KUGLER PUBLICATIONS

Volume 14 • Issue 4 • 2016 • 1560-2133

Asian Journal of OPHTHALMOLOGY

open access journal est. 1998

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Publisher:
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P.O. Box 20538,
1001 NM Amsterdam,
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www.kuglerpublications.com

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Publication frequency
The Asian Journal of Ophthalmology is published four issues per year (quarterly) electronically. Each issues will consist of approximately 48 pages. A selection of the best papers is published in print twice a year and distributed free of charge at congresses through Kugler Publications or partners.

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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. This resulted in collaboration with the Asia Pacific Ophthalmic Trauma Society (APOTS).

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.asjoo.com), which facilitates all aspects of the peer-review and publication process, from manuscript submission to publication.

For further information and manuscript submissions please visit our website: www.asjoo.com.

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Asian Pacific Glaucoma Guidelines 3

The Asia Pacific Glaucoma Society (APGS) is moving ahead with preparation of the 3rd Edition of our popular Glaucoma Guidelines that are distributed and read widely across the Asia-Pacific Region. The last edition (then known as the SEAGIG Guidelines was published 6 years ago), this version was downloaded thousands of times per year since 2003. The APGG are a very important educational tool for the Asia-Pacific region and are widely used.

This latest edition of the Guidelines will be co-chaired by Profs. Aung Tin (Singapore) and Jonathan Crowston (Melbourne). Currently the Working party is researching and preparing the necessary updates.

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Asian J Ophthalmol. 2016;14:149-153

Dry eye researchers and their publications in Asia and Europe

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Dry eye, a visually disabling disease that has been reported to be a major public health issue in many countries, is known to induce a significant decrease in quality of life.[1] In this report, we aim to compile information on the investigators of dry eye that published most frequently in peer reviewed scientific journals and the publications in Asia and Europe.

We performed the search on the NCBI Entrez Pubmed database on February 28, 2014. Dry eye-related publications were analyzed based on authorship, country of author, and year of the publication. Keywords used in our search consisted of the phrase 'dry eye' OR 'tear dysfunction' OR 'tear film' OR 'ocular surface inflammation' OR 'meibomian' OR 'lacrimal'. The resulting publications were curated manually and articles that focused only on allergic eye disease, trauma, tumors or surgical procedures unrelated to dry eye were excluded.

The thirteen authors in Asia (Table 1) with the highest individual number of papers accounted for 469 unique publications whereas the thirteen authors in Europe (Table 2) were responsible for 401 publications. These numbers are less than the total in the table because different authors may have co-authored the same publications.

We have noticed that majority of the publications from Asia originated from researchers from Japan (in fact all were from Tokyo and Kyoto) and two authors were from Singapore. Tsubota K was responsible for 260 publications, leading the Asia researchers. The most published European author was Baudouin C, responsible for 78 eligible publications. Interestingly, unlike Asia, where all the publications investigated were from three cities and two countries, these European researchers were spread across twelve cities and six countries. We also noticed that most of the papers published were in the last ten years, as shown in the right most column (Table 1 and Table 2).

However, we did not look into the total dry eye-related publications from a continent, particular country, city or research center. The total number of papers by

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region is perhaps not useful since the total number of ocular surface researchers at all levels cannot be easily captured. We also did not have any knowledge of where the published work was primarily performed, since collaborations can occur between people from different centers. We also would like to point out that the count included all types of journal papers in including reviews, commentaries, editorials and letters. The most frequent scientific journal in the list is Investigative Ophthalmology & Visual Science.

The trend gathered in this research may reflect increasing awareness and incidence of dry eye in Asia[1] and consequently targeted funding of major centers in Asia for dry eye. In 2012, Japan spent 3.34% of Gross Domestic Product (GDP) on Research and Development (R&D), 5th highest in Organisation for Economic Co-operation and Development (OECD) countries.[2] Although the distribution of R&D expenditure across the various sectors is unknown, it can be assumed that there is a general increase in the importance of research as well as funding opportunities. On the other hand, the robust dry eye research in Singapore, driven primarily by the Singapore Eye Research Institute,[3] could be fuelled by the associated high economic burden.[4] This is also consistent with Singapore being the most productive in eye publications per capita in the world.[5]

Meanwhile in Europe, centers performing dry eye research tend to be more widespread, perhaps because there were more countries with a longer tradition for research in ophthalmology.

The nature of journals that are published by these eye researchers from both Asia and Europe is similar to those published by the most prolific dry eye researchers in the world[6]. In fact, the most prolific author from Asia (Tsubota K) is also the most prolific author on dry eye research in the world.

Nevertheless, our data show that both in Asia and Europe, the majority of these dry eye related papers were published in the last ten years. Over the last decade, spending for R&D intensity grew in both Japan (from 3.00% to 3.26%) and the European Union (from 1.74% to 1.91%).[2] This increase in research funding, together with increased awareness of dry eye, would at least partially explain this publication trend. Recent efforts in Asia include the formation of the Asia Cornea Society, registered in Singapore in 2007, to promote regional and international cooperation in ocular surface and other cornea research.[7] Another reason for increased dry eye work may be related to commercially driven research. In Western Europe alone, the market revenue for dry eye products in 2013 was about 500 million US dollars.[8]

In conclusion, there is active dry eye research in Japan and Europe, particularly so in the last ten years. Asian countries, especially Japan, sees the development of a few specialised dry eye centers driven by a small number of academic individuals, resulting in clearly prolific authors in this field, who also tends to be key opinion leaders. On the other hand, dry eye research in Europe is more widespread across the continent.

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Table 1. Dry eye researchers in Asia.

		Country of research	City	Research Centre	Total number of publications	Total number of publications (2004-2014)
1	Tsubota K	Japan	Tokyo	Keio University School of Medicine	257	159
2	Dogru M	Japan	Tokyo	Keio University School of Medicine	119	109
3	Kinoshita S	Japan	Kyoto	Kyoto Prefectural University of Medicine	80	44
4	Yokoi N	Japan	Kyoto	Kyoto Prefectural University of Medicine	75	44
5	Matsumoto Y	Japan	Tokyo	Keio University School of Medicine	68	59
6	Shimazaki J	Japan	Tokyo	Tokyo Dental College Ichikawa Hospital	59	39
7	Goto E	Japan	Tokyo	Keio University School of Medicine	59	39
8	Toda I	Japan	Tokyo	Minamiaoyama Eye Clinic	41	9

		Country of research	City	Research Centre	Total number of publications	Total number of publications (2004-2014)
9	Shimmura S	Japan	Tokyo	Keio University School of Medicine	40	23
10	Tong L	Singapore	Singapore	Singapore Eye Research Institute	39	39
11	Beuerman RW	Singapore	Singapore	Singapore Eye Research Institute	37	19
12	Kojima T	Japan	Tokyo	Keio University School of Medicine	35	33
13	Uchino M	Japan	Tokyo	Keio University School of Medicine	28	27

Table 2. Dry eye researchers in Europe.

		Country of research	City	Research Centre	Total number of publications	Total number of publications (2004-2014)
1	Baudouin C	France	Paris	Quinze-Vingts National Ophthalmology Hospital	76	54
2	Bron AJ	UK	Oxford	University of Oxford	54	21
3	Geerling G	Germany	Dusseldorf	University of Düsseldorf	44	31
4	Tomlinson A	UK	Glasgow	Glasgow Caledonian University	41	25
5	Calonge M	Spain	Valladolid	University of Valladolid	38	28
6	Rolando M	Italy	Genoa	University of Genoa	33	17
7	Knop E	Germany	Berlin	Ocular Surface Center Berlin	29	22
8	Barabino S	Italy	Genoa	University of Genoa	23	20

		Country of research	City	Research Centre	Total number of publications	Total number of publications (2004-2014)
9	Bonini S	Italy	Rome	University Campus Bio-Medico	21	18
9	Cursiefen C	Germany	Cologne	University of Cologne	21	18
9	Tervo T	Finland	Helsinki	Helsinki University Hospital	21	5
12	Aragona P	Italy	Messina	University of Messina	19	12
12	Kruse FE	Germany	Erlangen	University of Erlangen-Nuremberg	19	15

Asian J Ophthalmol. 2016;14:154-165

Evaluation of the prevalence and severity of xerophthalmia in head and neck cancer patients undergoing curative radiotherapy

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Abstract

Background: *The study objective was to assess the development of xerophthalmia [dry eye syndrome (DES) or keratoconjunctivitis sicca] in head and neck cancer patients undergoing radiotherapy.*

Methods: *Twenty two head and neck cancer patients requiring more than 60 Gy of curative radiotherapy/chemoradiotherapy and ten patients requiring radiotherapy/ chemoradiotherapy for treating cancers in the non head and neck regions (like breast, oesophagus, prostate, cervix and rectal cancers) were also enrolled in the study. The development of DES was studied at the beginning (day 0, before the start of radiotherapy) at day 21 (after completion of 30 Gy) and on completion of the treatment (> 60 Gy). As a comparative cohort, people with non head and neck cancer needing curative radiotherapy were also evaluated for comparison.*

Results: *There was no difference in degree of DES between the Head and Neck cancer cohorts and non head and neck group at the beginning of treatment. However there was a statistically significant difference ($p < 0.001$) between the two groups at both mid and end of RT time point. Inter comparison between the various time points in the head and neck cancer group showed that the incidence of DES increased with the radiation exposure and was significant (pre to mid $p < 0.001$; and mid to end $p < 0.005$). A negative ($r = -0.262$) correlation was seen between DES and distance.*

Conclusions: *The study showed that lesser the distance from the epicenter of the radiation to the orbital rim more was the severity of DES.*

Key words: *xerophthalmia, dry eye syndrome, keratoconjunctivitis sicca, ionizing radiation, Head and neck cancer*

Introduction

Ionising radiation, which is an important modality in the treatment of head and neck cancers, is associated with various side effects like treatment induced oral mucositis, xerostomia, and dysphagia[1]. In addition to these, xerophthalmia [also known as dry eye syndrome (DES) or keratoconjunctivitis sicca], which develops

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when the field of radiation includes the orbit and the tissues adjacent to the eye like adnexa, the lacrimal system (including the major and accessory lacrimal glands, lacrimal canaliculi, lacrimal sac, and nasolacrimal duct) , the ocular surface (including the cornea and conjunctiva) , the motor nerves, the eyelids, the meibomian glands and associated sensory organs is also a commonly observed side effect.[2-5] Xerophthalmia occurs as a result of damage to glands within the eyelid, decreased conjunctival mucous production and reduced lacrimal gland secretion. The functional effects of all these alterations are conjunctival inflammation, chemosis, tear film instability and a resultant dry eye sensation, which generally subside but on occasion, be persistent.[6]

Fig 1a. Film pictures depicting the RT fields planned in various cancers. (Design: ...)

The incidence of DES is proportionate to the total dose of radiotherapy and results from the cytostatic effects of radiation on the cells with high turnover and to specific alterations in cell type and function.[5] These effects are dose-dependent and the incidence of dry eye increases steeply at doses > 40 Gy and observations have indicated the long term effects post irradiation.[7,8] DES increases osmolarity of the tear film and inflammation of ocular surface.[8] Reports indicate that the increase in the stratification of conjunctival epithelia and reduction in goblet cell numbers contributes to a dry eye following radiotherapy[6], and also that loss of serous acinar cells from the lacrimal gland contributes towards the DES.[9]

Clinically, the common symptoms of severe DES include dryness, stinging, burning, irritation, itching, scratchy eye, tired eye, photophobia, pain, redness, a foreign body sensation, mucous discharge, excessive tearing, blurry vision in the

early stages, and ulceration, vascularization, opacification, perforation and vision loss in advanced stages.[6,8] Although mild to moderate DES is often successfully manageable with supportive therapy, severe DES can result in ulceration and/or infection of the cornea, thickening of the corneal surface, corneal erosion, punctate keratopathy, epithelial defects, corneal abrasions, ulceration, neovascularization, scarring, thinning, perforation, and corneal necrosis, leading to irreversible corneal opacity with compromised vision, severe pain, and eye loss.[10]

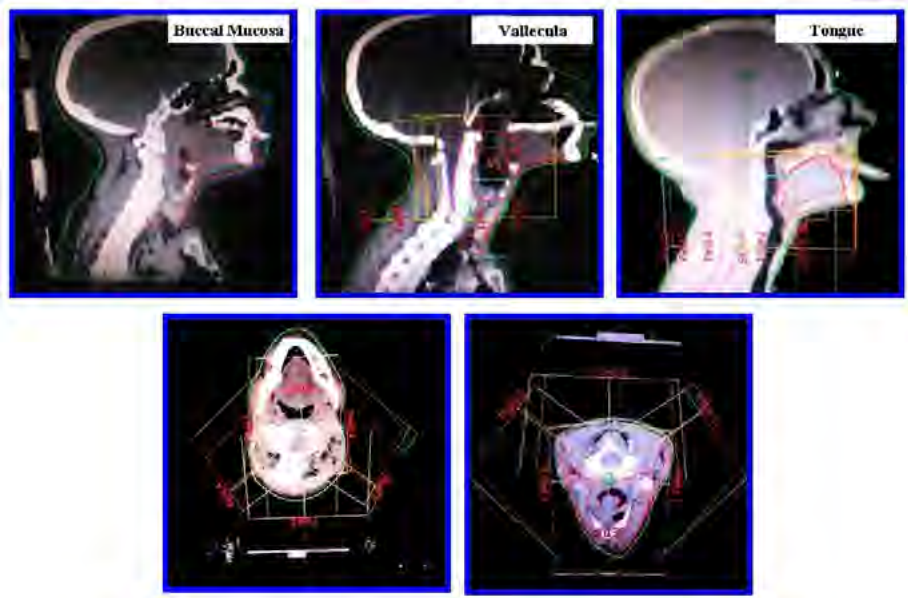

Fig 1b. Film pictures depicting the RT fields planned in various head and neck cancers. (Design: ...)

DES is classified in accordance to the guidelines set by The International Dry Eye Workshop and modified by the Delphi Panel Report in to four groups as mild, moderate, severe, and severe and/or disabling (Table 1). [10-12] Depending on the manifestation, the radiation-induced DES are classified as either early (acute) or late (delayed) effects and is dependent on the dose of radiation incurred. The early effects develop during the course of RT or shortly after completing RT (about 2-3 weeks), while the late effects manifest months to years after completing the therapeutic radiotherapy.[10-12]

When compared to other radiation-induced ill effects, DES is sparsely reported in patients being treated for their head and neck cancers. However reports do indicate that DES increases the morbidity and that this at times can severely affect the patient's quality of life and to increase medical hospitalization and treatment costs.[8] The present study was investigated to assess the incidence of dry eye syndrome during external beam radiotherapy for extra cranial head and neck tumours, and correlate its severity with distance from the epicenter of the field of radiation.

