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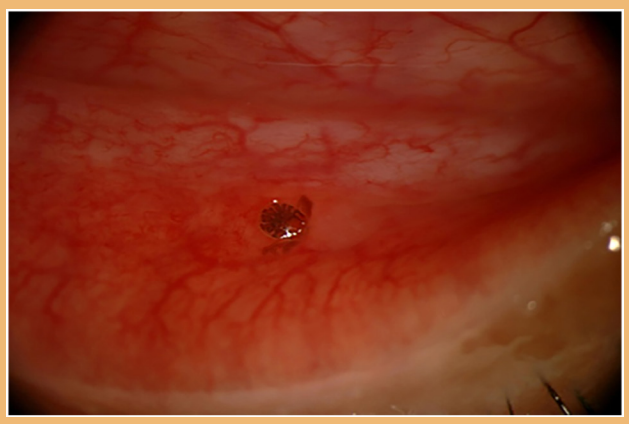
Original Articles

Case Reports



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จักษุเวชสาร
The Thai Journal of **Ophthalmology**

คณะกรรมการบริหารราชวิทยาลัยจักษุแพทย์แห่งประเทศไทย

วาระปี 2564 – 2565

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The Thai Journal of Ophthalmology

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จักษุเวชสาร
The Thai Journal of **Ophthalmology**

จักษุเวชสาร เป็นวารสารของราชวิทยาลัยจักษุแพทย์แห่งประเทศไทย และสมาคมจักษุแพทย์แห่งประเทศไทย

จักษุเวชสาร เป็นวารสารที่มีการทบทวนโดยผู้รู้เสมอกัน (Peer-review) เผยแพร่แบบฉบับตีพิมพ์ (ISSN 0875-5118) และแบบออนไลน์ (ISSN 2697-6005) จัดทำปีละสองฉบับ มีวัตถุประสงค์เพื่อให้ความรู้ในสาขาจักษุวิทยาที่ทันสมัย สนับสนุนการเรียนรู้ต่อเนื่องทางการแพทย์ เอื้อให้เกิดความร่วมมือ และแลกเปลี่ยนทัศนะในหมู่สมาชิกราชวิทยาลัยและผู้อ่าน

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จักษุเวชสาร
The Thai Journal of Ophthalmology

The Journal of the Royal College of Ophthalmologists and Ophthaomological Society of Thailand

The Thai Journal of Ophthalmology (TJO) is a peer-reviewed journal, and is published as printed (ISSN 0875-5118) and online journal (ISSN 2697-6005). The TJO is published biannually, and serves the objectives of providing up to date knowledge in the field of Ophthalmology, supports continuing education, promotes cooperation and sharing of opinion among readers.

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Guides for Authors

A. Basic Information

The Thai Journal of Ophthalmology (TJO) is a peer-reviewed, scientific journal published biannually for the Royal College of Ophthalmologists of Thailand and the Ophthalmological Society of Thailand. The objectives of the journal is to provide up to date scientific knowledge in the field of ophthalmology, provide ophthalmologists with continuing education, promote cooperation, and sharing of opinion among readers.

The copyright of the published article belongs to the Thai Journal of Ophthalmology. However the content, ideas and the opinions in the article are from the author(s). The editorial board does not have to agree with the authors' ideas and opinions.

The authors or readers may contact the editorial board via email at admin@rcopt.org.

At present, the TJO has evolved into the online journal platform to enhance the efficiency, transparency and of the fairness of the article selection, review and selection. This will improve the quality of the journal to be eligible for the Thai Journal Citation Index. The other benefit of the online journal platform is the articles can reach broader readers.

Authors may submit articles through the Royal College of Ophthalmologists of Thailand's website (http://www.rcopt.org/. After clicking "Article Submission" ("ส่งบทความวิชาการตีพิมพ์") the authors may go through the submission processes. Authors who encounter problems during article submission can contact staffs by email. (http://www.rcopt.org/)

B. Types of articles

The TJO publishes Original Articles (นิพนธ์ต้นฉบับ), Case Reports (รายงานผู้ป่วย), Reviews (บทความฟื้นฟูวิชาการ), Correspondence (จดหมายถึงบรรณาธิการ), Perspectives and Editorials (บทบรรณาธิการ). Articles submitted for publication should be original, with the understanding that they have not been and will not be published elsewhere. Authors may be requested to provide the data upon which the manuscript is based and answer any question about the manuscript during the peer review process.

Original Articles (นิพนธ์ต้นฉบับ)

Original articles are previously unpublished manuscripts to provide up to date information

to ophthalmic society. They include clinical trials, diagnostic tests, clinically relevant laboratory investigations, other clinical researches, public health or other related basic science researches.

Case Reports (รายงานผู้ป่วย)

Case reports are articles that describe clinical case(s) with unusual presentation, clinical course, and response to management. This includes new modality of management, surgical techniques etc.

