitivity of 27–82% depending on the training background of the examiner, or retinal photography and grading, which has better sensitivity of 87–100% and specificity of 83–96% but requires equipment and manpower, thus limiting the populace that can be effectively screened.[52] Hence, it would be of great significance if a simple blood test for a biomarker such as Nε-CML can be identified to aid in the diagnosis of DR, rather like how brain natriuretic peptide (BNP) is used as an indicator of heart failure in replacement of physical examination and echocardiography.[53]

One of the limitations of this study is its small sample size. Only 43 subjects out of the intended 52 required for an adequate sample size were recruited due to financial limitations. This may have reduced the statistical power of the study and therefore, the lack of effect of Tocovid compared to placebo on the outcomes of the study. Moreover, the treatment duration of 8 weeks was likely too short for most changes, especially long-lasting biomarkers and ophthalmic parameters, to take into effect. Future studies with a longer treatment duration are warranted. Another limitation is the long duration of T2DM among the recruited participant cohort. Although DR takes years of poor glycemic control to develop, future studies directed at newly diagnosed DR patients should be considered. Finally, measurement of baseline and end of study vitamin E is warranted for future studies to negate the potential confounding effects of vitamin E on the study results.

Conclusion

In conclusion, 8 weeks of Tocovid supplementation was able to improve the area of retinal hemorrhage and liver enzymes ALT and AST, suggesting its role as an adjunct to the current treatment of DR and possibly NAFLD. The novel method of quantifying retinal hemorrhage strongly correlated with grade of DR and can potentially be used to identify early changes in the retina in response to treatment. Serum Nε-CML was found to correlate with grade of DR independent of HbA1c levels. This indicates its potential role as a biomarker for DR.

Declarations

Author contributions

KAK and YC designed the pilot study. YC, SMQT, and BA performed the clinical trial and collected the data. SEK graded the retinal photographs. YC analyzed the data and prepared the manuscript. KAK and BA reviewed and edited the manuscript.

Competing interests

The authors declare no conflict of interest. The funders had no role in the design of the study, the collection, analyses, or interpretation of data, writing of the manuscript, or in the decision to publish the results.

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Comparison of clinical outcomes of implantable collamer lens versus femtosecond-laser *in situ* keratomileusis and small incision lenticule extraction for moderate-to-high myopia and myopic astigmatism correction

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Abstract

Purpose: *To compare safety, efficacy, stability, and predictability of implantable collamer lens (ICL) with femtosecond-laser in situ keratomileusis (FS-LASIK) or small incision lenticule extraction (SMILE) for the correction of moderate-to-high myopia/myopic astigmatism.*

Study design: *We retrospectively collected data from patients with moderate-to-high myopia/myopic astigmatism (spherical equivalent [SE] ≥ −3.00 diopters [D]) who underwent ICL (48 eyes), FS-LASIK (36 eyes), or SMILE (86 eyes) at Hai Yen Eye Center from October 2016 to February 2018.*

Materials and methods: *The Wilcoxon Mann-Whitney U test was used to compare pre- and postoperative patients' characteristics of ICL with SMILE or FS-LASIK. Generalized linear models with unstructured correlation matrix and robust standard errors were used to analyze efficacy and safety indices; logistic regression was used for cylinder predictability.*

Results: *After controlling for age, preoperative SE, and preoperative corrected distance visual acuity (pCDVA), SMILE had significantly lower safety indices (Coefficient = −0.04, 95% CI = −0.07–−0.01) and efficacy indices (Coefficient = −0.10, 95% CI = −0.20–−0.01) than did ICL, while FS-LASIK was not significantly different from ICL (Coefficient = −0.02, 95% CI = −0.06–0.02 and Coefficient = −0.01, 95% CI= −0.10–0.09, respectively). ICL SEs were stable over 12 months after surgery. However, in FS-LASIK and SMILE, SEs significantly decreased at 12 months compared with 6 months after surgery. The percentage*

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of eyes that underwent FS-LASIK and had target SEs within ±0.5 D at 12 months was significantly lower than those that underwent ICL (OR = 0.14, 95% CI = 0.02–0.85), after controlling for age, preoperative SE, and pCDVA.
Conclusions: *For the correction of moderate-to-high myopia/myopic astigmatism, ICL seems to perform better than SMILE and FS-LASIK.*

Keywords: *femtosecond-laser in situ keratomileusis, implantable collamer lens, myopia, myopic astigmatism, small incision lenticule extraction*

Introduction

Three main surgical options to treat refractive errors are corneal reshaping, lens replacement, and intraocular lens (IOL) implantation. In femtosecond-laser in situ keratomileusis (FS-LASIK), the cornea is reshaped by using an excimer laser to ablate the corneal stroma. The main step of this surgery is to create a flap with minimal tissue damage by using ultra-short infrared laser pulses of a femtosecond laser. In contrast, small incision lenticule extraction (SMILE) is a flapless corneal refractive surgery. Instead of creating a flap, this procedure uses a femtosecond laser to create a lenticule inside the corneal stroma and a small incision through which a whole lenticule is extracted. The incision size in SMILE is approximately 2–3 mm, 7–10 times shorter than the incision used in FS-LASIK (20–22 mm).[1] Another option for correcting refractive errors is to implant a collamer lens between the crystalline lens and the iris. The STAAR Surgical Co. (Monrovia, CA, USA) Visian implantable collamer lens (ICL) is currently the only posterior-chamber phakic IOL approved for use in the United States.[2]

All of these refractive surgeries can be used to correct myopia with or without astigmatism. Many studies have confirmed the safety and effectiveness of ICL in correcting low-moderate-to-high myopia and myopic astigmatism.[3-5] Several studies have compared refractive outcomes between FS-LASIK and SMILE among different populations.[6-9] However, few studies have compared ICL with FS-LASIK or SMILE,[10] and most of these studies were conducted on Caucasian populations, who may have different ocular characteristics to those of Asian populations.[11,12] One study in India showed that ICL had higher safety and efficacy indices than did FS-LASIK and SMILE for myopic astigmatism correction 1 year after surgery.[10] However, the authors did not examine these differences longitudinally. The present study aimed to compare the safety, efficacy, stability, and predictability between ICL and SMILE and between ICL and FS-LASIK for the correction of moderate-to-high myopia and myopic astigmatism among southern Vietnamese patients. Results from our research will contribute to the findings regarding three different refractive surgeries among a South East Asian population.

Methods

A retrospective cohort study was used to compare data of patients with moderate-to-high myopia and myopic astigmatism who underwent ICL, FS-LASIK, or SMILE. Different surgeons with minor variations in their techniques performed procedures from February 2016 to February 2018 at three clinics: Hai Yen Eye Center, An Sinh Hitec Eye Center, and 304 Hitec Eye Center. All patients had a bilateral procedure on the same day (SMILE and FS- LASIK) or within 1 week (ICL). Moderate-to-high myopia and myopic astigmatism were defined as having preoperative spherical equivalent (SE) worse than −3.00 diopters (D). No potentially identifiable information was collected. Only patients with available uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), spherical error, and cylindrical error before and after the surgery at 1 month, 6 months, and 12 months were included. Patients who had a history of other refractive surgery were excluded. We performed corneal topography, which was measured with the Pentacam (Oculus Optikgerate GmbH, Wetzlar, Germany), for all patients prior to surgery. The study protocol was approved by the Ethical Review Committee of the An Sinh Hospital (1062-18/AS-QD).