Materials and methods

This was a single-centre; investigator masked prospective study and was conducted from April to June 2013 in the Department of Radiation Oncology at Father Muller Medical College Hospital, Mangalore India. The subjects comprised of histopathologically confirmed adult patients of head and neck cancer scheduled to receive chemoradiotherapy for curative purpose. Patients with recurrence of cancer in the oral cavity were eligible. Exclusion criteria included patients less than 18 years of age; patients who were pregnant, patients who had oral surgery within the previous 6 weeks, received chemotherapy or radiation treatment previously to the head and neck region; patients with co morbid conditions like poorly controlled diabetes mellitus, hypertension, schizophrenia, bipolar disorders, severe depression.

The study also included a second group of patients requiring curative radiotherapy for non head and neck cancers (like for breast, oesophagus, prostate, cervix and rectal cancers) as control group. The study aimed to recruit subjects into two groups giving 80% power to detect an estimated 50% difference between the two groups. It was required to calculate the difference in proportions between two groups for which nMasterTM 1.0 software was used. Each group was calculated and it was observed that a minimum of eight subjects were required to achieve statistical results. The study was approved by the Institutional Ethical Committee. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Patient recruitment:

During the first visit, one of the investigators (DJ/ MRT/MSR) introduced the purpose of the study to eligible patients and their caregivers in English or in their mother tongue (Kannada, Tulu and Malayalam). The subjects were also informed that they had the right to withdraw from the study at any time during the course of the study and that their non-willingness to be a part of the study will not deprive them of the necessary treatment. Written informed consent was collected from all willing patients satisfying the inclusion criteria.

Radiation therapy treatment

All patients who participated in this study received external irradiation from a linear accelerator (Varian) at an average energy level of 6 KV MV using the intensity-modulated radiation therapy (IMRT) technique with suitable field planning as depicted in Figure 1a,b. All planned fields were treated every day with no more than one fraction of 2 Gy per day, five times a week without any intended gaps for a planned target dose of > 60 Gy (six to seven consecutive weeks) for head and neck cancers and 50 to 70 Gy for non head and neck cancers depending on the organ dependent protocols (breast and cervix 50 Gy, rectal, prostate and oesophagus > 60 Gy). Whenever chemo-irradiation was planned, cisplatin infusion was administered on a weekly basis before exposure to the first weekly radiation.

Patient Evaluation

The patients were assessed for the radiation-induced DES by a trained ophthalmologist (SV) unaware of the stage and dose of radiation delivered by the patients. The assessment was undertaken at the beginning (day 0, before the start of radiotherapy) at day 21 (after completion of 30 Gy) and on completion of the treatment. The DES was categorized as mild, moderate, severe, and severe and/or disabling in accordance to the guidelines stipulated by the International Dry Eye Workshop and adopted and modified the Delphi Panel Report, 2007 (Table 2).[10,12] On every investigation, the investigator considered the score for the worst toxicity in the treatment field. Patients who discontinued treatment or succumbed to cancer were not considered for the subsequent evaluation. As only one masked researcher evaluated all patients, calibration of assessors was not required.

Tests performed*:*

The following assays were performed on all the cases and controls before starting of RT, after 3 weeks of RT and at the end of RT completion: 1) Schirmer I (without local anesthesia) , which measures basic secretion of the lacrimal gland, 2) Schirmer II (with local anaesthesia) test, which measures reflex secretion of the lacrimal gland 3) Tear-film break up time (TFBUT) , which measures the time of onset of a random appearance of the first black spots on the cornea after one single palpebral (eyelid blinking) closure under standardized conditions which assess goblet cell function, 4) corneal and conjunctival fluorescein staining and 5) Rose Bengal staining of the ocular surface in accordance to the standard ophthalmological investigations in the department of ophthalmology. The patients were first also interviewed to survey the frequency of occurrence of various dry eye symptoms including dryness, grittiness, redness, excess tearing or watery eyes, sensitivity (to smoke, wind, air conditioning) and soreness. Response categories used for analyses included never, seldom (two to three times per week), often (four to five times per week), and always (everyday).

Statistical Analysis:

The significance of difference of the values between the study groups (control and test) was evaluated by Mann-Whitney U test. To observe for the progression of dry eye syndrome in the test through the treatment period (before RT, in the middle and post RT) was done using the Friedman test and inter time point comparison was done using Wilcoxon signed rank test. The correlation between the degree of dry eye severity with age, gender and distance was done using Pearson's correlation. A value of $p < 0.05$ was considered statistically significant.

Results

The details of age, gender, tumor site and staging, and radiation dose are represented in Table 2. During the study period we could enrol 10 patients requiring radiation treatment to eradicate their cancer in the non head and neck regions like breast, oesophagus, prostate, cervix and rectal cancers, and 22 patients requiring

radiotherapy for head and neck region. The first group served as the control while the second was the test or experimental cohort. In the control group all the ten patients completed the study and were available for evaluation at all the three time points while in the test group two out of the 22 patients discontinued the treatment (Figure 2).

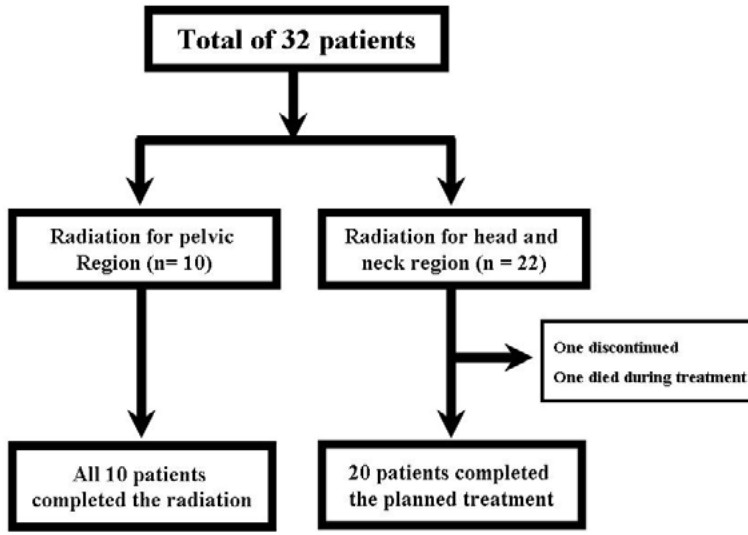

Fig 2. Flow chart of the study population in the two groups

It was observed that before start of radiotherapy majority of the head and neck cancer patients (19 of the 22 patients) did not have any signs of symptoms of DES, while three had level 1 DES (13.64%). After 3 weeks of RT only 2 (9.1%) patients did not show any signs or symptoms of DES whereas 9 (40.9%) showed level1 DES, 9 (40.9%) showed level 2 DES and 2 (9.1%) showed level 3 DES. After completion of radiotherapy i.e., after 6-7 weeks of radiotherapy 2 (10%) patients remained asymptomatic whereas 3(15%) showed level 1 DES, 10 (50%) showed level 2 DES and 5 (25%) developed level 3 DES. Over all 90% of the cases developed DES at the end of the radiotherapy to head and neck region (Figure 3, 4).

The statistical analysis to ascertain the difference of the values between the study groups (control and test) done by Mann-Whitney U test showed no difference at the beginning while a statically significant ($p < 0.001$) difference between the two groups at both Mid and end of RT time point. The Friedman's test used to assess the progression of dry eye severity in the test through the treatment period (before art, in the middle and post RT) showed a significant difference between the pre to mid ($p < 0.001$) and mid to end of RT ($p < 0.005$). The Wilcoxon signed rank test also showed significant difference in all the comparisons ($p < 0.001$ to 0.0001). The Pearson's correlation analysis showed no significant correlation between the degree of dry eye severity with both age and gender; while a negative ($r = -0.262$)

correlation was observed with the distance indicating that lesser the distance from the epicenter of the tumor radiation to the orbital rim more was the dry eye severity.

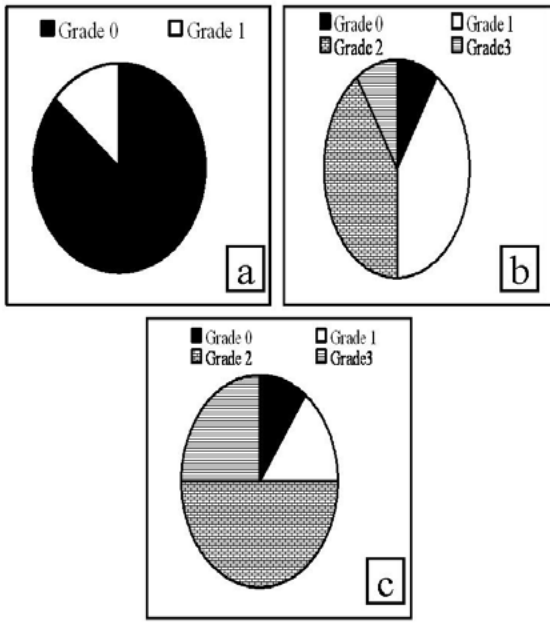

Fig 3. Incidence of different grades of dry eyes syndrome in pre (a), mid (b) and end (c) of the radiation therapy for head and neck cancers.

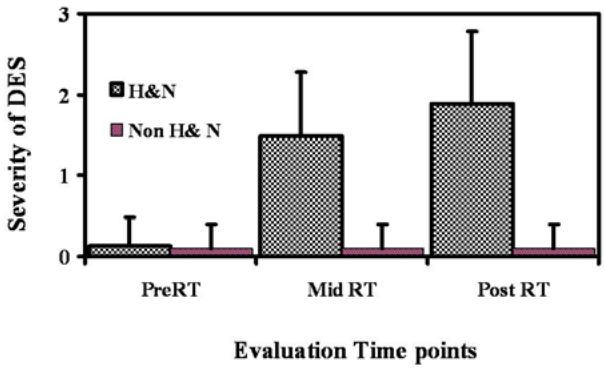

Fig 4. The mean value of the dry eyes syndrome in the pre, mid and post radiation therapy for head and neck.

An analysis stratifying the whole study group based on the distance between the epicenter of the treatment point with orbital margin (< 6.5 cm and > 6.5 cm) with the severity of DES at the end of the treatment showed that there was a statistically significant difference ($p = 0.037$) between the mean values of the two stratified groups (mean of 2.5±0.5 for < 6.5 cm group *vs* 1.56±0.86 for > 6.5 cm group Figure 5).

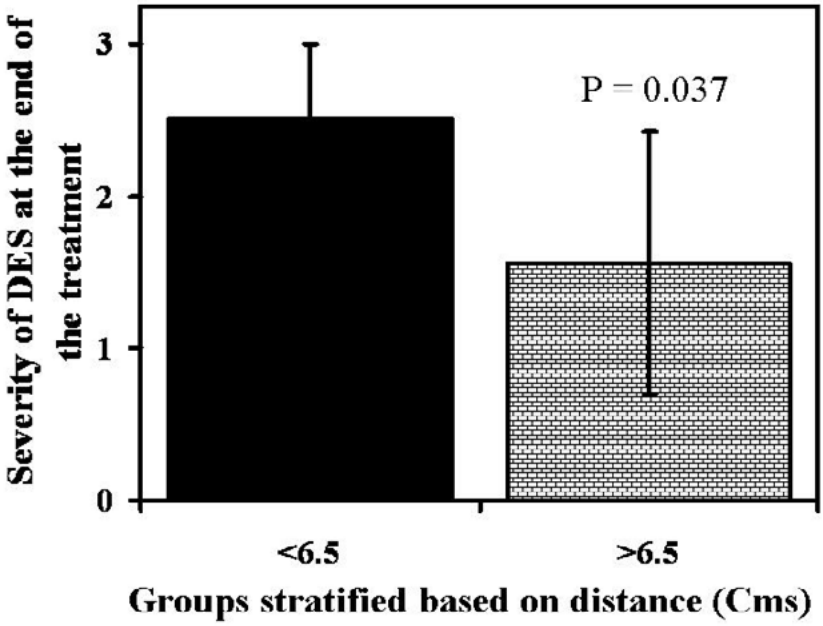

Fig 5. Difference in the degree of DES between the groups where the distance between the epicenter of the treatment point with orbital margin was less than 6.5 cm (solid) and more than 6.5 cm (bricks) at the end of the treatment

Discussion

Xerophthalmia or dry eye syndrome (DES) is an important side effect of therapeutic radiation to head and neck cancer and compromises the quality of life of the patient. However when compared to the other side effects seen in curative radiotherapy for Head and Neck Cancers there are limited data on DES especially during the course of the treatment. Exposure to ionising radiation affects proliferative cells and thereby impairs the optimal functioning of the lacrimal gland. This consequentially initiates the acute and long-term ophthalmic consequences for the patient. Besides the discomfort, the dryness of the eye may cause severe visual impairment due to the resulting corneal damage.[10,12]

In this study it was observed that all evaluable patients receiving radiation treatment for head and neck cancers developed DES over the course of the treatment and that the severity was proportionate to the exposure dose and inversely with the distance between the orbital margin and field of radiation. According to the authors this is the first study that has evaluated the DES during the course of the treatment. Previous reports on radiation-induced xerophthalmia have all been as a late effect of radiation[4,7,13]. These reports also indicate that exposure to 30–45 Gy of radiation causes the appearance of DES in 4–11 years, while those above 57 Gy causes the appearance of corneal vascularization and opacification usually within

9–10 months post completion of the stipulated therapy.[4,7,13]

The tear film consists of three layers: a superficial lipid layer, derived from meibomian and Zeis gland secretions, which helps retard evaporation; a middle aqueous layer, produced by the major and accessory lacrimal glands: and a deep mucinous layer secreted by goblet cells, which serves to wet the relatively hydrophobic cornea and conjunctival epithelium.[2,3] Deficiency of any of the three components may result in loss of tear-film stability.[2,3] Changes in quality and quantity of tear production lead to impairment of the dynamic stability of the tear film resulting in chronic dry eye and in turn damaging the conjunctival and cornea1 epithelium.[2,3] Of all the tests performed, it was also observed that the Schirmer test was more affected than other staining tests indicating that the lacrimal gland are affected the most during these interventions.