Reviews (บทความฟื้นฟูวิชาการ)

TJO welcomes authors to submit high quality reviews, systematic reviews, or meta-analysis to provide up to date knowledge for the readers.

Correspondence

Letters about recent articles published in the TJO are encouraged to provide different viewpoint and discussion on the subjects.

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Perspectives and Editorials are focused opinion on any issues related to ophthalmology, or analytic, interpretative opinion upon the submitted manuscript. These are intended to provide analytical opinion and stimulate discussion among the readers.

C. Manuscript Preparation

It is advised that the manuscript be prepared using Microsoft Word (Version 2013 or later). The manuscript is prepared for A4 paper, using font "Th SarabunPSK", font size 14 for Thai language; and font "Times New Roman" font size 12 for English language. The paragraph line spacing should be set as single. The figure should be saved separately in high resolution in either TIFF, PNG or JPEG format.

Component of the manuscript are as followings:

1. Cover letter

The cover letter should include the information of the article that the authors would like to convey to the editor. The principal investigator or corresponding author for the article containing original data should confirm in the cover letter that he or she "had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis as well as the decision to submit for publication."

2. Title page

The title of a manuscript should be as concise and clear as possible. The title page must include:

2.1 Title in English (no more than 140 characters)

2.2 Title in Thai (no more than 200 characters)

2.3 Authors' full name, address, and institutional affiliation (in Thai and English). All authors should provide the financial disclosure.

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- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

2.4 The name, address, phone number, fax number, and e-mail address of the Corresponding Author. The Corresponding Author will be responsible for all questions about the manuscript and for reprint requests. Only one author can be designated as Corresponding Author.

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All authors must declare about financial interests in any products mentioned.

Note: Number the pages of the manuscript consecutively, beginning with the Title Page as page 1.

3. Abstract

3.1 Abstract (in English), should not exceed 250 words. If possible, the abstract should be written as structured abstract, which includes: objectives or purpose, methods, main outcome measures, results and conclusions.

3.2 Abstract (in Thai), should not exceed 300 words.

3.3 Key words. The authors may provide 3-6 key words.

4. The article should compose of several sections as necessary. For the original article, the sections should be: introduction, materials and methods, results, discussion and acknowledge.

5. Tables

Each table should be in separate page.

6. Figures

Figures and legends should be separated from the article text. The figures should be saved in TIFF, JPEG, or PNG format. The required minimum resolution for publication is ≥ 350 ppi.

7. References.

The authors should write the references according to the AMA Manual of Style, A Guide for

Authors and Editors, Tenth Edition, ISBN 0-978-0-19-517633-9.

The authors should list up to 3 authors. If there are more than 3 authors, list only 3 authors and followed by et al.

Example of reference writing:

Reference to a journal publication:

1. Wong CW, Yanagi Y, Lee WK, et al. Age-related macular degeneration and polypoidal choroidal vasculopathy in Asians. Prog Retin Eye Res. 2016;53:107-139.

Reference to a chapter in an edited book:

2. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, eds. Introduction to the Electronic Age. New York, NY: E-Publishing Inc; 2009:281-304.

Reference to a website:

3. National Health Service (NHS) Diabetic Eye Screening Programme and Population Screening Programmes. Diabetic eye screening: commission and provide. https://www.gov.uk/government/collections/diabetic-eye-screening-commission-and-provide. 2015. Accessed September 24, 2017.

D. Editorial Policies for Authors

The authors are responsible to provide the most accurate information and logical interpretation of data. The opinions presented in the article are the authors' opinion. The editorial board may or may not agree with the published opinion.

All authors are required to report potential conflicts of interest related to the article.

For all manuscripts reporting data from studies involving human participants or animals, formal review and approval, or formal review and waiver, by an appropriate institutional review board or ethics committee is required and should be described in the Methods section.

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All submitted manuscripts are reviewed initially by one of the editors. Manuscripts are evaluated according to the following criteria: material is original and timely, writing is clear, study methods are appropriate, data are valid, conclusions are reasonable and supported by the data, information is important, and topic has general interest to readers of this journal. From these basic criteria, the editors assess a paper's eligibility for publication. Manuscripts with insufficient priority for publication are rejected promptly. Other manuscripts are sent to expert consultants for peer review. Authors' identification are made unknown to the reviewers. Final decision are made by editor in chief.