Surgical procedures

ICL

We used V4c Visian ICL (Staar Surgical AG, Nidau, Switzerland) with central hole. Toric ICL was used for suitable patients whose cylindrical errors were worse than −0.50 D. Posterior chamber IOL size and power calculation were performed with the software provided by the manufacturer (Online Calculation & Ordering System). Manifest refraction, white-to-white corneal diameter, and anterior chamber depth were measured to determine the appropriate size and refractive power of the V4c-ICL. White-to-white diameter and anterior chamber depth were measured with the Park1 and Pentacam (Oculus Optikgerate). Before surgery, cycloplegic and phenylephrine eye drops were applied. Peribulbar anesthesia was achieved using lidocaine 2%. After making a 3-mm temporal clear corneal incision, the viscoelastic material (hydroxypropyl methylcellulose) was placed into the anterior chamber. The viscoelastic material was completely washed out at the end of the surgery. Then, a surgeon used an ICL injector and manipulator to insert the lens into the posterior chamber.

After surgery, moxifloxacin and dexamethasone 0.1% eye drops were applied 4–6 times daily for 4 weeks. Surgery was performed on the second eye during the first postoperative week after surgery on the first eye.

FS-LASIK and SMILE

We used 0.5% proparacaine as a topical anesthetic. In the FS-LASIK procedure, a 500-kHz VisuMax femtosecond laser (Carl Zeiss Meditec AG, Jena, Germany) was used to create a flap (8.1-mm diameter and 110-μm thickness) with 59° hinges (4.20 mm length) and 45° side-cut angles. A pulse energy of 185 nJ was used to create lamellar and side cuts. We used a MEL-80 (Carl Zeiss Meditec) excimer laser with a frequency of 250 Hz to perform stromal tissue ablation using a 6.5-mm optical zone in all cases. In the SMILE procedure, the VisuMax femtosecond laser system was employed using femtosecond lasers with a frequency of 500 kHz and pulse energy of 130 nJ. Spot distance and track distance of lenticule and cap cut were 4.5 μm. Lenticule side and cap side-cut were 2.5 μm and 2.0 μm, respectively. The treatment parameters were set at a cap thickness of 120 μm, an incision width range of 2–4 mm, a lenticule diameter of 6.5 mm, and a lenticule side-cut angle of 90°. Immediately after surgery, patients received moxifloxacin and dexamethasone 0.1% eye drops. Patients applied moxifloxacin and dexamethasone 0.1% eye drops four times a day for 1 week. In addition, patients administered sodium hyaluronate 0.18% eye drops four times a day, beginning at 1 day after surgery and continuing for 6 months.

Measurement

The efficacy index was determined as a ratio between postoperative UCVA and preoperative CDVA. The safety index was measured by a ratio between postoperative CDVA and preoperative CDVA. The percentages of gain of 1, 2, or > 2 lines or loss of 1, 2, or > 2 lines of postoperative CDVA were compared with preoperative CDVA based on LogMAR values. Stability was measured by a change in the mean SE and cylindrical errors over 12 months after surgery. SE was calculated by adding spherical errors to half of cylindrical errors. Predictability was measured by percentage of eyes within ±0.5 D of target SE at 12 months after surgery.

Data analyses

Analyses were performed with Stata version 13 (StataCorp LP, College Station, TX, USA). Mean, standard deviation, frequencies, and percentages were used to describe the efficacy index, the safety index, and other characteristics. We used the Wilcoxon Mann-Whitney rank test to compare patients' pre- and postoperative characteristics between surgeries. Variables associated with type of surgery with $p < 0.25$ were included in the multivariate models. Generalized linear models with unstructured correlation matrix and robust standard errors were used to compare efficacy and safety indices longitudinally between ICL and SMILE or between ICL and FS-LASIK, controlling for other factors. We used multivariate logistic regression to compare cylinder predictability between

groups. The final model was selected if it had the least likelihood ratio score. A two-sided $p < 0.05$ was considered statistically significant.

Results

Our analyses included 170 eyes that underwent ICL (48 eyes), FS-LASIK (36 eyes), or SMILE (86 eyes). Table 1 provides patients' pre-operative demographics and refractive errors. The mean age was 23.35 years (*SD* = 3.55) in the ICL group, 26.78 years (*SD* = 6.29) in the FS-LASIK group, and 24.95 years (*SD* = 5.27) in the SMILE group. The mean preoperative SE was −10.46 ± 3.10 (*SD*) D in the ICL group, −6.12 ± 2.46 (*SD*) D in the FS-LASIK group, and −5.69 ± 1.58 (*SD*) D in the SMILE group. There were significant differences in terms of age and preoperative UDVA, CDVA, spherical errors, cylindrical errors, SE, and central corneal thickness (CCT) in the ICL group, compared with the FS-LASIK group or with the SMILE group (Wilcoxon Mann Whitney rank test, all $p < 0.05$). There was a statistically insignificant difference between these groups regarding intraocular pressure.

Table 2 shows the comparison of clinical outcomes between ICL, FS-LASIK, and SMILE. The mean efficacy indices of ICL were significantly higher at 1 month (0.98 ± 0.16), 6 months (0.98 ± 0.18), and 12 months (0.96 ± 0.18) after surgery than in SMILE (0.89 ± 0.20, 0.92 ± 0.17, and 0.86 ± 0.18, respectively). The ICL indices were lower than the FS-LASIK indices (1.00 ± 0.16, 0.98 ± 0.15, and 0.94 ± 0.16, respectively), but this difference was not statistically significant. Percentages of eyes were comparable among the three surgery types over the three time points. At 12 months, the percentages of ICL, FS-LASIK, and SMILE recipients with UCVA ≥ 5/10 were 97.92%, 94.44%, and 95.35%, respectively (Fig. 1). However, more eyes that had undergone FS-LASIK had UCVA ≥ 8/10 and ≥ 10/10 than eyes that had undergone ICL or SMILE; at 12 months after surgery, 41.67% of eyes that underwent ICL had UCVA ≥ 10/10, compared with 69.44% of eyes that underwent FS-LASIK and 36.05% of eyes that underwent SMILE.

The mean safety indices of the ICL group were 1.08 ± 0.13, 1.08 ± 0.14, and 1.07 ± 0.12 at the 1-, 6-, and 12-month follow-ups, respectively. These indices were significantly better than those of SMILE (1.01 ± 0.07, 1.01 ± 0.08, and 1.00 ± 0.05, respectively) at three time points, but only significantly better at the 12-month follow-up for the FS-LASIK group (1.03 ± 0.10, 1.04 ± 0.09, and 1.04 ± 0.16, respectively) (Table 2). At 6 months after ICL, 39 eyes (81.25%) showed no change in CDVA, 5 eyes (10.42%) gained 1 line, 4 eyes (8.33%) gained 2 lines, and 0 eyes lost 1 line or 2 lines. At the same time point after FS-LASIK, 30 eyes (83.33%) showed no change in CDVA, 6 eyes (16.67%) gained 1 line, 0 eyes (0.00%) gained 2 lines, and 0 eyes (0.00%) lost 1 line or 2 lines. Finally, 6 months after SMILE, 78 eyes (90.70%) showed no change in CDVA, 6 eyes (6.98%) gained 1 line, 0 eyes (0.00%) gained 2 lines, 1 eye (1.16%) lost 1 line, and 1 eye (1.16%) lost 2 lines (Fig. 2). At

Table 1. Preoperative demographic and clinical characteristics of patients who underwent ICL, FS-LASIK, or SMILE