Conclusion

The present study for the first time has made an attempt to assess the incidence of DES during the course of curative radiotherapy for head and neck cancers. The results suggest that DES was observed in all the patients available for the estimation at all three time points. It was clearly observed that the incidence and severity of DES was inversely proportional to the distance, indicating that lesser the distance from the center of the tumor radiation to the orbital rim, more was the dry eye severity. It is also suggestive that adequate shielding the anterior structures including cornea, conjunctiva and lacrimal gland should be followed to minimize DES. Future studies are planned to understand the role of lacrimal shield in reducing the adverse effects.

Acknowledgements:

The authors would like to express thanks to all participants of this study for their kind cooperation. They are also grateful to Dr MS Vidyasagar Former Head of Radiation Oncology, Father Muller Medical College for his support.

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Table 1: Dry Eye Severity Grading Scheme according to DEWS 2007

Dry Eye Severity scale	Level 1	Level 2	Level 3	Level 4#
Discomfort, severity and frequency	Mild and/ or episodic; occurs under environmental stress	Moderate eoisodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/ or activity limiting, episodic	Annoying, chronic and/ or constant, limiting activity	Constant and/ or possibly disabling
Conjunctival congestion	None to mild	None to mild	+/-	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining(severity/ location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/ tear sign	None to mild	Mild debris, reduced meniscus height	Filamentary keratitis, mucus clumping, increased tear debris	Filamentary keratitis, mucus clumping, increased tear debris, ulceration
Lid/ meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT(Second)	Variable	≤10	≤5	Immediate
Schirmer test(mm/5min)	Variable	≤10	≤5	≤2

TFBUT = Fluorescein Tear break-up time; MGD = Meibomian gland disease
 # Must have signs AND symptoms

Table 2: Patient and tumor characteristics

Age	50.3±8.57
Gender	
Male	18
Female	4
Site	
Buccal mucosa	6
Floor of the Mouth	1
Gingivo buccal sulcus	1
Lip	1
Pharynx (Oro and Hypo)	4
Retromolar trigone	1
Supraglottis	1
Tongue	6
Vallecula	1
TNM stage **Primary**	
T1	0
T2	16
T3	4
T4	1
TX	1

Regional nodes	
N0	6
N1	5
N2	1
N2a	1
N2b	8
N2c	1
Metastasis	
M0	22
MX	0
Treatment details	
Radiation only	3
Chemoirradiation	19
Dose of radiation	68.2±1.98

Asian J Ophthalmol. 2016;14:166-184

Long term outcome of 5-Fluorouracil (5-FU) augmented bleb needling revision of failed and failing filtration blebs

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Abstract

Purpose: *To evaluate the long term outcome of 5-Fluorouracil (5-FU) augmented bleb needling revision of failed and failing filtration blebs based on survival analysis and to identify risk factors for failure, indicators for success and complications.*

Methods: *This was a prospective, interventional case series with survival analysis. 32 eyes of 32 patients underwent bleb needling augmented with 5-FU and were then followed up. Statistical analysis was done to assess the association between study factors and time to failure. Main outcome measures were reduction in IOP (<21 mm of Hg), number of antiglaucoma medications (AGM's), complications and factors associated with outcome including indicators for success.*

Results: *At one year followup 9 (28. 13%) eyes had IOP <21 mmHg without the use of any antiglaucoma medications. 13 eyes (40. 63%) had qualified success with mean IOP <21 mm Hg after 1 or multiple needlings but with the help of one or more AGM's (1. 2±0. 4). 10 cases (31. 25%) failed and had to undergo repeat Trabeculectomy or shunt surgery. In the cases which achieved overall success, complete and qualified together (n = 22) the baseline IOP pre needling was 26. 7±8. 2 mmHg which was reduced to 13. 6±4. 6 mmHg at the end of the minimum follow up period of 1 year. The median interval between the "index" filtration surgery and the first (or only) needling procedure was 7. 5 months (Range 3 months to 4 years). Overall reduction in mean number of topical AGM's was from 2. 68±0. 82 to 0. 82±0. 34. Overall cross sectional success rate at 1 year follow up (complete and qualified) was 68. 76%(n=32) and the overall cross-sectional success rate (complete and qualified) at the 3 year follow up period was 66. 91%(n=24) and 65. 82%(n=16) at 5 year follow up. Strong evidence was found for association between pre needling IOP >28 mm of Hg and failure and immediate attainment of low IOP <11 mmHg and longer survival. None of the other proposed factors were identified as having statistically significant effect.*

Conclusions: *This long term study shows that bleb needling augmented with 5-FU is a safe and effective method by which a significant number of failed or failing filtration blebs can be rescued. Attaining an immediate reduction in IOP <11 mmHg seems to be a favorable factor with respect to reasonably long-term efficacy.*

Keywords: *5 Fluorouracil, Antiglaucoma medication, Bleb Needling, Failed bleb, Trabeculectomy.*

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Introduction

Trabeculectomy is presently the surgical treatment of choice for many patients with glaucoma, and, overall, the success rate of the procedure is reasonably high.[1,2] The introduction of intraoperative and postoperative antimetabolite application for the manipulation of wound healing have greatly enhanced the success rates of surgery.[3,4] However, a proportion of the procedures fail, both in the early postoperative period and, in a smaller proportion of patients, after a number of years. In a 20 year follow up study on trabeculectomy done by Landers *et al.* the authors noted that 13% of the eyes failed to achieve complete success during the first year (6% in the first 2 months and 7% in the subsequent 10 months). Thereafter, 1. 6% of eyes failed to achieve the criteria of complete success per year for the next 19 years.[5] If qualified success was taken as the criteria of success then the authors noted that seven percent of eyes failed the definition of qualified success during the first 5 years, with 0. 3% of eyes failing per year for the next 15 years thereafter. The failure rate of trabeculectomy with 5-fluorouracil in the Fluorouracil Filtering Surgery Study (FFSS) was 16% at 1 year, 29% at 3 years, and 51% at 5 years.[6] In the Tube versus Trabeculectomy study, which was designed to evaluate the safety and efficacy of Baerveldt-350 tube shunt implant compared to trabeculectomy with MMC in eyes with prior cataract or trabeculectomy surgery, the failure rates in the trabeculectomy group were 13. 5% at 1 year, 28. 2% at 2 years, 30. 7% at 3 years and 46. 9% at 5 years.[7] Failure is usually the result of scarring in the subconjunctival space with resultant intrableb fibrosis and the development of a failed bleb, instead of a functioning, filtering bleb.[8,9,10,11]

In addition to the use of antimetabolites, there have also been developments in the manipulation of flow resistance after surgery. Traditionally, the triangular or rectangular flap was closed with fixed sutures, which allowed no postoperative manipulation apart from massage.[12] Subsequently, laser suturelysis came into being and a single or multiple sutures could be cut to manipulate the flow.[13,14] This was followed by the development of releasable sutures, which when removed at the slit lamp could alter the outflow facility and, most recently, the development of adjustable sutures where the tension can be altered by suture loosening with a specially designed pair of forceps has come into being.[15,16,17]

Many approaches for managing dysfunctional filtration blebs have been proposed.[18] Several reports have advocated needling revision with adjunctive 5-Fluorouracil (5-FU) or Mitomycin-C (MMC) as an effective and relatively simple method of re-establishing filtration in eyes with failed filtering blebs.[18,19,20,21,22,23] Some studies however indicate that successful outcome may require multiple needling revisions.[23,24,25,26] We wanted to study the outcome of postoperative needle revision of failing or failed trabeculectomy blebs performed with the use of adjunctive 5-fluorouracil (5-FU) to inhibit postneedling fibrosis in a south Indian population and evaluate the results based on survival analysis.

Purpose

The aim of this study was to evaluate the long term outcome of 5-Fluorouracil (5-FU) augmented bleb needling revision of failed and failing filtration blebs based on survival analysis and to identify risk factors for failure, indicators for success and complications.

Materials and Methods

This was a prospective, noncomparative, interventional case series. The study population included patients who satisfied the inclusion criteria, had undergone a Trabeculectomy and then subsequently presented for follow up at the Glaucoma clinic.

Thirty two eyes of 32 patients were included and analyzed. At the time of entry into the study, a past ophthalmic history was obtained, with all previous surgery, laser and topical therapy being documented. Visual acuity was recorded using the Snellen's chart. The failed blebs were assessed and the bleb characteristics noted. In addition, it was documented whether part of the bleb or surrounding conjunctiva was injected and whether conjunctival microcysts were evident. A routine anterior segment examination was performed at the slit lamp. Applanation tonometry was performed and the intraocular pressure (IOP) recorded.

After failure of a releasable suture (if a releaseable suture had been placed) or suture lysis (if non releaseable sutures had been placed), bleb massage, or a combination thereof, any patient with a failed or failing trabeculectomy bleb was included in the study. Gonioscopy was performed to confirm that the internal ostium of the trabeculectomy was patent. The posterior pole of the eye was examined at the slit lamp using a 90-diopter lens.

The target IOP set for each patient was based on the severity as well as the history of progression of glaucomatous optic nerve damage. If the IOP did not reach its goal and the filtration bleb showed signs of failure, such as a flat bleb inspite of suturelysis and bleb massage and a highly vascular bleb inspite of a patent internal ostium on gonioscopy, then a decision for needling revision was taken. After approval of the ethics committee the needling procedure was performed. Only patients unwilling to give consent for the procedure were excluded.

Bleb Needle Revision Technique

After obtaining informed consent an antibiotic (Ofloxacin 2%) was instilled in the eye. A drop of povidone-iodine was used before the procedure and anaesthesia was obtained by a topical anaesthetic (Proparacaine 0. 5%). A sterile lid speculum was inserted for separation of the eyelids. Using sterile technique and viewing the infraducted eye with an operating microscope, the subconjunctival space was entered with a with a 26-gauge needle, with an attached syringe containing Xylocaine 1%, 0.1 ml, at approximately 10 to 12mm distal to the site of the failed filtration bleb. The Xylocaine was delivered and the subconjunctival drug spread out with a cotton tip applicator. A 30-gauge needle attached to an insulin syringe was used for needling. The needle was introduced subconjunctivally about 10 mm away from

the bleb or 5 to 6 mm temporal to the site of the scleral flap in the supero-temporal quadrant. The needle was then advanced subconjunctivally toward the failed filtration bleb site, then over the trabeculectomy scleral flap, repeatedly if necessary, until local elevation of the conjunctiva due to egress of the aqueous humor was observed. Using a sweeping motion, the cutting edges of the needle tip were used to disrupt any episcleral fibrosis. If local elevation of the conjunctiva did not occur, the needle tip was deliberately introduced underneath the scleral flap and, if still not successful, into the anterior chamber underneath or through the scleral flap in an attempt to reestablish the fistula. Another 30 gauge needle attached to a 1cc syringe containing 0. 2 ml of 5 Fluorouracil (25 mg/ml) was taken. The needle was pushed through the subconjunctival space in a zigzag manner to reduce the risk of subsequent antimetabolite leakage. The needle tip of this syringe was placed as distally as possible from the reestablished filtration fistula and the puncture site, and the 5-FU solution was injected subconjunctivally, with the bevel of the needle directed away from the reestablished filtration fistula. Care was taken throughout the procedure not to buttonhole the conjunctiva. (Figs: 1–6)

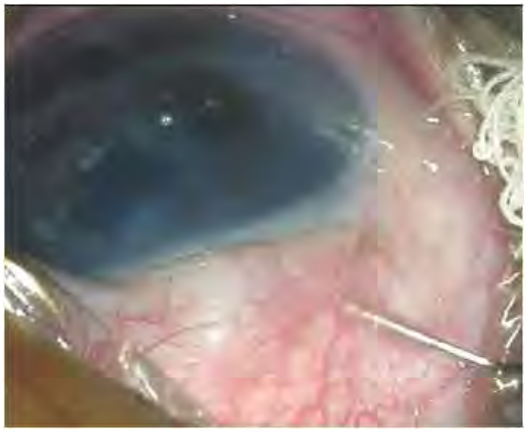


Fig 1: A 30 G needle attached to a syringe being used to dusrupt the episcleral fibrosis.

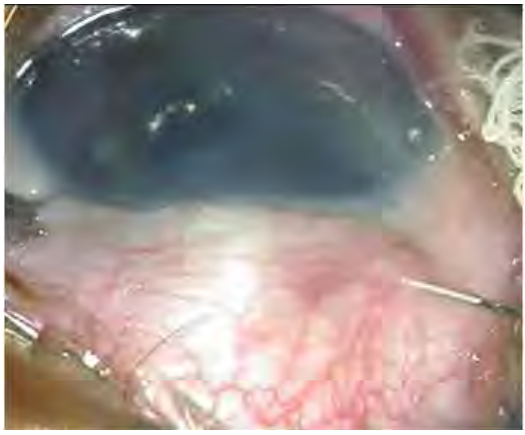


Fig 2: A sweeping motion being used and the cutting edges of the needle tip being utilized to disrupt the fibrotic tissue.

Because of the oblique nature of needle entry, no suturing of the conjunctiva was required. Only a brief tamponade with a cotton applicator soaked with topical anaesthetic solution was required to close the conjunctival puncture wound. After additional antibiotic drops, antibiotic-corticosteroid and atropine 1%eye drops were instilled. The eye was examined approximately 1 hour later with a slit-lamp. The patient was then discharged with antibiotic-corticosteroid eye drops and Homatropine eye drops to be gradually tapered as the ocular inflammation subsided.

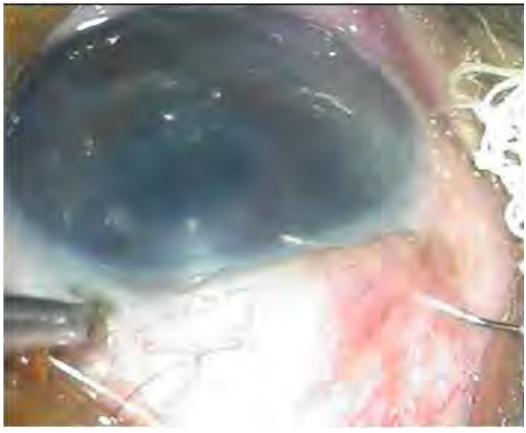


Fig 3: If local elevation of the conjunctiva was not achieved even after disrupting fibrosis underneath the scleral flap then the needle is advanced into the anterior chamber underneath the flap in an attempt to reestablish the fistula

The patients were seen routinely at 1, 2, 4, 8 and 16 weeks, with subsequent follow-up visits at 3 monthly intervals. The dosage of topical antibiotic-steroid was tapered as clinically indicated. Depending on the IOP control achieved as well as the appearance of the filtration bleb further steps were taken. The successful cases showed varying degrees of improvement of the appearance of their blebs. If signs of failure appeared in the bleb or if the IOP rose, digital massage or focal pressure was applied to the globe. On the basis of bleb morphologic features and IOP the examining ophthalmologist decided whether an additional subconjunctival 5-FU injection was clinically indicated.