Authors may appeal decisions. All appeals are reviewed by the editor in chief

จักษุเวชสาร
The Thai Journal of Ophthalmology

บรรณาธิการแถลง

สังคมไทยเราปรับตัวกับสถานการณ์โควิด19 ได้ดี เราค่อย ๆ ปรับตัวเข้าสู่ “สภาวะปกติใหม่” (new normal) แม้ว่าโรคจะไม่หมดไป แต่เราก็ปรับตัวใช้ชีวิตอยู่กันได้ การประชุมวิชาการของราชวิทยาลัยจักษุแพทย์แห่งประเทศไทยในกลางปีนี้ก็คงจะจัดประชุมในสถานที่ได้ ดังนั้นนอกจากจะให้ข้อมูลความรู้ทางวิชาการแล้ว สมาชิกยังได้มาพบหน้าค่าตากัน เป็นการเชื่อมโยงความสัมพันธ์ซึ่งกันและกันระหว่างหมู่สมาชิก

จักษุเวชสารฉบับนี้ มีบทความที่น่าสนใจอยู่เช่นเคย มีการศึกษาการใช้ขมิ้นชันเพื่อรักษาโรค Leber Hereditary Optic Neuropathy (LHON) ซึ่งแม้ว่าในการศึกษานี้ยังไม่พบผลการรักษาที่ชัดเจนนัก แต่นับเป็นการเริ่มต้นศึกษาสมุนไพรต่าง ๆ ที่ใช้กันในประเทศไทยว่ามีฤทธิ์ในทางยามากน้อยเพียงใด มีการศึกษาผลการใช้ลูกตาเทียมชนิดที่มีรูพรุนที่ทำจากเครื่องพิมพ์สามมิติ นำมาใช้ในการผ่าตัดเอาตาออก ซึ่งพบว่ามีความปลอดภัยดี การศึกษาภาวะสายตาเอียงในผู้ป่วยที่ผ่าตัดแก้ไขภาวะหนังตาตาตั้งแต่กำเนิด พบว่าผู้ป่วยมีสายตาเอียงลดลงหลังการผ่าตัด นอกจากนี้เรายังมีรายงานผู้ป่วยที่น่าสนใจ โดยเฉพาะผู้ป่วยชายอายุ 39 ปี ที่การมองเห็นลดลงหลังฉีดโควิดวัคซีนไปสามวัน สมาชิกน่าจะไปอ่านรายละเอียดว่าเกิดจากอะไร และสภาวะโรคคลี่คลายไปอย่างไร

ขอเชิญชวนให้สมาชิกส่งบทความมาตีพิมพ์เพิ่มขึ้น เพื่อเป็นการเผยแพร่ความรู้และประสบการณ์ต่าง ๆ ในหมู่สมาชิก และพัฒนาวิชาการด้านจักษุวิทยาของเราให้ก้าวหน้ามากขึ้น

กองบรรณาธิการ

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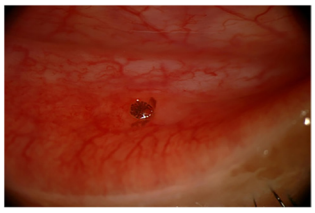
สารบัญ



ภาพปก A 100X magnification image shows a rounded body, six-legged insect-like organism with its head burrowed under the lower palpebral conjunctiva.

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The Thai Journal of **Ophthalmology**

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รายงานผู้ป่วย

จักษุเวชสาร
The Thai Journal of Ophthalmology

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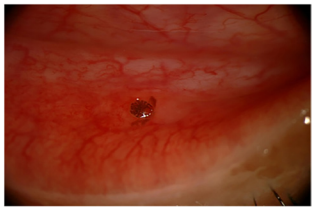
Contents



ภาพปก A 100X magnification image shows a rounded body, six-legged insect-like organism with its head burrowed under the lower palpebral conjunctiva.

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Original Article/นิพนธ์ต้นฉบับ

A Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Curcuminoids in Leber Hereditary Optic Neuropathy

การศึกษาโดยการสุ่มตัวอย่างเพื่อเปรียบเทียบการรักษาโรค Leber Hereditary Optic Neuropathy (LHON) ด้วยขมิ้นชันและยาหลอก

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Abstract

Purpose: To investigate the role of curcuminoids, an antioxidant property, in vision and blood oxidative status in G11778A Leber hereditary optic neuropathy (LHON) patients.

Methods: A total of 49 G11778A LHON patients (97 eyes) were randomly assigned to receive either 250 mg of oral curcuminoids capsules (500 mg/day) or placebo capsules twice a day for 48 weeks. The visual parameters including visual acuity, Humphrey visual field, visual evoked potential and electroretinogram were assessed at 0, 12, 24, 36 and 48 weeks after the intervention. The marker for oxidative stress, malondialdehyde (MDA) in plasma, and endogenous antioxidants in erythrocytes comprising superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px) and total glutathione (GSH) were measured at 0, 12, 24, and 48 weeks. Adverse events were recorded.