Characteristics	ICL (*N* = 48 eyes)		FS- LASIK (*N* = 36 eyes)			SMILE (*N* = 86 eyes)		
	Mean ± SD	Range (Min, Max)	Mean ± SD	Range (Min, Max)	*p*-value*	Mean ± SD	Range (Min, Max)	*p*-value*
Age, years	23.35 ± 3.55	(18, 33)	26.78 ± 6.29	(20, 41)	0.007	24.95 ± 5.27	(18, 38)	0.164
CDVA, LogMAR	0.042 ± 0.087	(0.00,0.52)	0.015 ± 0.052	(0.00, 0.22)	0.001	0.003 ± 0.010	(0.00, 0.04)	< 0.0001
CDVA, Decimal	0.92 ± 0.13	(0.3, 1.0)	0.97 ± 0.10	(0.6, 1.0)	0.001	0.99 ± 0.02	(0.9, 1.0)	< 0.0001
Spherical errors, D	−9.52 ± 3.26	(−18.25, −0.75)	−5.73 ± 2.24	(−10.75, −2.75)	< 0.0001	−5.18 ± 1.45	(−8.50, −2.50)	< 0.0001
Cylindrical errors, D	−1.87 ± 1.27	(−6.00, 0.00)	−0.77 ± 0.64	(−2.25, 0.00)	< 0.0001	−1.01 ± 1.01	(−5.00, 0.00)	< 0.0001
SE, D	−10.46 ± 3.10	(−18.50, −3.00)	−6.12 ± 2.46	(−11.625, −3.00)	< 0.0001	−5.69 ± 1.58	(−9.50, −3.00)	< 0.0001
Intraocular pressure, mmHg	15.82 ± 1.90	(12, 19)	16.44 ± 2.99	(11, 23)	0.530	16.28 ± 2.29	(10, 20)	0.201
Central corneal thickness, mm	523.17 ± 42.95	(466, 663)	542.17 ± 21.96	(487, 586)	0.003	542.47 ± 34.58	(454, 638)	0.002

CDVA: corrected distance visual acuity; D: diopter; FS-LASIK: femtosecond-laser in situ keratomileusis; ICL: implantable collamer lens; LogMAR: logarithm of the minimum angle of resolution; SE: spherical equivalent; SMILE: small incision lenticule extraction; UDVA: uncorrected distance visual acuity
***Wilcoxon Mann Whitney rank test results between FS-LASIK and ICL, or between SMILE and ICL.**

Table 2. Summary of clinical outcomes comparing ICL with FS-LASIK or SMILE

Clinical outcomes	ICL	FS-LASIK		SMILE	
	Mean ± *SD*	Mean ± *SD*	*p*-value*	Mean ± *SD*	*p*-value*
UDVA, LogMAR					
1 month after surgery	0.06 ± 0.09	0.02 ± 0.10	0.005	0.07 ± 0.13	0.562
6 months after surgery	0.06 ± 0.10	0.03 ± 0.11	0.030	0.05 ± 0.10	0.676
12 months after surgery	0.07 ± 0.10	0.05 ± 0.11	0.037	0.08 ± 0.12	0. 557
CDVA, LogMAR					
1 month after surgery	0.010 ± 0.067	0.003 ± 0.069	0.120	-0.001 ± 0.031	0.217
6 months after surgery	0.011 ± 0.052	-0.001 ± 0.050	0.019	-0.001 ± 0.038	0.010
12 months after surgery	0.013 ± 0.066	0.002 ± 0.035	0.236	0.003 ± 0.018	0.681
Spherical errors, D					
1 month after surgery	0.35 ± 0.30	0.11 ± 0.30	0.001	-0.12 ± 0.33	< 0.0001
6 months after surgery	0.34 ± 0.29	0.15 ± 0.31	0.005	-0.06 ± 0.29	< 0.0001
12 months after surgery	0.16 ± 0.38	-0.03 ± 0.37	0.011	-0.11 ± 0.30	< 0.0001
Cylindrical errors, D					
1 month after surgery	-0.75 ± 0.54	-0.20 ± 0.26	< 0.0001	-0.29 ± 0.26	< 0.0001
6 months after surgery	-0.71 ± 0.59	-0.28 ± 0.32	0.0002	-0.27 ± 0.27	< 0.0001
12 months after surgery	-0.61 ± 0.59	-0.19 ± 0.28	0.0003	-0.28 ± 0.27	0.0007
Spherical equivalent, D					
1 month after surgery	-0.02 ± 0.38	0.01 ± 0.34	0.536	-0.26 ± 0.35	0.0006
6 months after surgery	-0.02 ± 0.32	0.01 ± 0.31	0.810	-0.19 ± 0.31	0.004
12 months after surgery	-0.14 ± 0.40	-0.13 ± 0.45	0.926	-0.25 ± 0.31	0.010
Within ±0.5 D of target SE at 12 months after surgery (SE predictability)			0.627**		0.555**
No	5 (10.42%)	5 (13.89%)		12 (13.95%)	
Yes	43 (89.58%)	31 (86.11%)		74 (86.05%)	
Efficacy index					
1 month after surgery	0.98 ± 0.16	1.00 ± 0.16	0.529	0.89 ± 0.20	0.007
6 months after surgery	0.98 ± 0.18	0.98 ± 0.15	0.676	0.92 ± 0.17	0.011
12 months after surgery	0.96 ± 0.18	0.94 ± 0.16	0.556	0.86 ± 0.18	0.0009
Safety index					
1 month after surgery	1.08 ± 0.13	1.03 ± 0.10	0.055	1.01 ± 0.07	0.0001
6 months after surgery	1.08 ± 0.14	1.04 ± 0.09	0.072	1.01 ± 0.08	< 0.0001
12 months after surgery	1.07 ± 0.12	1.04 ± 0.16	0.042	1.00 ± 0.05	< 0.0001

CDVA: corrected distance visual acuity; D: diopter; FS-LASIK: femtosecond-laser in situ keratomileusis; ICL: implantable collamer lens; LogMAR: logarithm of the minimum angle of resolution; SE: spherical equivalent; SMILE: small incision lenticule extraction; UDVA: uncorrected distance visual acuity

***Wilcoxon Mann Whitney rank test results between FS-LASIK and ICL or between SMILE and ICL.**

****Chi-squared test between FS-LASIK and ICL or between SMILE and ICL.**

Table 3. Multivariate analyses for selected clinical outcomes

Variables	Efficacy index			Safety index			SE predictability		
	Coef.	95% CI	*p*-value*	Coef.	95% CI	*p*-value*	OR	95% CI	*p*-value**
Age	−0.01	(−0.01–−0.00)	0.027	0.00	(−0.00–0.00)	0.826	0.92	(0.84–1.00)	0.062
Surgery type									
ICL	1			1			1		
FS-LASIK	−0.01	(−0.10–0.09)	0.889	−0.02	(−0.06–0.02)	0.275	0.26	(0.05–1.38)	0.112
SMILE	−0.10	(−0.20–−0.01)	0.048	−0.04	(−0.07–−0.01)	0.005	0.14	(0.02–0.85)	0.033
Preoperative spherical error									
−3.0 D– −5.9 D	1			1			1		
−6.0 D–−8.9 D	−0.05	(−0.11–−0.01)	0.082	−0.01	(−0.03–0.00)	0.126	0.60	(0.19-1.89)	0.385
≤ −9.0 D	−0.09	(−0.19–−0.01)	0.086	−0.02	(−0.06–0.02)	0.368	0.10	(0.02-0.60)	0.011
Preoperative CDVA	0.81	(0.41-1.21)	<0.0001	1.12	(0.33–1.91)	0.006	0.15	(0.00-156.82)	0.593

CDVA: corrected distance visual acuity; Coef: regression coefficient; D: diopter; FS-LASIK: femtosecond-laser in situ keratomileusis; ICL: implantable collamer lens; LogMAR: logarithm of the minimum angle of resolution; OR: odds ratio; SE: spherical equivalent; SMILE: small incision lenticule extraction; UDVA: uncorrected distance visual acuity

***Generalized linear model with unstructured correlation matrix and robust standard errors**

****Logistic regression**

12 months after ICL, 39 eyes (81.25%) showed no change in CDVA, 7 eyes gained 1 line (14.58%), and 2 eyes gained 2 lines (4.17%). At the same time point after FS-LASIK, 27 eyes (75.00%) showed no change in CDVA, 7 eyes (11.11%) gained 1 line, and 2 eyes (5.56%) gained 2 lines. Finally, at 12 months after SMILE, 84 eyes (97.67%) showed no change in CDVA, 2 eyes (2.33%) gained 1 line, and 0 eyes (0.00%) gained 2 lines (Fig. 2). However, there were 3 eyes that lost 1 line at the 12-month follow-up after FS-LASIK (8.33%).