At each postneedling clinic visit, visual acuity was recorded using the Snellens's chart and the needled bleb was reassessed and categorized. A routine anterior segment examination was performed at the slit lamp, IOP was recorded, and the posterior pole of the eye was examined using a 90-D lens. All complications considered to be a direct consequence of the needling procedure were recorded. If additional needling of the bleb was considered necessary, the procedure was carried out in the same manner as the initial procedure. The decision regarding whether to proceed with a subsequent bleb needling was based on the response to the previous procedure, together with the morphologic features of the bleb, gonioscopy findings and intraocular pressure.

When recommencing medical therapy, patients were initially prescribed a topical β-blocker (unless contraindicated). If β-blocker therapy was contraindicated or ineffective, therapy was switched to a prostaglandin analog. If β-blocker therapy

was effective, but inadequately so, a combination therapy of β blocker and Dorzolamide was started. Subsequent changes in therapy were based on clinical need.

Success was defined on the basis of IOP and morphological features of the bleb. For a procedure to be considered successful, the IOP had to be reduced to <21 mmHg with no antiglaucoma therapy, or less therapy than had been used before the needling. In the cases where the preneedling IOP (on antiglaucoma therapy) was <21 mmHg, success was defined as an IOP <21 mmHg with less or no antiglaucoma therapy. Complete success was defined as IOP > 5 and <21 mm of Hg without the use of antiglaucoma medications. Qualified success was defined as IOP <21 mmHg with the use of anti glaucoma medication and failure was defined as IOP> 21 mmHg even with the use of medication.

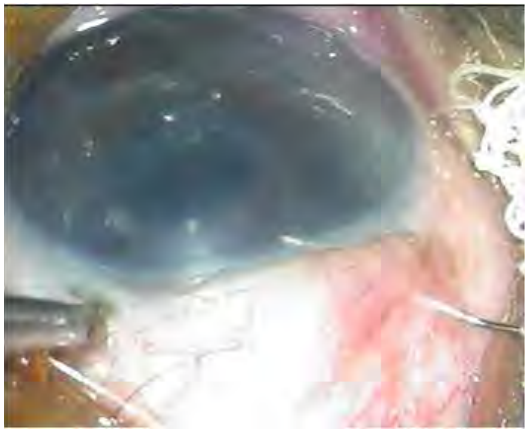


Fig 4: This figure clearly shows the needle inside the anterior chamber after dispruption of the fibrosis of the flap.

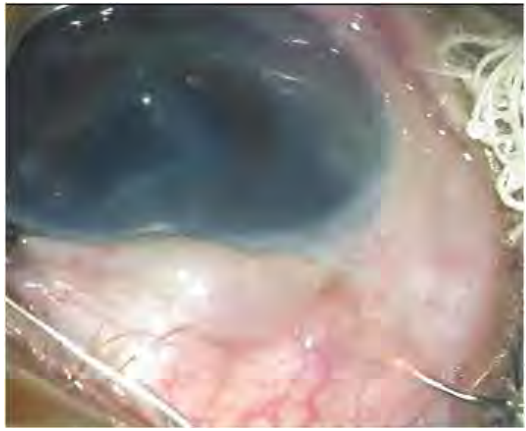


Fig 5: Figure showing clearly the elevation of the bleb after the withdrawal of the needle from the anterior chamber.

Potential risk factors for failure considered were age, gender, laterality, glaucoma diagnosis, previous topical therapy, previous exposure to antifibrotic agent, the interval between the index operation and the bleb needling procedure, preneedling IOP, immediate postneedling IOP, and number of needling procedures performed.

The data were duty noted into the case sheets and then collected and analysed.

Kaplan–Meier plots were constructed to estimate the probability of IOP "survival" over time after treatment with respect to the arbitrarily set level of 21 mmHg. For the purpose of the Kaplan– Meier plots, failure of treatment was defined to have occurred if IOP was more than 21 mmHg on 2 successive visits, having initially been at or below these levels on 2 successive visits after the most recently performed bleb needling procedure. The IOP after needle revision was compared with the preneedle revision IOP using the paired Student's *t* test. The Wilcoxon signed-rank test was used to compare the use of ocular hypotensive agents before and after needle revision and the Fisher's exact test was used to show the outcome in relation to type of bleb. Cox proportional hazards regression analysis was used to assess the association between each study factor and the time to IOP failure. Statistical analyses were performed using an established software package (SPSS v9. 0. 0; SPSS Inc., Chicago, IL).

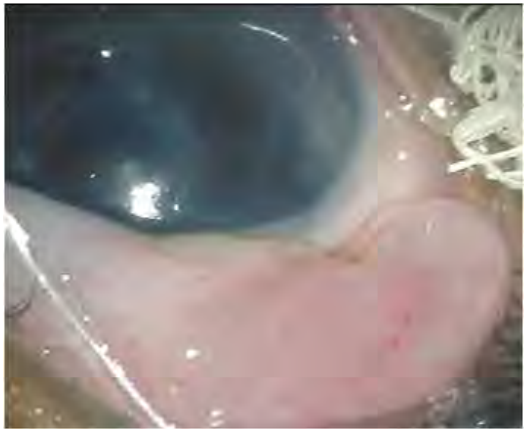


Fig 6: 5 FU being injected subconjunctivally with the needle tip being placed as distally as possible from the reestablished filtration fistula and the puncture site.

Results

Thirty two eyes of 32 patients underwent the postoperative bleb needle revision with adjunctive 5-FU. Patient demography is shown in Table 1. The mean age ± standard deviation (SD) of the patients was 67. 2±11. 4 years (Range 38–89 years). The blebs undergoing rescue related to 32 trabeculectomies of which 8 were repeat procedures. The trabeculectomy after which the needling procedure was done will henceforth be referred to as the index procedure. Thirty of these index procedures had been augmented with adjunctive antifibrotic therapy. In 6 cases (18. 75%) MMC 0. 02%had been used for 2 minutes while in the rest 24 cases (75%) MMC 0. 04% had been used for 2 minutes. In 2 cases (6. 25%) no antifibrotic agents had been used during the index procedure. Some of the cases had high risk characteristics for bleb failure. 8 cases (25%) were repeat trabeculectomies, 1 case (3. 1%) was a case of uveitic glaucoma, 1 case (3. 1%) was a patient with age <40 years and 2 cases (6. 25%) had multiple risk factors.

Management before the index procedure varied between eyes as expected and is summarized in Table 1. After the index procedure, 26 eyes had been restarted on topical antiglaucoma therapy, and 12 were still receiving some postoperative topical steroid therapy.

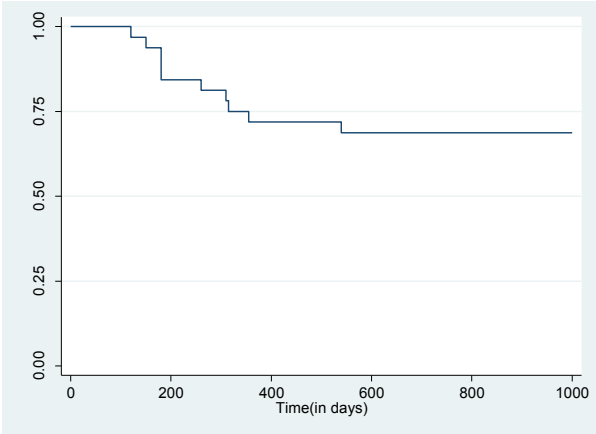
Table 1: Patient demographics and details of Glaucoma variables

	n (%)	Mean	SD
Gender **Male** **Female**			
	17 (53. 125)		
	15(46. 875)		
Age (Years)		67. 2	11. 4
Eyes **Right** **Left**			
	18(56. 25)		
	14(43. 75)		
Diagnosis **POAG** **PACG** **PXF Glaucoma** **Pseudophakic Glaucoma** **Uveitic Glaucoma**			
	14 (43. 75)		
	13 (40. 63)		
	2 (6. 25)		
	2 (6. 25)		
	1 (3. 13)		
Pre operative MD (29/32)		-15. 3	8. 1
Pre operative PSD (29/32)		8. 6	3. 4
Pre needling IOP		28. 2	7. 6
Filtering procedure **First Trabeculectomy** **Repeat Trabeculectomy**			
	24(75)		

	n (%)	Mean	SD
	8(25)		
Previous therapy **Topical** **SLT** **Laser PI** **Iridoplasty**			
	26(81. 25)		
	2 (6. 25)		
	13(40. 63)		
	1 (3. 13)		

The median duration of topical steroid therapy for the 28 eyes after the index procedure and before bleb needling was 3 months (range, 3 month–6 months). The duration of topical antiglaucoma therapy for the 26 treated eyes after the index operation and before bleb needling was 4. 6±1. 2 months. The median interval between the index filtration surgery and the first (or only) needling procedure was 7. 5 months with a range of 3 months to 4 years.

Twenty-one eyes (65. 63%) underwent only a single 5-FU needling revision; 9 eyes (28. 13%) required two revisions and 2 eyes (6. 25%) underwent three revisions with an overall mean of 1. 41 needling revisions with adjunctive 5-FU. At the minimum follow up period of 1 year complete success was noted in 9 cases (28. 13%) and qualified success was seen in 13 cases (40. 63%) thus the total overall success was achieved in 22 cases (68. 75%). In 10 cases (31. 25%) either the IOP was not controlled even with medications or the patient had to undergo a repeat filtering procedure and thus they were considered as failure. The Kaplan–Meier survival analysis success rates were 68. 76% at 1 year and 66. 91% after 3 years of follow-up (Graph 1).



Graph 1: Kaplan Meier Analysis showing the survival rate.

The statistical analysis comparing the number of needling procedures and comparing it to the success rates showed that the cases which underwent a single needling procedure (n=21) had the highest percentage of success with complete success being noted in 8 cases (38. 1%) and qualified success in 9 cases (28. 1%). In cases which underwent 3needling procedures (n=2) none of the cases achieved complete success while qualified success was seen in one case (50%). (Table 2)

Table 2: Table showing the number of needling procedures compared to success rates

Number of needlings	Complete Success	Qualified success	Failiure
1 (n =21)	8	9	4
2 (n = 9)	1	3	5
3 (n = 2)	0	1	1

In 11 cases an IOP of <11 mmHg was achieved immediately post needling. This group noted the highest percentage of success with complete success being seen in 7 cases (63. 64%) and qualified success in 4cases (36. 36%). There were no cases which showed failure in the group which achieved an immediate post needling IOP of <11 mmHg. In the group which achieved an immediate post needling IOP between 14 and 16 mmHg (n = 9) there was a high percentage of failure noted (7 cases, 77. 78%). A low immediate post needling IOP (<11 mm Hg) was associated with a higher success rate (P< 0. 001). (Table 3)

Table 3: Table showing the number of cases with pre needling IOP > 28 mm Hg and those with immediate IOP <11 mm of Hg and the percentage of success and failure in each group.

IOP	n (number)	Complete success (n/%)	Qualified success (n/%)	Failiure (n/%)	P value
Pre needling IOP Pre needling IOP > 28 Pre needling IOP < 28	 14 18	 1 8	 6 7	 7 3	<0. 001
IOP immediate post needling <11 mm Hg 11 – 13 14 - 16	 11 12 9	 7 1 1	 4 8 1	 0 3 7	<0. 001

For all 32 eyes, the overall mean±SD pre-needling IOP was 27. 7±7. 5 mmHg, with a range of 18 to 48mmHg. In the cases which achieved overall success, complete and qualified together (n = 22) the baseline IOP pre needling was 26. 7±8. 2 mmHg which was reduced to 13. 6±4. 6 mmHg at the end of the minimum follow up period of 1 year. When these cases were further followed up this IOP was 13. 4±4. 3 mmHg (n=24) at the end of a follow up of three years and 13. 6±4. 7 mm Hg (n=16) at the end of five years of follow up.

A pre needling IOP of <28 mmHg (n=18) was associated with a higher success rate with complete success seen in 8 cases (44. 44%) and qualified success in 7 cases (38. 89%) whereas cases which had a pre needling IOP of >28mmHg (n = 14) achieved complete success in 1 case (7. 14%) and qualified success in 6 cases (42. 86%)(P<0. 001)(Table 3)

The mean age ±SD of those patients in whom bleb needling was successful was 65. 34±8. 21years (range, 38– 87 years), whereas for the failures the mean age ±SD was 68. 22±7. 44 years (range, 42–89 years)(P=0. 36). As a continuous variable, younger age was not identified as a significant risk factor for failure. There was no significant difference with respect to gender or laterality. (Table 4)

Table 4: Hazard Ratios for Failure of Bleb Needling relating to potential risk factors for failure

Study Factor	Category	Hazard ratio	95% CI
Gender	Male	1	(0. 53 , 1. 56)
	Female	0. 9	
Eye	Right	0. 94	(0. 74, 2. 78)
	Left	1	
Diagnosis	POAG	1	(0. 46, 1. 64)
	Non-POAG	1. 54	
Previous exposure to antimetabolites	Yes	1	(0. 81 , 2. 44)
	No	1. 44	
Pre needling IOP	>28 mm Hg	1. 65	(0. 60 , 2. 71)
	<28 mm Hg	1	
Previous filtering procedures	Single index procedure	1	(0. 44 , 1. 48)
	Repeat Trabeculectomy	1. 36	
Immediate post needling IOP	<11 mm Hg	0. 5	(0. 26 , 0. 92)
	>11 mm Hg	1	

The success rate was greater for eyes with primary open-angle glaucoma (POAG) compared with eyes with other diagnoses, however it did not reach statistical significance (p=0. 173). (Table 5)

Previous exposure to MMC, 0.04% for 2minutes, n=24, during the index procedure was associated with a higher success rate post needling (20/24 cases, 83. 33%)

compared to an MMC concentration of 0. 02% for 2 minutes, n=6 (2/6 cases, 33. 33%) and this was statistically significant (p=0. 005)(Table 5)

Table 5: Showing the diagnosis and the concentration of MMC in relation to success and failure

Parameter	Number (n)	Complete success	Qualified success	Failiure	P value
Diagnosis					
POAG	14	8	4	2	0. 173
PACG	13	1	7	5	
PXF Glaucoma	2	0	1	1	
Psedophakic Glaucoma	2	0	1	1	
Uveitic Glaucoma	1	0	0	1	
Conc of MMC					
0. 04%	24	8	12	4	0. 005
0. 02%	6	1	1	4	
Nil	2	0	0	2	

The use of topical antiglaucoma therapy, or topical steroid, immediately before the needling procedure had no apparent effect on the outcome, and there was little difference between the types of antiglaucoma agent being administered at the time of needling, although exposure to pilocarpine had occurred in more of the failures (14%) compared with successes (8%) and vice versa with topical carbonic anhydrase inhibitors (6% vs. 16%).

The interval between the index operation and bleb needling had no significant effect on the outcome but the mean cumulative duration of antiglaucoma therapy administered between the index procedure and bleb needling was more for the failed cases (3. 2 ±1. 1 months) in comparison with successes (2. 8±0. 8 months), but not to a degree to reach statistical significance (P=0. 23)

The blebs which were characterized as being flat (n =8) at the time of the needling procedure had the highest failure rate at 62. 5%. Blebs which were characterized as encapsulated (n=6) and those which were fibrotic and cystic in part (n=6) had a much lower failure rate at 16. 67% each (Table 6).

Table 6: Outcome in relation to the type of bleb

		Complete success	Qualified success	Failure	P value
Flat blebs	8	2(25%)	1(12. 5%)	5(62. 5%)	0. 363
Low diffuse blebs with high vascularity	7	1(14. 26%)	4(57. 14%)	2(28. 57%)	
Cystic+Fibrotic	6	2(33. 33%)	3(50%)	1(16. 67%)	
Cystic+Thick Conjunctiva Tenons complex	5	1(20%)	3(60%)	1(20%)	
Encapsulated	6	3(50%)	2(33. 33%)	1(16. 67%)	

No serious complications were encountered with the procedure. However, transient complications were encountered in 5 eyes. Two eyes had corneal epithelial defects post procedure (6. 25%), 2 eyes (6. 25%) had hyphaema and one eye (3. 13%) had bleb leak post needling. None of the complications that occurred in eyes that had an unsuccessful needling procedure were considered to have been directly causative of the failure and all the cases were managed conservatively. In most cases, there was no significant change in visual acuity after bleb needling. Visual acuity decreased by 2 or more Snellen lines in 4 patients, but increased by 2 or more lines in 3 patients.

Discussion

Failure of filtration surgery may be managed in a number of ways, but if a revision or repeat surgical treatment is chosen, the clinician has to accept a technically more difficult procedure with an increased risk of failure.

Since 1941, many authors have described bleb-needling procedures and although a variety of methods have been described, the principle remains the same, which is to disrupt subconjunctival and scleral scar tissue and to restore bleb function.[20,21,22,23]

Needles used have ranged from 25 gauge, 28 gauge or Saunder's needle to 30gauge. Other, more complicated, methods described have involved the use of a 30-gauge needle with a small needle knife or a Zeigler knife with Vannas scissors.[21,23,24,25,26] The latter method required conjunctival suturing, but probably allowed more extensive disruption of the fibrous tissue. Some authors have advocated the additional use of subconjunctival 5-FU or MMC.[23,24,25,27]

Reported success rates for bleb needling procedures have been variable. Cohen *et al.* reported success (IOP< 22 mmHg) in 9 of 15 cases (60%) with or without additional therapy (complete and qualified success) at 1 year follow up.[20] A slightly

higher success rate, using similar criteria (9/13; 69%), was reported by Pederson and Smith, with 3 patients requiring 2 needlings. However, of their 13 cases, only 3 (23%) achieved complete success (IOP<22 mmHg, no antiglaucoma therapy, and no bleb dysesthesia).[22] Ewing and Stamper reported success in 11 of 12 patients (91. 6%; complete in 58. 3% and qualified success in 33. 3%), 7 of whom had undergone multiple post needling inferior subconjunctival 5-FU injections.[23] The authors had a clinical impression that the use of 5-FU was advantageous, but some of the patients had a follow-up of only 2 months. The range of follow up in the study by Ewing and Stamper was from 2 months to 31 months with a mean follow up of 9 months. Gilles and Brooks reported success in 12 of 16 patients (75%), who were administered additional 5-FU injections with follow up ranging between 9 and 15 months, but their criteria for success were not specified.[24] Hodge *et al.* reported success (IOP <21 mmHg) in 16 of 17 patients (94%; complete in 47% and qualified in 47%) using a technique involving an intrableb injection of 5-FU at 1 year follow up.[25] In their series, 12 patients underwent between 2 and 4 needling procedures each. Of the 5 patients in whom a single procedure was performed, complete success was achieved in only 2 patients.

In a study done by Shin *et al.* 24 of 30 procedures (80%) augmented with intrableb 5-FU were reported as complete or qualified successes (the latter patients being on less medication than before the needling) after a mean number of 2. 6 needlings at 1 year of follow up.[26] In the study by Shin *et al.* the success rate for a single needling procedure was considerably lower (9/30; 30%) and the authors emphasized the importance of considering bleb rescue as a potential course of needlings, rather than a one-off procedure. Allen *et al.* reported a 100% success rate in achieving an IOP <22 mmHg after a mean number of 2 needlings of encapsulated blebs after a mean interval ±SD between surgery and needling of 9. 7 ±26. 9 weeks and a follow-up period of 10. 7± 2. 9 months.[28]

In our study, however, we noted that the results were better in the group which underwent a single needling procedure. Our results are similar to those of Greenfield *et al.* who reported that success was more likely after 1 needling procedure rather than multiple procedures. They reported a successful outcome in 46 (73%) of 63 eyes at a minimum follow-up of 3 months after needling revisions of failing filtration blebs following trabeculectomy with MMC.

Our overall cross sectional success rate (complete and qualified) was 68. 76%(n=32) at 1 year, 66. 91%(n=24) at 3 year and 65. 82%(n=16) at 5 year follow up. The success rates of previous studies have been variable and range from 52% to 95%.[22, 23, 24, 25,26,27,28,29] Our results are comparable to a lot of the mentioned studies and the percentage of success over a long term follow up shows that single or multiple needlings can be used to save a lot of failed or failing blebs.

One of the reasons for the results being so variable could be that the various studies have taken different types of blebs for manipulation and thus since the types of blebs needled are different the results vary greatly between the studies. The study done by Allen *et al.* included only those blebs with Tenon's capsule cysts and not those with other morphologic appearances.[28] Another reason could be that

even though studies show that 5-FU needling revision is an effective and safe way of restoring patency to previously fibrosed passageways of aqueous flow within failed or failing filtration blebs, it may need to be repeated more than once and it may not be successful in some patients even with repeated needling revisions.[26] Thus some patients may not respond even to multiple needling procedures because there may be other factors responsible for failure and unless those are addressed the needling will not be successful. Therefore, it is important to identify the risk factors for failure of the initial trabeculectomy and the subsequent 5-FU needling revision procedure.

The comparison of success rates between studies are not always meaningful, considering the fact that the techniques used for needling are different, the bleb morphologies are different and the studies are being done in different ethnic groups. Since the different techniques applied in the various studies poses a problem when it comes to comparison between studies, we used a standard technique in our study but it may not be comparable to a few studies who have used slightly different techniques.

As mentioned previously the morphology of the blebs undergoing needling are different in different studies and thus since the types of blebs needled are different the results vary greatly between the studies. Most previous studies have related to Tenon's cysts or encapsulated blebs alone.[22,25] In the study by Gilles *et al,* half of the needled blebs were encapsulated.[24] Very few studies have considered other specific types of blebs. The studies by Ewing *et al.* and Shin *et al.* considered nonencapsulated failed blebs and the study by Cohen at al included blebs which were flat, small, or thick-walled.[20,23,26]

In our study we included various types of blebs like flat blebs, low diffuse blebs with high vascularity, small cystic blebs with fibrotic regions, encapsulated blebs and partly cystic blebs with thick conjunctiva-tenons complex. It has generally been accepted that encapsulated blebs respond to needling better than flat, scarred blebs. High success rates for surgical revision of encapsulated blebs have been reported, but it has been proposed that the results for scarred-down blebs is poor, even when the procedure is augmented with antimetabolites. Hawkins *et al.* classified blebs using 5 characteristics (encapsulation, thickness, vascularity, elevation, and microcysts), but reported that these had no effect on outcome.[30] Our study results showed that needling was least successful with blebs which were flat and the best post needling results were achieved for encapsulated blebs but this did not reach statistical significance.

Many authors have advocated initial massage or laser suture lysis in nonencapsulated, failed blebs, and others have suggested initial medical therapy or massage before needling, particularly with encapsulated blebs.[20,22,25] The Advanced Glaucoma Intervention Study results reported that digital massage and topical steroid therapy (without needle revision) led to similar outcomes with respect to IOP for encapsulated blebs compared with nonencapsulated blebs, albeit on additional medical therapy.[32] However massage and suture removal or lysis, although useful in the early postoperative period, usually becomes less effective with increasing time after surgery.

In our study the success rates were greater for the POAG patients, with a complete success 57. 14% and qualified success 28. 57% thus having an overall success rate of 85. 71% compared with eyes with other diagnoses which together had a complete success rate of 5. 56% and a qualified success rate of 50% thus having an overall success rate of 55. 56%. This is similar to the study done by Broadway *et al.* where the success rate was greater for eyes with primary open-angle glaucoma compared with eyes with other diagnoses (49% vs. 37%).[33]

In our study we found that the overall success rates were greater for the eyes where a higher concentration of MMC (0. 04%) was used during the index procedure , 83. 33%, compared to a lower concentration of MMC (0. 02%) which achieved an overall success rate of 33. 33%. There were two cases where no anti fibrotic agent had been used during the index procedure and both of them went into failure after the needling procedure. This is in contrast to the study done by Broadway *et al.* where the authors noted that previous exposure to 5-FU, MMC, or β-irradiation was associated with a lower success rate (54% vs. 39%).[33] The authors explained that this perhaps reflected only the fact that such antifibrotic agents had been used in eyes that may have been considered to be at a greater risk of failure of their index procedure. However our results are similar to the study done by Shin *et al.* where the authors found that the use of MMC during the original glaucoma filtration surgery seemed to be a beneficial factor in the future success of 5-FU needling revision.[34] They found that only 20% (7 of 35 cases) of the initial 5-FU needling revisions were successful in the group that had not received MMC during the filtration surgery. In contrast, 51% (15 of 29 cases) were successful in those who had received MMC during the previous filtration surgery. The authors stated that this significant difference seemed to support the findings that the effects of MMC on local fibroblasts may be long lasting, if not irreversible.[35]

A further factor of potential importance is the interval between initial surgery and needling. In some reports, some blebs have been needled as early as 3 days after surgery.[20,26] In another study, the needlings were performed within a 6-week postoperative period, whereas in others, the interval was a number of years in a proportion of the cases.[20,22,23,24] A short interval between the initial surgery and needling has been associated with success, although, in 1 report, an interval of more than 1 month was found to be advantageous.[21,24] In the present study, massage and suture removal were tried before needling, but a period of intensive medical therapy was not attempted as we felt that the time delay would reduce the chances of success post needling. In the present study, the interval between initial surgery and needling seemed to make no difference to the outcome. Our results are similar to the studies done by Cohen *et al.*, Ewing *et al.* and Greenfield *et al.* in which the authors also could not find any correlation between the time interval of needling and the outcome.[20,23,29]

Other factors identified to be associated with needling failure have included young age, aphakia or pseudophakia, fornix-based conjunctival flap trabeculectomy, previous surgery involving a conjunctival incision, lack of MMC use during the previous filtration surgery, long-term previous exposure to topical

sympathomimetics, and higher preneedling IOP. In the present study, however, none of these risk factors were identified as having a statistically significant effect on outcome. It would seem, therefore, from the results of the present study, that bleb needling is worth attempting in any eye with apparent bleb failure associated with inadequate IOP control, if not otherwise contraindicated. Thus we recommend attempting at least one needling procedure for these patients.

The most significant factor identified in the present study to have an effect on success was the immediate attainment of a low IOP of <11 mm Hg, a finding that was also reported by Shin *et al.*[26] Thus attaining a low IOP of <11 mm Hg immediately after needling seems increase the chance of success and in this study 7/11(63. 63%) cases achieved complete success, 4/11(36. 36%) cases achieved qualified success and there were no failures at the 1 year follow up period. Although none of the other proposed factors that may have affected outcome were identified as having a statistically significant effect, this may have been the result of low statistical power for some of the proposed factors; a larger study would be required to identify such factors.

Very few serious complications have been reported after bleb needling. Some studies which have mentioned some serious complications include significant hypotony, malignant glaucoma, suprachoroidal haemorrhage and a case of endophthalmitis has also been reported.[29,32,36] Most of the reported complications are usually minor and include temporary conjunctival wound leaks, small hyphaemas, transient shallowing of the anterior chamber and corneal epithelial 5-FU toxicity.[22,23,25,26] The incidence of minor complications has been reported to lie between 20% and 38%.[25,26]

The complications encountered in the present study were corneal epithelial defects, hyphaema and a case of bleb leak. The overall percentage of complications was 15. 63% which is lower than the quoted studies but the potential for complications should never be underestimated.

This present study identified three independent risk factors for failure of the initial 5-FU needling revisions: preneedling IOP >28 mmHg, lack of MMC use during previous filtration surgery, and immediate post-needling IOP >11 mmHg. In patients with one or more of these three risk factors, it is especially important to monitor IOP closely following the initial needling revision. They are more likely to require additional therapeutic intervention, including repeat needling revision.

Thus bleb needling should be considered in the management of failing or failed filtration blebs. Bleb needling has a number of advantages compared to repeat surgery. The procedure is simple and repeatable, and has the potential to be equally effective as initial filtration surgery. The method is safe, is performed at the original site, carries no additional theoretical complications over trabeculectomy, and does not preclude resorting to other methods for IOP control if it fails.