The mean change in SE over time for the three surgical types is depicted in Fig. 3 and Table 2. The differences in SE between ICL and FS-LASIK at 1, 6, and 12 months after surgery were not statistically significant (p = 0.536, 0.810, and 0.926, respectively). However, the differences in SE between ICL and SMILE at 1, 6, and 12 months after surgery were significant, with p = 0.0006, 0.004, and 0.010, respectively.

Stability of cylindrical error and SE of the three surgery types are shown in Fig. 3. Before surgery, the ICL group had higher SE and cylindrical error than did the FS-LASIK and SMILE groups. Cylindrical error remained higher in the ICL group after surgery. Comparisons of SE between 6 months and 1 month or between 12 months and 6 months in the ICL group showed no significant difference (p = 0.945 and 0.110, respectively) (data not shown). For both the FS-LASIK and SMILE groups, although there was no significant difference in SE at 6 months and 1 month (p = 0.778 and 0.075, respectively), SE at 12 months significantly increased compared with SE at 6 months (p = 0.010 and 0.018, respectively).

SE predictability at 12 months after surgery was within ±0.5 D in 89.58% of eyes in the ICL group compared with 86.11% of eyes in the FS-LASIK group and 86.05% of eyes in the SMILE group. However, there were no significant differences between eyes in the ICL and FS-LASIK groups or between eyes in the ICL and SMILE groups (Table 2). The percentage of eyes that had target SEs within ±1.0 D was higher in the ICL (95.83%) group than in the FS-LASIK (91.67%) group, but lower than in the SMILE (97.67%) group (Fig. 4).

Table 3 presents the results of the longitudinal multivariate analyses. Variables were selected for the multivariate model if they had $p < 0.25$ in our univariate analyses. Although CCT was significantly associated in the univariate analyses ($p <$ 0.05), it was not significantly different among these surgery types in the multivariate analyses. In addition, the multivariate model with CCT had lower goodness of fit than did the model without CCT. So, this variable was removed from the final model. The final model showed that ICL had significantly better safety and efficacy indices than did SMILE over 12 months (Coefficient = −0.04, 95% CI = −0.07−−0.01 and Coefficient= −0.10, 95% CI= −0.20−−0.01, respectively), after controlling for age, preoperative SE, and preoperative CDVA. The percentage of eyes that underwent ICL and had target SEs within ±0.5 D at 12 months was

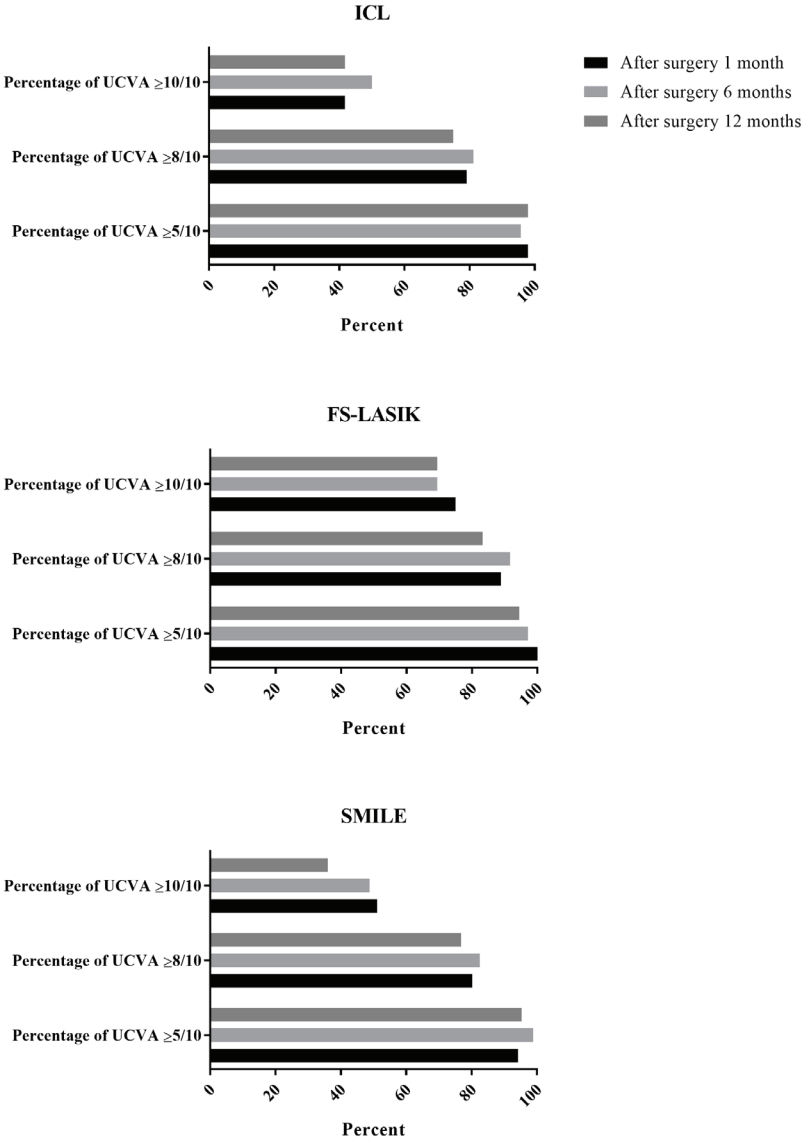
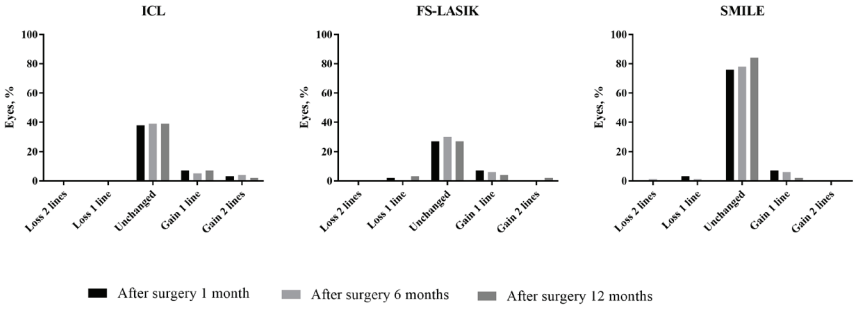


Fig. 1. Percentage of uncorrected distance visual acuity (UCVA) ≥ 5/10, 8/10, and 10/10 at each time point, by surgery type.



	After surgery 1 month			After surgery 6 months			After surgery 12 months		
	ICL	FS-LASIK	SMILE	ICL	FS-LASIK	SMILE	ICL	FS-LASIK	SMILE
Loss 2 lines	0.00%	0.00%	0.00%	0.00%	0.00%	1.16%	0.00%	0.00%	0.00%
Loss 1 line	0.00%	5.56%	3.49%	0.00%	0.00%	1.16%	0.00%	8.33%	0.00%
Unchanged	79.17%	75.00%	88.37%	81.25%	83.33%	90.70%	81.25%	75.00%	97.67%
Gain 1 line	14.58%	19.44%	8.14%	10.42%	16.67%	6.98%	14.58%	11.11%	2.33%
Gain 2 lines	6.25%	0.00%	0.00%	8.33%	0.00%	0.00%	4.17%	5.56%	0.00%

Fig. 2. Changes in corrected distance visual acuity (CDVA) at each time point, by surgery type.