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Asian J Ophthalmol. 2016;14:185-191

Comparison of accuracy of Partial Coherence Interferometry based Zeiss IOL Master 500 and Immersion Ultrasound (Ocuscan RXP) for intraocular lens power calculation

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Abstract

Aim: *To compare accuracy of intraocular lens power (IOL) calculation using Partial coherence Interferometry based Carl Zeiss IOL master 500 and Immersion ultrasound (Alcon Ocuscan RXP).*

Methods: *A prospective randomized study of patients who underwent clear corneal phacoemulsification with foldable (IOL) by a single surgeon, during the period September 2010 to 2012. Group A included those patients in whom IOL power calculation using Immersion ultrasound (Ocuscan RXP) was used. Group B included those patients in whom IOL power calculation using Partial coherence Interferometry based Zeiss IOL master was used. SRK T formula was used to calculate the IOL power in both the groups. Postoperative final refraction was done at 6 weeks. Unaided visual acuity and best corrected visual acuity was assessed. Postoperative refractive error was compared with predicted refractive error with each biometry method. Statistical analysis was done using SPSS 16.5. Continuous variables expressed as mean (standard deviation). $P < 0.05$ was considered significant.*

Results: *There were 50 patients in Group A, 44 patients in Group B. Axial length of the patients varied from 22-26mm in both the groups. The postoperative refraction using Ocuscan, 88% had refractive error ≤± 0.5 D, 94% had ≤±1.00D, and 100% had ≤±2.0D of emmetropia. Using Zeiss IOL Master 72.7% had ≤± 0.5 D, 100% had ≤±1.00D of refractive error. Difference in absolute postoperative refractive error using Ocuscan vs. IOL Master was not statistically significant.*

Conclusion: *In our study both ultrasound Ocuscan and IOL master were accurate in calculating intraocular lens power and achieving postoperative refraction closer to emmetropia.*

Key words: *Intraocular lens power calculation, IOL master, Ultrasound A scan.*

Cataract removal and intraocular lens implantation is one of the most frequent and successful ophthalmic procedure performed today. For a successful refractive outcome, the appropriate intraocular lens power must be selected, accuracy of which is highly dependent on preoperative biometry and keratometry. Newer diagnostic and therapeutic instruments with potentially improved precision, diagnostic capabilities and efficiency and convenience are now available for preoperative biometry. We conducted this study to compare accuracy of intraocular lens power (IOL) calculation using Partial coherence Interferometry based Carl Zeiss IOL master 500 Advanced Technology, Version 7.1.2.0042 and Immersion ultrasound (Alcon Ocuscan RXP)

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Materials and methods

This was a prospective randomized study of 94 patients who were scheduled for phacoemulsification with implantation of posterior chamber intraocular lens (AcrysofSN60WF/SA60AT) during the period, September 2010 to September 2012. Ethical committee clearance was obtained for the study. For a range of axial length measurements between 22-26mm for power of 80%, a total minimum sample size as determined by statistician was 63 eyes for 5% level of significance. The formula, Hypothesis testing of two means was used to calculate the sample size.

All the patients above the age of 40 years who were to undergo cataract surgery were screened for inclusion in the study. Those with any ocular condition which prevented good visual outcome like macular pathology, , patients with astigmatism of more than 1D, corneal scars, previous ocular surgery, complicated cataract due to uveitis, trauma & silicone oil, ocular conditions in which partial coherence interferometry was not able to calculate IOL power, intraoperative complications like posterior capsular tear were excluded from the study. Axial length measurements between 22-26 mm were included in the study. In all the patients IOL power calculation was done using both partial coherence interferometry and immersion A-scan. Both the partial coherence interferometry and immersion A-scan axial length was measured by the same ophthalmologist. For immersion A scan keratometry value from automated keratometry was used. IOL power was calculated using SRK /T formula. Post-operative refractive error was aimed within +/-0.5D of emmetropia. The patients were alternatively allotted to Group A (immersion A-scan), Group B (partial coherence interferometry) for choosing the IOL. In 29 eyes partial coherence interferometry was not able to calculate the axial length and was not included in the study. All the patients underwent phacoemulsification through temporal clear corneal incision with a 2.8 mm keratome by a single surgeon under local anesthesia. The IOL was implanted in the capsular bag. Postoperative final refraction was done at 6 weeks. Unaided visual acuity and best corrected visual acuity was assessed. The postoperative refractive error was compared with the predicted refractive error in each biometry method. Statistical analysis was done using SPSS 16.5. Continuous variables expressed as mean (standard deviation). $P < 0.05$ was considered significant.

Results

A total of 94 eyes were included in the study. Group A (immersion A-scan group) had 50 eyes and Group B (partial coherence interferometry) had 44 eyes because 6 patients in Group B cataract surgery got postponed due to coexisting medical problems. The age of the patients ranged from 45 to 87 years. The mean age was 66.83 years with a standard deviation of 8.955 years. Mean age of patients in group A was 65.66 years with a standard deviation of 9.4 years and in group B 68.16years with a standard deviation of 8.32 years. 54% of the patients were males and rest females.

IOL power calculated was in the range of 16.5D to 27.5D in Group A and in Group B the range was from 19 D to 24 D. (Table 1).

Table 1: Range of intraocular lens power in both the groups.

IOL power (Diopter)	Minimum	Maximum	Mean	SD
Group A (Immersion A scan)	16.5 D	27.5D	21.52D	2.10
Group B (partial coherence interferometry)	19D	24D	21.59D	1.27

Postoperatively refractive error was calculated in spherical equivalent. Numerical error was defined as the difference between spherical equivalent and the predicted error. Absolute error was defined as absolute difference between spherical equivalent and the predicted error (Table 2).Group A showed higher positive skewness for both numerical and absolute error as against group B (Table 2). Comparison of the skewness coefficients between the two groups demonstrated a statistically significant difference for both the numerical (z= 2.338, p= 0.01) and absolute error (z=6.269, p<0.001).

Table 2: Comparison between Immersion A scan and Partial coherence Interferometry in terms of numerical error and absolute error.

	Group (A) Immersion A-scan	*Group (B)* Partial coherence interferometry	p- value
Numerical error(Median)	0.09	-0.105	0.132
Range	(-1.03, 1.90)	(-0.75, 0.87)	
Interquartile range	(-0.17, 0.34)	(-0.33, 0.30)	
Skewness coefficient + standard error of skewness	1.148+0.337	0.338+0.357	<0.0001
Absolute error(Median)	0.26	0.2975	0.363
Range	(0.01, 1.90)	(0.01, 0.90)	
Interquartile range	(0.13, 0.42)	(0.14, 0.54)	
Skewness coefficient+ standard error of skewness	2.729+0.337	0.557+0.357	<0.0001

As the data did not follow a normal distribution, a non-parametric test (Mann Whitney -U test) was used for comparison between the groups. P value obtained was (0.256) not statistically significant. In group A 88% of the patients had post op refractive error ≤±0.5 D, 94% had residual refractive error ≤± 1.0 D. In group B 72.7% had residual refractive error of ≤±0.5 D, and no patient had refractive error greater than 1D (Table 3). In our study immersion A scan showed hyperopic shift in (58%) and partial coherence interferometry showed a hyperopic shift in (43.2%).

Table 3: Group wise percentage of eyes that were within ≤±0.5 D, ≤±1.0D, ≤±2.0D of emmetropia.

	≤±0.5 D	≤±1.0D	≤±2.0D
Group (A) (Immersion A scan)	88.0%	94%	100%
Group(B) Partial coherence interferometry	72.7%	100%	100%

Table 4: Showing the results of previous studies and the present study

Study	Formula	≤±1D (US))	≤≤±1D (IOLM)	±2D (US)	≤±2D (US)	SS
Drexler[1] (US&PCI)	SRKII	73%	85%	96.4%	100%	PCI>US
MS Rajan[2] (US&PCI)	SRK/T	80%	87%			Nil
H Eleftheriadis[5] (US&PCI)	Holladay 1	93%	96%			PCI>US
Haigis [9] (US&PCI)	Haigis	86.7%	84.7%	99%	99%	Nil
Loreto[2] (US&PCI)	SRK/T	79%	81%	98%	100%	PCI>US
Present study (US&PCI)	SRK/T	94%	100%	100%	100%	Nil

US- ultrasound, PCI- Partial coherence interferometry, SS-statistical significance

Discussion

The refractive outcomes following phacoemulsification cataract surgery is dependent on a number of factors. They include axial length measurement, keratometry, anterior chamber depth, IOL power formula and quality of IOL. Since predictability of refractive outcomes is based on accuracy of preoperative biometry, the methods used in biometry continue to evolve.

The main limitation with the A scan ultrasound is the poor image resolution

due to use of a relatively long, low resolution wavelength (10MHZ) to measure a relatively short distance.

The newer partial coherence interferometry advanced technology software upgrade (version 5) is designed to enhance signal to noise ratio in order to improve measurement of axial length in eyes with media opacity[7].

In the present study we included patients with age>40 years. However studies done by Loreto T Rose[1], MS Rajan[2], Wolfgang Haigis[9], and Drexler[10] did not have a criteria for age. In the Study by Eleftheriadis[5] they included patients with only age related cataract. Those eyes whose axial length could not be measured with partial coherence interferometry due to dense media opacity were excluded to prevent any bias in refractive error calculation which could affect the postoperative refractive outcome. MS Rajan[2], Eleftheriadis[5] had similar exclusion criteria whereas Loreto T Rose[1], Drexler[10] did not have any exclusion criteria; hence there was a possibility of bias in the final refractive outcomes obtained. In our study in 29 eyes partial coherence interferometry was not able to calculate axial length and was not included in the study. In MS Rajan[2] study failure rate was 8% with partial coherence interferometry. Loreto T Rose[1] did not have any failure rate with partial coherence interferometry. Previous reports have demonstrated a failure rate with partial coherence interferometry which varied from 5 to 15%.[1,2,3,4,6,7,8,9]

In our study the desired postoperative refractive error was aimed at ±0.5D. However this was not done in other studies. In our study all the surgeries were performed by a single surgeon in a standardized manner. Previous studies done by Loreto T Rose[1], MS Rajan[2] Eleftheriadis[5], Drexler[10] were also done in a similar manner. However in the study by Wolfgang Haigis[9] three surgeons performed the surgery and the surgical technique was not standardized. Hence this could have accounted for an error in the final refractive outcome.

In our study Group A showed higher positive skewness for both numerical and absolute error as against group B. Though the axial length was comparable in both the groups the range of IOL power in Group A was +16. 5 D to 27D, where as in Group B the range of IOL implanted, was +19 D to +24 D. We believe the keratometry difference may be responsible for this difference in the IOL range and the skewness of the numerical and absolute error. However we did not analyse the keratometry values separately. In the study by Elftheriadis[5] distribution of the absolute error did not follow the normal distribution.

In the present study postoperative refraction using immersion scan, residual refractive error was ≤± 0.5 D in 88%, ≤±1.00D in 94%, ≤±2.0D in 100%.Using partial coherence interferometry 72.7% were ≤± 0.5 D, 100% were within ≤±1.00D and 100% were ≤±2.0D of emmetropia. This showed that optical biometry was clinically superior to ultrasound to achieve a refractive error closer to emmetropia. Loreto TRose[1] Eleftheriadis[5], Drexler[10] found partial coherence interferometry to be superior to immersion A scan whereas MS Rajan[2], Haigis[9] did not find such difference. Table 4 shows the results of these studies and our study.

Studies done by Loreto TRose[1], MS Rajan[2], Eleftheriadis[5]; Drexler[10] compared applanation ultrasound with partial coherence interferometry. A study done by

LoretoT Rose[1] showed a 35% improvement in absolute postoperative refractive error with partial coherence interferometry compared to applanation ultrasound which was statistically significant. MS Rajan[2] study showed that using mean absolute error there was no statistically significant difference between partial coherence interferometry and ultrasound. This was in concordance with present study.

In the study done by Eleftheriadis[5] retrospective optimization of surgeon factor was done. Mean absolute error of optimized partial coherence interferometry was significantly smaller than that of the optimized ultrasound. With partial coherence interferometry there was an improvement in refractive outcome by 39%. Using ultrasound, postoperative refractive error in 93% were within ≤±1.0D of emmetropia and using partial coherence interferometry 96%were within ≤±1.0D of emmetropia. We did not find such difference between the two groups. Optimization of the surgeon factor was not done in our study.

MS Rajan[2] also demonstrated that eyes that underwent partial coherence laser interferometry had increased tendency for hyperopic shift (65%) when compared to the eyes in ultrasound group (50%). He suggested that this was probably because axial length measured with partial coherence laser interferometry is 100um longer than applanation ultrasound. However this was not seen in the present study. In our study immersion A scan showed hyperopic shift in (58%) and partial coherence interferometry showed a hyperopic shift in (43.2%).

Conclusion

In the present study immersion scan group, 88% of the patients had post op refraction of ≤± 0.5 D, 94%of the patients had refractive correction ≤±1.00D. Using partial coherence interferometry 72.7% of patients had postop refractive error ≤± 0.5 D, 100% were within ≤±1.00D. Differences in absolute postoperative refractive error using immersion scan vs. partial coherence interferometry was not statistically significant. This study showed that both the machines were accurate in calculating intraocular lens power and achieving postoperative refraction with values closer to emmetropia.