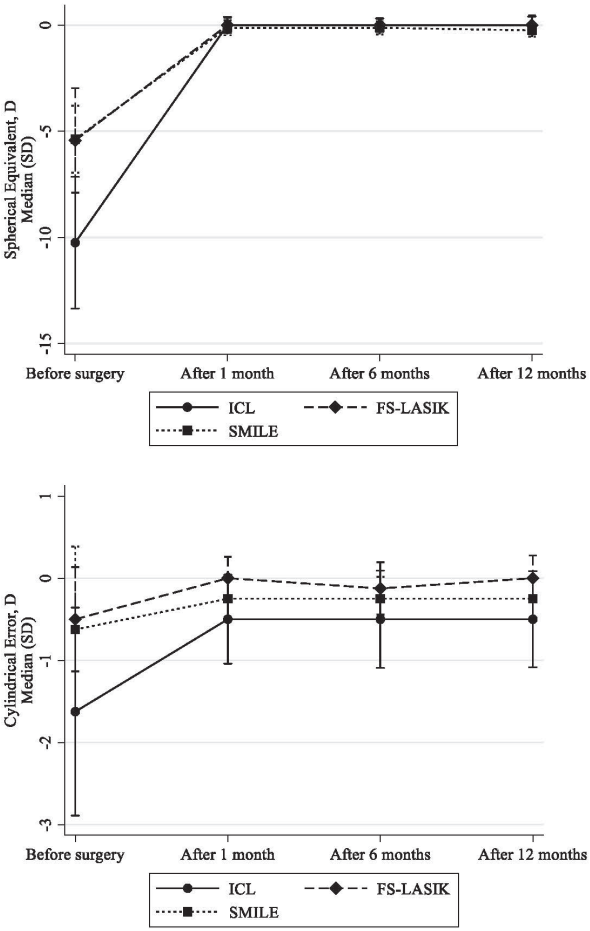
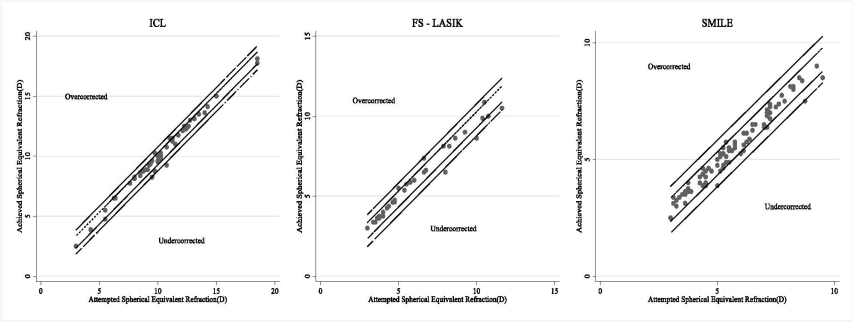


Fig. 3. Stability of spherical equivalent and cylindrical error at each time point, by surgery type.



SE predictability at 12 months after surgery

	N	Target SE within ± 0.25 D *n* (%)	Target SE within ± 0.5 D *n* (%)	Target SE within ± 1 D *n* (%)
ICL	48	33 (68.75%)	43 (89.58%)	46 (95.83%)
FS-LASIK	36	28 (77.78%)	31 (86.11%)	33 (91.67%)
SMILE	86	57 (66.28%)	74 (86.05%)	84 (97.67%)

Fig. 4. Scattergram of attempted versus achieved spherical errors (SE) by surgery type at 12 months after surgery.

significantly seven times higher than that of eyes that underwent SMILE (OR = 0.14, 95% CI = 0.02–0.85), after controlling for age, preoperative SE, and preoperative CDVA.

Discussion

Our results showed that ICL had favorable outcomes compared with FS-LASIK and SMILE in terms of efficacy, safety, stability, and predictability throughout 12 months after surgery to correct moderate-to-high myopia and myopic astigmatism. Our findings are consistent with those of the study of an Indian population by Ganesh *et al.*[10] However, the safety and efficacy indices in our three groups were lower than those in the Ganesh study. This discrepancy might be due to a different preoperative SE range and our larger sample size. Our patients had SEs higher than −9 D, while patients in the Ganesh *et al.* study had SEs in the range of −3 to −8 D.

Before surgery, the mean SE among our ICL group (−10.46 ± 3.10) was significantly higher than that among the FS-LASIK (−6.12 ± 2.46) and SMILE groups (−5.69 ± 1.58). At 1-, 6-, and 12-month follow-ups, the SE means (−0.02 ± 0.38, −0.02 ± 0.32, and −0.14 ± 0.40, respectively) of the ICL group were significantly lower than those of the SMILE group (−0.26 ± 0.35, −0.19 ± 0.31, and −0.25 ± 0.31, respectively) and were comparable to those of the FS-LASIK group (0.01 ± 0.34, 0.01 ± 0.31, and −0.13 ± 0.45, respectively). Eyes that received ICL showed no loss of lines at 1, 6, and 12 months after surgery. These findings suggest that ICL

had better efficacy and safety than did FS-LASIK and SMILE in correcting moderate-to-high myopia and myopic astigmatism. This result was confirmed again in our longitudinal multivariate analysis, which showed that after controlling for age, preoperative SE, and preoperative CDVA, ICL had higher efficacy and safety indices than did SMILE (p =0.048 and 0.005, respectively) and FS-LASIK (p = 0.889 and 0.275, respectively). However, other studies with larger sample size and with prospective follow-up are needed to reinforce the result.

With regard to stability and predictability, ICL scored better than did either FS-LASIK or SMILE. The refractive regression was observed after both types of laser vision correction, while ICL implantation showed stable results throughout 12 months after surgery. This finding may be due to the small corneal incision (3 mm) and no need for removal of corneal tissue during ICL, which induces fewer corneal wound healing responses and fewer changes in corneal biomechanics.[13] The percentage of SE predictability within ±0.5 D at 12 months was higher in the ICL group than in the FS-LASIK and SMILE groups.

Our study had some advantages. First, to our knowledge, the current study was one of the few studies comparing the efficacy and safety indexes and the stability of ICL to those of FS-LASIK or to those of SMILE in an Asian population.[10] Ocular characteristics of Caucasians are different from those of Asian populations,[11,12] which may influence evaluation of refraction surgery outcomes. Second, instead of matching some preoperative patient characteristics, which might cause selection bias, we used multivariate analyses to control for the confounding factors. In order to longitudinally analyze repeated refractive outcomes over time, the generalization estimate equation was employed. Finally, our sufficient sample size assisted us in detecting significant results.

However, this study had some limitations. First, the study was retrospectively conducted, which may decrease the quality of evidence. Although this is a multicenter study with a large cohort of patients, a prospective randomized control trial would be ideal to confirm our results. Second, only patients who had available refractive errors at 1-, 6-, and 12- months after surgery were included. This approach might cause selection bias. Third, ICL, FS-LASIK, and SMILE were performed by different experienced surgeons. Variations in surgical technique may have influenced our results. However, according to Yo and colleagues, results of refractive surgery between surgeons are comparable under standardized surgical techniques.[14]

Overall, our results favored ICL over SMILE and FS-LASIK for the treatment of moderate-to-high myopia and myopic astigmatism. However, the appropriate surgical procedure should be chosen based on preoperative parameters and patient preferences.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Ethical Review Committee of the An Sinh Hospital (1062-18/AS-QD).

Competing interests

None to declare.

Funding

None to declare.

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Epstein-Barr virus uveitis after intravitreal triamcinolone injection

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Abstract

Purpose: *To report a case of Epstein-Barr virus (EBV) uveitis after intravitreal triamcinolone injection.*

Methods: *Observational case report.*

Results: *A 66-year-old male presented with bilateral intermediate uveitis, left macular branch retinal vein occlusion, and left macular edema 3 months following acute infectious mononucleosis. He received systemic prednisolone, methotrexate, and intravitreal bevacizumab with partial response. Intravitreal triamcinolone was given for recurrent macular edema, which led to the development of severe panuveitis with positive EBV PCR in aqueous humour. This was successfully treated with high-dose systemic valaciclovir and topical prednisolone.*

Conclusion: *Non-infectious uveitis may become infectious following intravitreal steroid administration triggering intraocular viral replication. Intraocular fluid should be tested in cases which are suspicious for infection and EBV should be considered a differential diagnosis, particularly if PCR is negative for more common viral etiologies.*

Keywords: *Epstein-Barr virus, panuveitis, uveitis, triamcinolone*

Introduction

Epstein-Barr virus (EBV), a ubiquitous herpes virus associated with infectious mononucleosis, may uncommonly affect any part of the eye during acute systemic infection. In chronic ocular inflammation, however, its PCR presence in ocular fluid specimens is usually regarded as contamination through its dormant presence in resident lymphocytes. We have identified four reports of likely intraocular EBV infection supported by positive EBV PCR in aqueous humour.[1,2] We present a case of probable intraocular EBV infection resulting in uveitis after intravitreal triamcinolone injection.

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Case presentation

A 66-year-old obese male with metabolic syndrome developed acute infectious mononucleosis confirmed by positive EBV VCA IgG and IgM with atypical monocytosis. EBNA IgG was negative.

Acute infection was followed by chronic fatigue which was treated with oral prednisolone. Within 3 months, he developed a left macular branch retinal vein occlusion with macular edema followed by onset of bilateral floaters. Investigation for common causes of intermediate uveitis was negative. Increased prednisolone dose resulted in decreased vitritis but this recurred once the dose was tapered below 20 mg daily. Methotrexate was used as a steroid-sparing agent. The macular edema and fatigue were controlled but the vitritis never fully resolved. He had bilateral uncomplicated cataract surgery with intraoperative bevacizumab to treat mild left macular edema. After 30 months, methotrexate was ceased permanently because of recurrent respiratory tract infections and impending orthopedic surgery.

Off methotrexate, the vitritis paradoxically decreased but the left macular edema recurred. Due to the concern of a possible systemic viral etiology, the macular oedema was treated locally with left sub-Tenon's triamcinolone 40 mg. There was a short-lived improvement in the macular edema with no change in the vitritis. Left intravitreal triamcinolone 4 mg resulted in remission of the macular edema lasting a year with minimal change in the vitritis. A year later, increasing macular edema became visually significant and intravitreal triamcinolone 4 mg was repeated.

Two months later, the patient presented with loss of vision and severe anterior and posterior uveitis. There were dense clusters of tiny white (non-stellate) inferior keratic precipitates. Intraocular pressure was 45 mmHg and visibility was too poor to image the macula for edema. An anterior chamber tap was performed. PCR was positive for EBV and negative for herpes simplex virus 1, herpes simplex virus 2, and varicella-zoster virus.

A diagnosis of EBV panuveitis was thought likely and the patient was started on valaciclovir 1 g TDS with intensive topical prednisolone-acetate/phenylephrine-hydrochloride and full ocular hypotensive therapy excluding prostaglandin drops. Within 2 weeks, the anterior uveitis had settled. The ocular hypotensives and topical steroids were tapered and the vitritis gradually improved over 3 months. Optical coherence tomography confirmed absence of macular edema. Interestingly, the microaneurysms previously associated with the vein occlusion became almost undetectable.

More than a year later, the patient developed left steroid-induced, progressive, uveitic glaucoma in the left eye despite maximal tolerable intraocular pressure-lowering therapy. He was on topical steroid treatment with no antiviral

therapy or systemic immunosuppression. At the time there was mild vitritis with minimal anterior uveitis and no macular edema. During XEN trabeculectomy surgery, an anterior chamber tap was PCR negative for all previously tested pathogens, including EBV.

Discussion

In this case, the strongly positive PCR result, absence of other herpes viruses, and good response to valaciclovir all strongly suggest intraocular EBV infection and viral replication. Pathogens isolated by metagenomic deep sequencing in uveitic eyes highlight the eye's potential to act as an infectious reservoir.[3] Intraocular infection may occur through direct invasion of ocular tissue or through infected B-cells which enter the eye during inflammation.[1] Systemic immunity was apparently strong enough to prevent fulminant infection during treatment with oral steroids, methotrexate, and sub-Tenon's triamcinolone, but the ongoing chronic intraocular inflammation may have been a marker of some viral activity. On this occasion, intravitreal triamcinolone appears to have weakened ocular defenses sufficiently to allow significant EBV activation.

The authors acknowledge that the current literature does not support a high prevalence of EBV uveitis. Sampling of aqueous humor of uveitic eyes revealed a low PCR yield for EBV (1%) in a Netherlands study of 297 patients.[4] However, concurrent positive results for other viruses, most commonly varicella-zoster virus, were often found in patients with positive EBV in aqueous humor.[4] This was one of the study's findings, leading the authors to conclude that intraocular assessment for EBV in uveitis patients has limited value. Our patient had negative PCR for other viruses. Fourteen patients had results indicating only EBV infection with no alternative explanation for uveitis for six patients.[4] Clinical signs of these patients included anterior chamber inflammation with small KPs and severe vitritis with no involvement of the retina or choroid. All six patients had a chronic, recurrent course of inflammation. The clinical findings described in these patients with potential EBV uveitis are similar to the signs observed in our case.

Several studies demonstrate a reduction of viral replication with acyclovir therapy, the commonest antiviral treatment for ocular EBV infection.[5] Keorochana reported a case of EBV-associated retinal vasculitis successfully treated with 14 days of intravenous acyclovir, 3 months of oral acyclovir, and vitrectomy.[5] We found high-dose valaciclovir to be effective in our patient. Intravitreal foscarnet inhibits EBV DNA polymerase and would also be an option for future flares.

Next generation sequencing techniques identifying pathogens in intraocular fluid from patients with uveitis are increasingly demonstrating that intermediate uveitis is not always non-infectious.[3] Treatment of acute infectious mononucleosis

with systemic steroids may result in prolonged viral activity. It is possible that the intermediate uveitis in this patient was viral from the start.

Our case is an example of the potential role of steroids in reactivation of EBV from latency, which has been demonstrated in the literature.[6] Possible mechanisms may include direct promotion of viral replication or inhibition of memory T-cell control of latent virus.[6]

This case illustrates that even when there has been an initial partial favorable response to immunomodulation, a tipping point may be reached at which viral replication may be triggered and non-infectious uveitis becomes infection. Prior to adding immunosuppression to recalcitrant cases or those where treatment is followed by deterioration, intraocular fluid should be tested for infectious causes.

Declarations

Consent for publication

The patient provided informed consent for the use of the clinical information contained in this case report.

Competing interests

None to declare.

Funding

None to declare.

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Complete dislocation of the eye globe into the maxillary sinus: a rare case

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Abstract
Blowout fracture with entrapped orbital contents within the maxillary sinus is common due to the fragility of the inferior wall, but complete herniation of the eye globe is extremely rare and emergent. Dealing with such a case appears to be a real challenge for any ophthalmologist. We herein present a case of a 31-year-old woman with the entire eyeball missing from the orbit following a road traffic accident. Imaging revealed a complete herniation of the globe into the maxillary sinus. The patient underwent surgery for repositioning the herniated orbital contents and reconstructing the orbital walls. The outcome was satisfactory in terms of aesthetic effect, although the patient's vision could not be restored as it still depends on various factors, especially the survival of ganglion cells after trauma.