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Asian J Ophthalmol. 2016;14:192-205

Dietary intake and retinal microvasculature: a systematic review

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Abstract

Aims: *To summarise the available findings from published research that has focussed on the effect of diet on retinal microvascular characteristics.*

Design: *Systematic review.*

Methods: *A systematic Medline, EMBASE and PubMed search of relevant articles was conducted with coverage from the January 1, 1970 up to the January 10, 2013. Search terms were pilot tested for accuracy and modified. Articles were systematically excluded if the title and abstract were not relevant and full text manuscripts were obtained for all studies that were potentially relevant.*

Results: *After combining all searches, 5370 abstracts were identified and screened. Of these 20 were considered potentially relevant and full articles were retrieved for further evaluation. Eleven of these studies did not meet the inclusion/exclusion criteria, leaving 9 studies to be included in the review.*

Conclusions: *To date, it has been suggested that a low glycemic Index (GI) diet, high dietary fibre intake and regular fish consumption attenuate retinal arteriolar narrowing and retinal venular widening which has been associated with adverse cardiovascular outcomes. Conversely, it has been suggested that a high GI diet may predispose an individual to adverse retinal microvascular changes.*

Keywords: *Microvasculature, retinal blood flow, retinal vascular calibre, diet, nutrition.*

Background

Retinal blood vessels are readily viewable via non-invasive retinal photography.[1] Previous methods of measuring retinal vascular characteristics involved subjective clinical examination of arterio-venous ratio (AVR) via fundoscopy, which proved variable and of limited value as a predictor of increased risk of cardiovascular related diseases. More recently, reproducible computer-based imaging programs have been employed to quantitatively measure retinal vasculature.[2] These assessments provide a means to study early structural changes that provide important information regarding the state of retinal microcirculation.[3]

The vascular architecture of the retina is believed to follow an optimal pattern which allows for best possible blood distribution while utilising the least amount of energy.[4] Any deviations from this normal structure, most notably in the form of retinal arteriolar narrowing and retinal venular dilation, can be an indication of

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pathogenic processes.[4] Research suggests that retinal microvascular dysfunction may be a predictive factor in the development of various cardiovascular, cerebrovascular and metabolic-related diseases.[5] Strong associations have been found between wider retinal venular calibre and narrower retinal arteriolar calibre and the incidence of coronary heart disease (CHD)[6] and vascular abnormalities in cerebral microcirculation.[5] Furthermore, a definitive link between narrower retinal arteriolar calibre and hypertension development[7] and wider retinal venular calibre and the increased risk of incident stroke[8] has been reported in the literature.

Previous research has established strong links between diet and the development of macrovascular[9-11] and microvascular complications.[12,13] To date, several studies have suggested that diet may be a determinant of retinal vascular structure. Dietary fibre and fish consumption as well as the consumption of high glycemic index (GI) foods have been associated with retinal vascular alterations. Despite this, large gaps in current knowledge exist, including the association between diet and retinal vascular calibre in healthy children and adolescents. This information would reveal the physiological influence of diet on microcirculation while minimising confounding systemic factors. The main aim of this review is to summarise the available information from published research that has focussed on the effect of diet on retinal microvascular characteristics.

Methods

Information sources and search strategy

A systematic Medline, EMBASE and PubMed search of relevant articles was conducted with coverage from the January 1, 1970 up to the January 10, 2013. Search terms were pilot tested for accuracy and modified until a final search strategy could be used to achieve the desired outcome using all 3 databases. All searches included a combination of the key terms: retinal vascular calibre, retinal vascular caliber, retinal dilatation, retinal blood flow, retinal blood vessel*, retinal vessel*, retinal vessel diameter, retinal microvascular caliber, diet*, food, nutrition and nutrients. The search was not restricted by language but was limited to studies conducted in humans. The reference lists of retrieved articles were utilised to identify additional resources.

Study selection

Two reviewers (SK & KK) independently searched the 3 databases and screened the resultant titles and abstracts. Articles were systematically excluded if the title and abstract were not relevant and full text manuscripts were obtained for all studies that were potentially relevant.

Eligibility and exclusion criteria

Randomised controlled trials, prospective, retrospective, cohort, case control, and cross sectional studies were eligible for inclusion in the review. Studies that involved any dietary factor and incorporated retinal vessel characteristics as a primary outcome measure were included. There was no restriction placed on the

method of vascular microvascular analysis. Nor was there any restriction on participant ethnicity. Those studies that examined associations between lifestyle factors (E.g. smoking, supplement consumption and physical activity) and retinal microvasculature were excluded. Review articles were excluded.

Results

After combining all searches, 5370 abstracts were identified and screened. Of these 20 were considered potentially relevant and full articles were retrieved for further evaluation. Eleven of these studies did not meet the inclusion/exclusion criteria, leaving 9 studies to be included in the review (Table 1). Of the excluded studies, 3 were review articles, 2 were duplicates and 6 did not directly examine the association between dietary factors and retinal vasculature (Fig 1). There was complete agreement between the reviewers for eligibility. A meta-analysis was not performed due to the small number of articles.

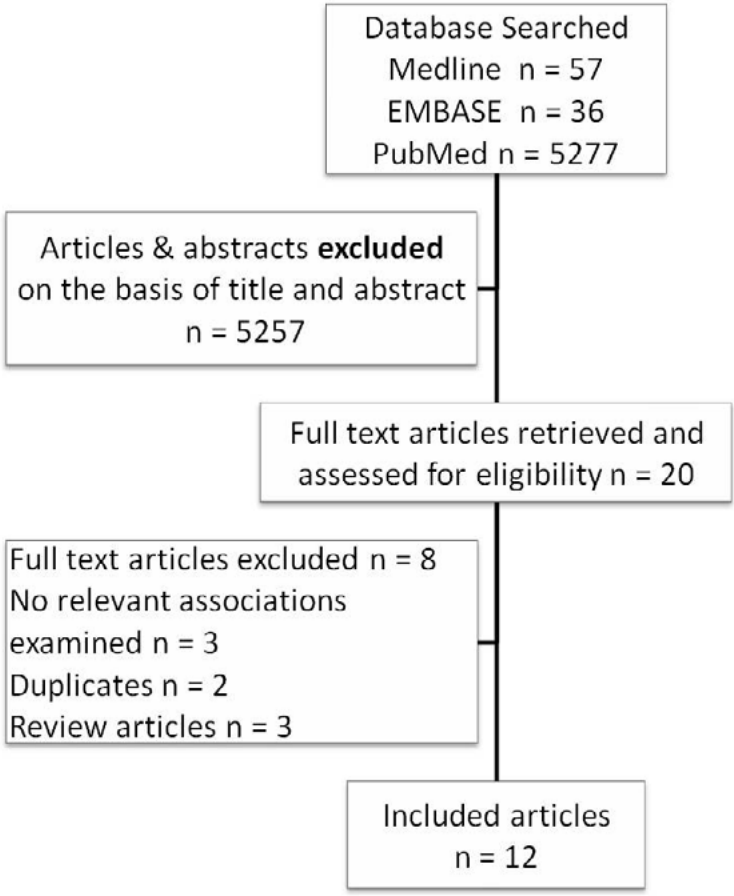

Fig 1. Summary of study selection process

Glycemic index

Dietary glycemic index (GI) provides a measure of carbohydrate quality, ranking carbohydrates according to their effect on postprandial blood glucose excursions.[14] Previous studies have suggested that diets high in cereal fibre are associated with a lower risk of cardiovascular disease and lower blood pressure.[14] Conversely, it has been proposed that in the absence of a high fibre diet, diets with a high glycemic load have been associated with small vessel dysfunction and therefore may contribute to the development of diabetes, cardiovascular disease and stroke.[15] Gopinath[14] examined the effects of high-GI and high-glycemic load diets, carbohydrates and main carbohydrate containing food groups on retinal vascular calibre changes in 2353 pre-adolescent individuals and found that those children who consumed soft drink once or more per day had a narrower retinal arteriolar calibre than those who never or rarely consumed soft drinks (p=0.03). A higher-GI diet was associated with narrower retinal arteriolar calibre in girls only. Overall, a greater consumption of carbohydrates and soft drinks was associated with narrower retinal arterioles (p=0.01) and wider retinal venules (p=0.002). As previous research[6,8,16] has found associations between microvascular signs of narrower retinal arterioles and wider venules to the future risk of cardiovascular disease this finding may support the promotion of healthy dietary patterns, including lower consumption of soft drinks and high-GI foods to children.

In alignment with Gopinath's[14] findings, associations between a high-GI diet and wider retinal venular calibre have also been found in adults.[17] Kaushik[17] assessed the relationship between dietary-GI and low cereal fibre and retinal vascular calibre characteristics in a large cohort of individuals (n=2897) over the age of 49 years and noted that a higher dietary-GI and lower cereal fibre intake were associated with wider retinal venular calibre (p=<0.01). They further suggested that higher dietary-GI and lower cereal fibre intakes were associated with double the risk of stroke related death, suggesting that a high-GI diet may produce adverse changes in the bodies microvasculature.[17] Although the mechanisms underlying the changes in retinal venular calibre are still largely unknown it has been postulated that a high GI diet may result in the formation of advanced glycation end products in venular walls resulting in endothelial dysfunction and vascular damage.[15,18]

Dietary fibre

Diets high in dietary fibre have been associated with a reduced risk of cardiovascular morbidity.[19] Previous researchers have suggested that fibre may guard against hypertension, dislipidemea and incident diabetes by attenuating arteriolar narrowing and venular widening, which are emerging risk factors associated with these conditions.[7,20,21] To date, only one study has examined the association between dietary fibre intake and retinal vascular calibre in adults.[22] The Atherosclerosis Risk in Communities Study (ARIC) recruited a large sample (n=15,792) of white and African Americans and found that a higher intake of fibre was associated with wider retinal arteriolar calibre (p=0.002) and narrower retinal venular calibre (p=0.011). These findings are associated with a lower risk of cardiovascular disease

and support other findings in highlighting the benefit of fibre intake in protecting against cardiovascular disease. By contrast, a similar population based cohort study conducted on children is not in agreement with these findings.[23] Lim[23] assessed the relationship between dietary fibre along with a number of other dietary factors (protein, fat, cholesterol, carbohydrate and sugar intakes per day) and retinal vascular calibre in 823 healthy Singapore Chinese children (mean age; 12.8±0.8) and found that no significant association existed between any of the dietary constituents and retinal vascular calibre. These findings suggest that the effect of diet on microvasculature may only become evident later in life which could provide evidence for a potential cumulative effect of diet on the retinal microvasculature.[23] Despite this, additional research is required to clarify these findings as unexplained or unmeasured confounders may exist.

Fish consumption

Omega-3 polyunsaturated fatty acids appear to lower the risk of CHD and stroke.[24] To date only one study has examined the effects of fish consumption on retinal microvasculature.[24] Kaushik[24] utilised a large sample (n=2683) of Australian adults (>49yrs) and found higher frequency of fish consumption was significantly associated with wider retinal arteriolar (p=0.002) and narrower retinal venular calibre (p=0.02). These findings suggest that a higher consumption of fish may help protect against vascular changes associated with coronary heart disease and stroke.[24] This association, however, was mainly seen in persons with hypertension which may confound the outcome as retinal microvascular changes have been strongly associated with hypertension in adults. As this is the only study to date to evaluate the association between fish consumption and retinal vascular calibre before any conclusions can be drawn concerning this relationship further research needs to be conducted.

Antioxidants

Several studies have highlighted the potential benefit of selected antioxidants on various eye diseases such as diabetic retinopathy, uveitis and age related macula degeneration.[25-28] However, the relationship between antioxidants and retinal vasculature remains poorly understood. Pemp's[29] study on 21 adults aged 18-35 years found that the administration of antioxidants attenuated arteriolar vasoconstriction during systemic hypoxia (p=0.04). This supports the suggestion that antioxidants may reduce oxidative stress by reducing reactive oxygen species which has been shown to contribute to cellular damage through endothelial dysfunction.[29] Although these results suggests that dietary antioxidant consumption may be associated with positive microvascular outcomes, no inferences can be made until the long term relationship between antioxidant intake and retinal vascular calibre is explored.

Caffeine

Caffeine is the most frequently consumed stimulant worldwide, acting by increasing blood pressure while increasing heart rate. Several studies have demonstrated the

effects of caffeine on cerebral, coronary and ocular blood flow.[30-32] A small prospective study (n=17) by Terai [33] is the only study to date that has investigated the effect of caffeine on retinal vessel diameter. A significant vasoconstrictory response of retinal arterioles (p=0.004) and venules (0.005) occurred one hour following caffeine intake.[34] This finding is consistent with earlier studies that assessed the effect of caffeine on retinal circulation and found that caffeine significantly reduced retinal blood flow in the optic nerve head and choroid retina.[30,35] It has been hypothesised that these changes may be elicited by an auto-regulatory response of retinal blood vessels to the increased blood pressure changes associated with caffeine intake. Despite this, these results must be viewed with caution due to the small sample size and the fact a control group was not employed to control for non-drug related effects on the measured variables. Furthermore, Terai's[33] findings are contradictory to previous research that has suggested that the long term influence of high caffeine consumption is not associated with cardiovascular disease risk[36] and in fact may lower the risk of type 2 diabetes in younger to middle aged women.[37] This highlights the need for further research before any judgements can be made on the role caffeine plays on human microvasculature.

Salt Intake

The role of sodium intake in end organ damage remains largely unknown, however, it is increasingly becoming a focus of researchers due to its well described association with cardiovascular disease. Most notably, strong associations have been reported between high sodium intake and systolic hypertension.[38] Raff [39] analysed the association between salt intake and retinal arteriolar structure in 40 adults aged 44-75 years with treatment resistant hypertension. They found that retinal arteriole wall thickness was directly associated with urinary sodium excretion (p=0.008). This suggests that salt intake may influence the structure of retinal arterioles, independent of blood pressure.[39] However, as this study examined only structural changes in arterioles, the results cannot be directly related to retinal vascular diameter measurements. Furthermore, these results may be confounded by the presence of treatment resistant hypertension in participants as well as the use of multiple antihypertensive drug therapies which have been shown to have different influences on vascular structure.[40,41] Further research is required to aid in understanding the relationship between sodium intake and retinal microvasculature. These studies should utilise standardised methods for retinal vascular calibre assessment and focus on non-hypertensive participants as high current and previous blood pressure has been consistently associated with retinal arteriolar narrowing in children and adult cohorts.[42-45]

Plant sterol and –stanol consumption

Sterols such as sitosterol and campesterol are derived from various plant products such as plant oils, nuts and seeds. Sterol and –stanol are often used as additives in foods such as margarine to reduce serum LDL cholesterol concentrations.[46] Although these products have been suggested to lower cardiovascular risk, some researchers have indicated that high sterol concentrations may be atherogenic

(the deposition of atheromas, lipids, and calcium in the arterial lumen).[46] Kelly's[46] randomised control trial on 30 participants aged 18 to 65 years is the only study to date to assess the effects of long term plant sterol and -stanol consumption on retinal vessel diameter changes. They found that increased serum campesterol concentrations were associated with a wider retinal venular diameter (p=0.033). These results suggest that plant sterols may be a biomarker for pathological vascular function. However, before any judgements can be made on plant sterol rich foods further research into the relationship between plant sterol consumption and our microvascular system is required.