Keywords: *blowout fracture, hernia, maxillofacial, orbital trauma, titanium mesh*

Introduction

Orbital cavities are conical structures that resemble four-sided pyramids. Each orbit is made up of seven bones, forming four walls. With the medial wall and orbital floor being the thinnest, they are more prone to fracture following trauma. The orbit contains the globe, extraocular muscles, nerves, blood vessels, and fat. When being hit by a blunt object at high speed, the created force exerts equally on four walls and other orbital structures. Blowout fracture occurs as the medial or inferior wall breaks due to its vulnerability. Consequently, orbital contents prolapse into the maxillary sinus and posterior ethmoidal sinus. Depending on the severity of the injury, orbital structures can be partly or completely entrapped in the sinuses. The whole globe might fall into the maxillary sinus, abruptly tugging the optic nerve, making the central retinal artery stretched and twisted, destroying the blood supply to the optic nerve as a result. In that case, even if the eyeball is placed back into its original position, visual loss is almost inevitable. Kim and Baek reported that until 2005 there had only been three cases of intact eyeballs herniating into the maxillary sinus, only one of which had the globe completely

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Table 1. Clinical profile of cases of traumatic globe dislocation into the maxillary sinus

Authors	Eye	Etiology	Time to surgery	Approach	Orbital reconstructive material	Final visual acuity	Ocular motility
Berkowitz *et al.* (1981)5	OS	Punched with a fist	Same day	Transantral	Square silicone implant	Recovery; 20/20; preserved VF	Limited depression. Retained motility in other directions
Kim and Baek (2005)1	OD	Traffic accident	Same day	Transorbital (transconjunctival)	Porous polyethylene	No	Globe deviated to superolateral position; possible elevation and abduction
Ramstead *et al.* (2008)6	OS	Stepped on by a bull	Same day	NA	Titanium mesh	Recovery; 20/200	Minimal horizontal gaze; no vertical gaze
Damasceno (2010)2	OD	NA	Same day	Transantral	Metallic plate implant	Recovery; 20/20; preserved VF	Retained abduction; loss in other directions.
Zhang *et al.* (2012)3	OD	Traffic accident	Same day		Silastic sheeting implant	Recovery; 20/25 centrally; central tunnel of vision	NA
Amaral and Nery (2016)4	OS	Struck by gym weight	4 days	Transantral	Titanium mesh	Recovery; 20/50	Limited ocular motility in all directions
Nguyen *et al.* (2020)	OS	Traffic accident	2 days	Transorbital (under the inferior eyelid 1.5 mm)	Titanium mesh	No; NLP	Limited ocular motility in all directions

NA: not applicable; NLP: no light perception; VF: visual field

entrapped within the sinus.[1] In 2010, Damasceno reported a case of dislocation of the globe into the maxillary sinus, in which the patient had improved visual acuity with preserved visual field (VF) after surgery.[2] By 2012, the medical literature had recorded approximately 14 patients of ocular herniation, 8 of whom had partially restored vision.[3] There has been no such report in Vietnam. At the Department of Oculoplasty and Neuro-Ophthalmology in Ho Chi Minh City Eye Hospital, for the first time, we successfully treated a blowout fracture with complete dislocation of the globe after trauma. The data from all previous relevant studies are presented in Table 1.

Case report

A 31-year-old woman was admitted following a road traffic accident. She fell and directly hit her face against a thick square piece of wood. The patient was rushed to the emergency room of a local health center with a bleeding left eye and no eyeball in the orbital cavity; hence, she was referred to Ho Chi Minh City Eye Hospital. On examination, her left eye had ptosis, upper eyelid laceration, and edema, and the globe went missing from the orbit (Fig. 1). Computed

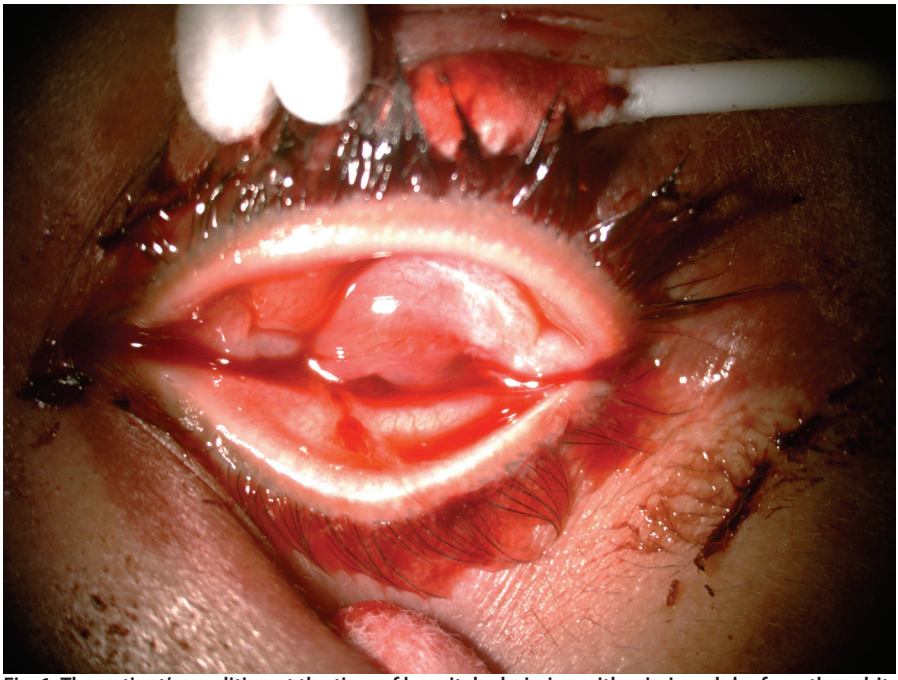

Fig. 1. The patient's condition at the time of hospital admission with missing globe from the orbit.

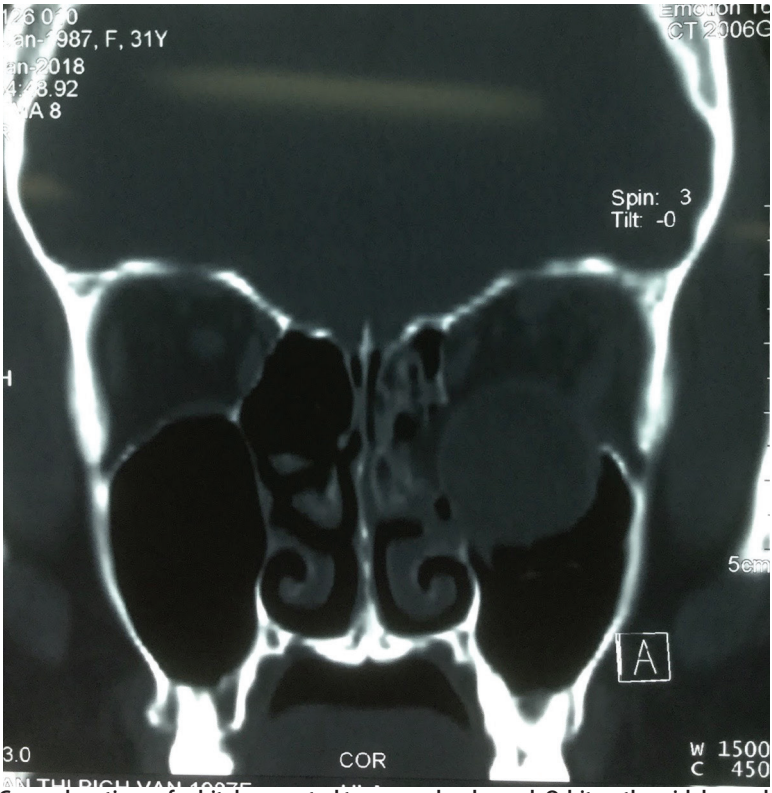

Fig. 2: Coronal sections of orbital computed tomography showed: Orbito-ethmoidal complex fractures, orbital floor fractures, with associated sinus effusion. No damage to the meninges, brain and skull. Normal right eye.

tomography scans, including coronal (Fig. 2) and sagittal (Fig. 3) planes, revealed complex orbital fractures with herniated orbital contents in the maxillary sinus and the optic nerve being tugged down by 25 mm, respectively. the diagnosis was blowout fracture with complete dislocation of the left eye globe into the maxillary sinus following a road traffic accident.

We had a hospital consultation with an ear, nose, and throat specialist. A suggested treatment strategy for this case was to restore the globe to its original position, to reconstruct the orbital floor and orbital wall with a titanium mesh, and to use antibiotics and anti-inflammatory drugs for surgical prophylaxis and edema reduction, respectively.