Discussion

Previous research has found associations between reduced risk of vascular disease and the regular consumption of fish, dietary fibre and low GI foods. Therefore, the finding that some correlation exists between diet and retinal vessel diameter could be expected and may not add to clinical practice.[47,48] However, emerging evidence has highlighted that the relationship between diet and vascular disease may in fact be partly mediated by associated changes in the microcirculation.[17,22,24] As such, the use of retinal imaging to visualise human microcirculation may potentially provide additional prognostic information beyond current traditional risk factors.

To date it has been suggested that a low GI diet, high dietary fibre intake, and greater frequency of fish consumption may protect against vascular disease by attenuating retinal arteriolar narrowing and retinal venular widening.[17,22,24] Conversely, it has been suggested that a high GI diet may predispose an individual to adverse microvascular changes.[14] Although some link between changes in retinal microvasculature and caffeine and antioxidants intake has been suggested, further research is required before any judgements can be made as only short term changes were examined. Furthermore, it is difficult to draw inferences into the role sodium and sterol and –stanol play on human microvasculature until dietary intakes of these agents are the primary exposure.

Emerging evidence suggests that retinal vascular calibre assessment has the potential to become a tool to better understand the pathophysiology of the body's microvasculature and aid in the prediction of several vascular diseases. ARIC found that wider retinal venular calibre and narrower retinal arteriolar calibre were associated with a 10 year increased risk of incident CHD in women.[6] Retinal arteriolar narrowing has also been found to precede the development of clinical hypertension by years in patients who displayed blood pressure in the normal range at baseline.[5] It has been postulated that decreases in internal arteriolar lumen calibre occur early in the development of hypertension and these changes are responsible for altering the body's hemodynamics and ultimately resetting blood pressure to a higher level.[5,7,49] Furthermore, changes in retinal arterioles have been linked to changes in small cerebral arteries that cause white matter lesions, while the presence and severity of coronary artery occlusion has also been strongly associated with vascular calibre changes.[5,50] A wider retinal venular calibre on the other hand, has been to increased risk of incident stroke, independent of traditional risk factors.[8]

The mechanisms behind the retinal microvascular changes in calibre are incompletely understood. Possible mechanisms for the development of smaller retinal arteriolar calibre is that it is associated with hypertensive and arteriosclerotic microvascular changes, endothelial dysfunction, and inflammatory changes which are thought to be involved in the pathogenesis of various cardiovascular diseases.[51,52] A widening of retinal venular calibre on the other hand, may reflect an increase in blood flow to maintain the tissue oxygen levels which also may be attributed to the reduced supply of nutrients and an increased concentration of waste products, e.g. lactic acidosis associated with retinal hypoxia.[53,54] An alternate hypothesis behind venular dilation suggests that inflammation associated with increased nitrous oxide levels may be partly responsible for this variation in retinal venules.[55] From this it appears that variations in retinal arteriolar and venular calibre may reflect different pathophysiological processes.

Whilst many of these studies[14,17,22-24] included large sample sizes, caution must be observed in interpreting the findings of Raff,[39] Pemp,[29] Terai[34] and Kelly[46] due to the inclusion of a relatively small sample sizes. Furthermore, several studies included in this review[29,30,34,35,39] did not utilise standard protocols for retinal vascular diameter assessment and therefore the results must be viewed cautiously. Additionally, some of the studies[14,24] reported only small variations in retinal vascular calibre. Despite this, it has been shown that even a small reduction in retinal arteriolar calibre is associated with clinically significant changes in blood pressure. For example, a 1.1 micron reduction in arteriolar calibre was associated with a 10 mmHg higher systolic blood pressure.[56] As computerised methods are not available clinically, subjective AVR measurements may still have some utility clinically. More guidance surrounding AVR assessment is required in future research.

The majority of the studies included in this review most assessed associations between dietary factors and retinal microvasculature in adults. However, to develop an understanding of the effect of dietary factors on retinal vessels the study of calibre in children may provide additional insights as they are generally exposed to fewer potentially confounding systemic and environmental factors than adults. Lim's[23] study suggested that the effect of diet on microvasculature may only become evident later in life and therefore studying the effect of dietary factors on retinal vasculature in children is not warranted.[23] However, the food frequency questionnaire utilised in that study was not validated in children and exposures that have been shown to influence retinal vasculature, such as birth parameters, were not assessed and as such their findings may have been confounded. Furthermore, more recent studies that have examined the effect of carbohydrates on retinal vascular calibre in children and young adults have found significant associations.[14,34] These contradictory findings highlight that the physiological influence of diet on retinal vascular calibre remains relatively unclear.

In summary, an individual with a healthy diet, including low GI foods, high dietary fibre intake and regular fish consumption, is more likely to have a characteristic retinal microvascular pattern of wider retinal arteriolar and narrower retinal venular diameters. Conversely, the opposite (narrower retinal arterioles and wider venules)

is more likely in those with a poor diet, consisting of high intakes high-GI foods. Narrower retinal arterioles and wider venules have been suggested to reflect microvascular dysfunction associated with the development of various cardiovascular, cerebrovascular and metabolic diseases. Despite this, it is important to note that most of the inferences in this review are based on the findings from one study and as such a major gap in the literature has been highlighted. Perhaps most importantly, the association between diet and retinal vascular calibre in healthy child and adult cohorts in whom the association is less likely to be confounded by disease states should be investigated.

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Table 1. Studies examining the association between dietary factors and retinal microvasculature, by year of publication.

Reference; country/ setting of study	Nutrient/s examined	Sample size; age	Ethnicity	Study type	Method of retinal vessel measurement	Adjustments	Outcome; p value
Terai *et al* (2012) Germany	Caffeine	n=17; 22-35yrs	German	Prospective	Retinal Vessel Analyser	None stated	Significant vasoconstrictory response of retinal arteriolar (p=0.004) and venular diameters (p=0.005) occurred following caffeine intake
Raff *et al* (2012) Germany	Sodium	n=40; 44-75yrs	German	Observational	Scanning laser Doppler flowmetry	Age & BMI	Vessel diameter of retinal arterioles was associated with urinary sodium excretion (p=0.008)
Gopinath *et al* (2012) Australia	Carbohydrates	n=2353; mean age 12yrs	Australian	Random cluster sample	IVAN	Age, sex, ethnicity, axial length, BMI, MAPD, & fellow vessel calibre	Children who consumed soft drinks once or more per day had significantly narrower retinal arterioles (p=0.03), a greater consumption of carbohydrates was associated with a narrowing of retinal arterioles (p=0.01) and a widening of retinal venular calibre (p=0.002)
Kelly *et al* (2011) Netherlands	Plant sterol and -stanol	n=30; 18-65yrs	Dutch	Randomised control trial	IVAN	None stated	Increased serum campesterol concentrations were associated with a wider retinal venular diameter (p=0.033)

Table 1 continued. Studies examining the association between dietary factors and retinal microvasculature, by year of publication.

Reference; country/ setting of study	Nutrient/s examined	Sample size; age	Ethnicity	Study type	Method of retinal vessel measurement	Adjustments	Outcome; p value
Kaushik *et al* (2009) Blue Mountains Eye Study	Glyceamic index	n=2897; >49yrs	Australian	Population based cohort study	IVAN	Age, sex, systolic and diastolic blood pressure, BMI, smoking, educational qualifications, fair of poor self-rated health, diabetes mellitus, history of coronary heart disease, and total vegetable, saturated fat and fish consumption	Increasing GI diets were associated with retinal venular calibre widening (p=<0.01)
Pemp *et al* (2010) Vienna	Antioxidants	n=21; 18-35yrs	Italian	Randomised, double-masked, placebo controlled, parallel group study	Dynamic Vessel Analyser	None stated	The administration of antioxidants was associated with a significant reduction in vasoconstriction of retinal arterioles (p=0.040)
Lim *et al* (2009) Singapore	Dietary fiber, protein, fat, cholesterol, carbohydrate and sugar intakes	n=823; mean age 12.8yrs	Singapore Chinese	Population based cohort study	IVAN	Age , gender, BMI, and mean arterial blood pressure	No significant association existed between any of the dietary constituents and retinal vascular calibre
Kaushik *et al* (2008) Blue Mountains Eye Study	Fish	n=2683; >49yrs	Australian	Population based cohort study	IVAN	Age , gender, MABP, BMI, smoking, glucose, cholesterol, white cell and platelet counts, qualifications, self-rated health, past history of heart disease and total vegetable and fat intakes	Statistically significant associations were found between an increased frequency of fish consumption and wider retinal arteriolar (p=0.002) and narrower retinal venular calibre (p=0.02)

Table 1 continued. Studies examining the association between dietary factors and retinal microvasculature, by year of publication.

Reference; country/ setting of study	Nutrient/s examined	Sample size; age	Ethnicity	Study type	Method of retinal vessel measurement	Adjustments	Outcome; p value
Kan *et al* (2007) USA	Dietary Fiber	n=15792; 45-64yrs	American	Population based cohort study	IVAN	Sex, race, smoking status, occupation, education, alcohol intake, diabetes status, BMI, physical activity, systolic and diastolic blood pressure, serum lipids, dietary factors from both food and supplements and other sources of fiber	A high fiber consumption was positively correlated with wider retinal arteriolar calibre (p=0.002) and narrower venular calibre (p=0.011)

Asian J Ophthalmol. 2016;14:206-209

Congenital Absence of Meibomian Glands: report of two cases

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Abstract
A 36-year-old man with his 11-year-old son presented with ocular surface irritation symptoms and blurred vision since early childhood, on exam visual acuity of the man was 5/10(OD), 4/10(OS) and his son was 6/10(OD), 5/10(OS), other exams of these patients were similar: eyelid examination showed absence of meibomian gland orifices, after application of fluorescein dye there was a thin tear film layer and diffuse punctuate epithelial erosions on the cornea, remaining exams were unremarkable.
Key words: *absent meibomian gland, ectodermal dysplasia, dry eye, congenital meibomian gland anomalies, congenital absence of meibomian gland*

Introduction

The meibomian glands play a key role in maintaining a healthy ocular surface by secreting lipids that help to stabilize the tear film, the meibomian glands minimize the evaporative loss of tear fluid. Maintaining aqaqueous tear volume keeps the ocular surface protected throughout the blink cycle and reduces the risk of hyperosmolaritiy ,meibomian glands abnormalities may create significant ocular surface problems, when patients don't have enough of the meibomian gland-secreted lipids in tear film to prevent evaporation , they can develop dry eye , even if aqueous production remains normal.

Case presentation

A 36-year –old with his 11-year-old son were referred to farabi eye hospital cornea clinic complaining of ocular surface irritation symptoms like foreign body sensation , tearing and blurred vision since early childhood, the man mentioned similar symptoms in his father. On presentation visual acuity of the man was 5/10(OD), 4/10(OS) and his son was 6/10(OD), 5/10(OS), other exams were similar in both patients: external exams including eyelid and adnexa showed absence of meibomian orifices both in the upper and lower eyelids, conjunctiva was mildly injected, the corneal surface was irregular and staining with fluorescein showed diffuse punctuate epithelial erosions and a very thin tear film layer (figures 1–4).

The anterior chamber, lens and fundus were unremarkable.Their past medical history was negative and they didn't have any systemic complaints except for difficulty in swallowing.

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Fig.1: Absence of meibomianglands and orifices in the lowereyelid of the Son

Fig. 2: Absence of meibomian orifices in the lower eyelid of the Son

Fig.3: Absence of meibomian glands and orifices in the upper eyelid of the Father

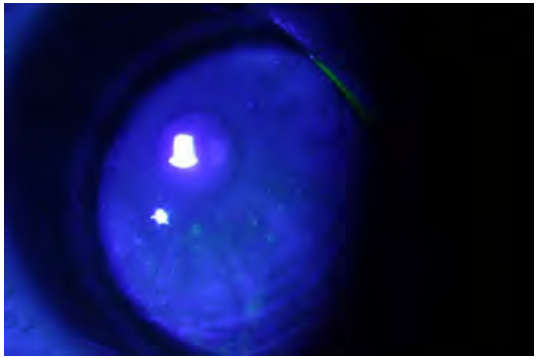

Fig 4: Irregular corneal surface stained with fluorescein showed diffuse punctuate epithelial erosions and a very thin tear film layer

Discussion

The ectodermal dysplasia syndromes are congenital disorders that are identified by the absence or deficient function of at least two derivatives of the ectoderm such as teeth, hair, nails and sweat glands[1].

Meibomian gland deformities and tear film disorders have been described in patients with ectodermal dysplasia syndrome.[2-4] Congenital absence of meibomian glands is exceedingly rare,[3,5] but has been reported in ectodermal dysplasiasyndrome and ill anhidrotic ectodermal dysplasia.[2-6]

T. Kaercher studied thirty-six patients with ectodermal dysplasia syndromes. Transillumination of the meibomian glands was performed on 22 of them and revealed alterations of the meibomian glands in 21 patients (95.45%). These alterations included partial loss of the glands, coarsening of the acini and complete absence of meibomian glands.[7] Mondino[8] histologically showed an absence of meibomian orifices at the upper and lower lid.

The biomicroscopic absence of meibomian orifices was reported by Koniszewski[9], but not confirmed by histologic series. Full -thickness biopsies cannot be performed routinely for clinical purposes. The technique of transillumination (meibomianoscopy) provides useful information,and in contrast to histologic techniques ,all areas of the upper and lower lid can be inspected. The meibomianoscopy provides information about regularity, differentiation, size and number of the meibomian glands. Therefore, we chose this technique for our case report. In our cases, there were no meibomian glands based on biomicroscopic study, (Fig 1-2) but there was no histopathologic study. Our patients showed no other sign of ectodermal dysplasia syndromes except for complete absence of meibomian glands in both lids of both eyes.

In the study by Bron and Tripathi, a particular form of epithelial surface change was observed, which was associated with the meibomian blockade.[5] In that situationepithelial cysts are observed in the exposed region of the cornea, together with punctate erosions and punctate epithelial keratopathy. In our patients, due to lack of normal meibomian glands secresions, conjunctival injection, altered tear film and punctuate epithelial erosions were seen (Fig 3). Our cases showed absence of meibomian glands in both lids of both eyes, but they were otherwise healthy with difficulty in swelling.

Preservative-free artificial tears (Artelac®, Bausch and Lomb Company, Rochester, NY) was prescribed every 6 hours as well as eye gel (Liposic® Ophtalmic Liquid Gel) before sleep for both patients.

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