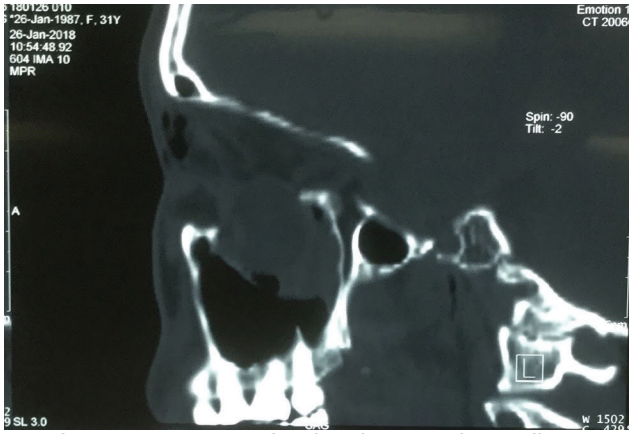

Fig. 3. Sagittal view showing an optic nerve bending down into the maxillary sinus.

Surgical technique

The patient underwent surgery under systemic anesthesia. In order to widen the surgical field of view and to leave room for flexible maneuvering, we made an incision 1.5 mm below the inferior eyelid to approach the orbital cavity. On the dissection along the orbital rim, we had to detach adhesive tissue to the orbital floor and medial wall as well as remove surrounding bone fragments for the protection of the eyeball when repositioning. To preserve the optic nerve, the globe was gently lifted with a spatula while avoiding meddling with the posterior pole. The entrapped globe was pushed in an upward and outward direction back from the maxillary sinus, returning it to its original position. The eyeball was fully intact but showed corneal abrasion. The extraocular muscles did not suffer any damage. Subsequently, we restored the orbital floor and medial wall with titanium mesh, then repaired the eyelid lacerations.

Postoperative assessment

At postoperative day 1, the left eye showed complete ptosis, chemosis, diffuse subconjunctival hemorrhage, corneal abrasion, 5-mm pupil, negative direct pupillary reflex, positive RAPD, limited ocular motility in all directions (- 4), posterior pole retinal hemorrhage, grade 1 disc edema, and no light perception. On postoperative day 5 (Fig. 4), visual acuity had not improved. However, swelling of the eyelid had reduced, ptosis subsided from complete ptosis to grade 2, chemosis had reduced, corneal epithelium was healing, ocular motility improved from -4 to -2, and retinal hemorrhage still existed with grade 1 disc edema. The patient was satisfied with the outcome. On postoperative week 2 (Fig. 5), the patient still had enophthalmos, but other signs had recovered significantly. The eye had light perception.

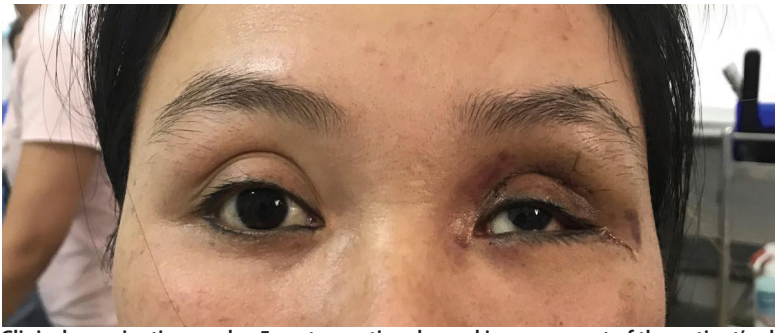

Fig. 4. Clinical examination on day 5 postoperative showed improvement of the patient's physical appearance with subsided ptosis and edema.

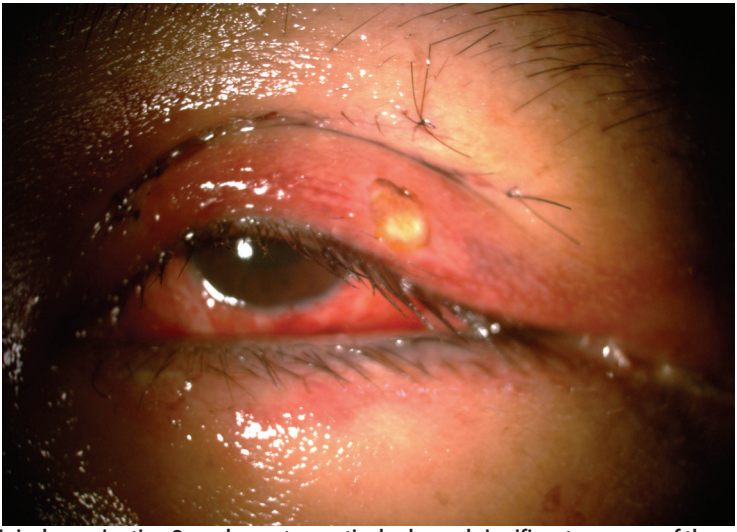

Fig. 5. Clinical examination 2 weeks postoperatively showed significant recovery of the patient.

Discussion

Complete dislocation of the globe into the maxillary sinus through blowout fracture is a very rare ophthalmic emergency. Ischemia of ocular and other herniated orbital contents follows immediately. Therefore, intervention is required within the first few hours for those structures to be released. The patient must therefore present early and must be operated by a skilled oculoplastic and orbital surgeon. In this case, however, the patient was operated on her second day after trauma. At that time, the ischemia had lasted too long for vision to be restored. The etiology for permanent visual loss could be inferred as traumatic optic neuropathy

due to the sudden distortion of the optic nerve, as the twist and stretch of the central retinal artery behind the lamina cribrosa destroyed the blood supply to the optic nerve. The longer the time to surgery takes, the higher the risk of complications due to edema compressing nearby structures, especially the optic nerve and blood vessels, aggravating the vicious cycle of ischemia.[4] Recovery of vision depends greatly on the severity of the injury, timely intervention, and most importantly, the survival of ganglion cells following trauma, regardless of the surgeon's attempt in returning the eyeball to its original position.[3-6] For that reason, early diagnosis, and intervention to minimize the time lost and to limit the damage caused are crucial to help preserve the patient's vision.

There are two surgical approaches to release entrapped orbital contents recommended in the medical literature: the transorbital and the transantral approach.[4] The surgeon will choose the most appropriate route, contingent on their proficiency. Having experienced many cases of restructuring orbital wall, we chose the transorbital approach due to its familiarity and to minimize damage for the patient. At that time, the edematous herniated contents made it impossible to be put back through the original pathway. After dissecting through the periosteum, we had to remove sharp bone fragments for the enlargement of an already existing hole created by trauma. Consequently, the globe and its associated structures were lifted successfully without being damaged.

Once the prolapsed structures had been brought back in place, we still had to reform bony orbital defects for them to be fixed in the cavity. Many reconstructive materials have been described in the literature, such as iliac crest autografts or mesh made of silicon, ceramic, titanium, polyethylene, etc. We chose a titanium mesh for this case because of its solidity and malleability. The implant can be molded along the orbital wall accurately and can be fixated with self-drilling bone screws. Other herniated tissue became so swollen that other reconstructive materials would not have been able to endure.

Conclusion

Dislocation of the globe into the maxillary sinus is an extreme situation. Recovery of vision depends on the severity of injury, partial or complete herniation of the eyeball, early diagnosis and intervention, and most importantly, the survival of ganglion cells following trauma. If the optic nerve can still function, with early diagnosis and intervention vision can be restored. Conversely, even if late hospital admission with optic nerve distortion has already caused irreversible loss of vision, we should still proceed to operate with the aim of returning all orbital herniated contents to their original position, ensuring a positive cosmetic and psychological effect for the patient.

Declarations

Informed consent

The patient provided informed consent for the use of the clinical information and images contained in this case report.

Competing interests

None to declare.

Funding

None to declare.

Acknowledgements

None to declare.

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