Results: Twenty-seven (53 eyes) and 22 (44 eyes) patients were randomized to the curcuminoids and placebo groups, respectively. The two groups were comparable in age of onset, baseline VA and duration of LHON. There were no significant changes in any visual or oxidative parameters between the two groups. There seemed to be slight improvement of the mean deviation of HVF from baseline at week 36 and 48 (P = 0.027), which was statistically significant in the curcuminoids group but not in the placebo groups. A trend of reduction of erythrocyte GSH-Px, indicating improvement of oxidative status, was observed in curcuminoids but not in the placebo group. No significant difference of adverse events between both groups was found.

Conclusions: Curcuminoids at this dose did not have significant effects on the visual and blood oxidative status compared to the placebo. However, the slight improvement of HVF-MD, a trend of reduction of GSH-Px in the curcuminoids group and the safety of curcuminoids suggested that further studies with higher doses and especially in the acute stage of LHON should be considered.

Key words: Leber hereditary optic neuropathy (LHON), 11778 mutation, curcuminoids

บทคัดย่อ:

วัตถุประสงค์: เพื่อศึกษาการใช้ขมิ้นชันซึ่งมีคุณสมบัติต้านอนุมูลอิสระในการรักษาโรค Leber Hereditary Optic Neuropathy (LHON) ที่มีการกลายพันธุ์ของยีนไมโตคอนเดรียที่ตำแหน่ง G11778A เปรียบเทียบกับการใช้ยาหลอก โดยการวัดผลระดับสายตาและสารอนุมูลอิสระในกระแสเลือด

วัสดุและวิธีการ: ทำการศึกษาโดยการสุ่มตัวอย่างในผู้ป่วยโรค Leber Hereditary Optic Neuropathy (LHON) ที่มีการกลายพันธุ์ของยีนไมโตคอนเดรียที่ตำแหน่ง G11778A จำนวน 49 คน (97 ตา) แบ่งออกเป็น 2 กลุ่ม กลุ่มแรกได้รับขมิ้นชันชนิดแคปซูล รับประทานขนาด 500 มิลลิกรัมต่อวัน กลุ่มที่สองได้รับยาหลอก เป็นเวลา 48 สัปดาห์ติดต่อกันและวัดระดับสายตา ลานสายตา ชนิด Humphrey ตรวจประสาทตาและจอประสาทตาด้วยคลื่นไฟฟ้า ก่อนและหลังเริ่มให้ยา ในสัปดาห์ที่ 12, 24, 36 และ 48 สัปดาห์ในกลุ่มที่ 1 และ 2 ตรวจวัดระดับ oxidative stress ได้แก่ ระดับ malondialdehyde (MDA) ในพลาสมา ระดับ superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px) and total glutathione (GSH) เม็ดเลือดแดง ที่สัปดาห์ที่ 0, 12, 24 และ 48 บันทึกอาการข้างเคียงที่เกิดขึ้นหลังการให้ยา

ผลการศึกษา: จากการสุ่มตัวอย่าง มีผู้ป่วยจำนวน 27 คน (53 ตา) ได้รับขมิ้นชัน และ 22 คน (44 ตา) ได้รับยาหลอก ทำการศึกษาเปรียบเทียบ อายุที่เริ่มมีอาการ ระดับสายตาและระยะเวลาที่มีอาการโรค LHON ไม่พบความแตกต่างของระดับสายตาและสารอนุมูลอิสระ ในกลุ่มที่ศึกษาทั้ง 2 กลุ่ม ในกลุ่มขมิ้นชัน พบค่าลานสายตาที่สัปดาห์ที่ 36 และ 48 ดีขึ้นอย่างมีนัยยะสำคัญ (P = 0.027) ค่า GSH-Px ที่ลดลงแสดงถึงค่า oxidative status ดีขึ้นในกลุ่มขมิ้นชัน ไม่พบอาการแทรกซ้อนในกลุ่มการศึกษาทั้ง 2 กลุ่ม

สรุป: ผลการใช้ขมิ้นชันไม่มีผลต่อระดับสายตา และ ค่า oxidative status ในเลือด ในกลุ่มขมิ้นชัน พบค่าลานสายตาที่ดีขึ้นอย่างมีนัยสำคัญทางสถิติ GSH-Px ที่ลดลงแสดงถึงค่า oxidative status ดีขึ้นในกลุ่มขมิ้นชัน ตลอดจนเกิดความปลอดภัยจึงควรมีการศึกษาการใช้ขมิ้นชันขนาดสูงในการรักษาโรคดังกล่าวต่อไป

Introduction

Leber Hereditary Optic Neuropathy (LHON) is the most common mitochondrial genetic disease characterized by acute to subacute, nonsynchronous bilateral, painless visual loss, predominantly in young adult males.[1] The clinical findings in LHON can be divided into acute and chronic phases. In the acute phase, patients experience blurring of central vision with severe dyschromatopsia. Visual field demonstrates central or caecocentral scotoma.

The fundal appearances typically include optic disc hyperemia and swelling and microangiopathy and the optic disc becoming pale in chronic phase.[2] Visual acuity often drops to less than 6/60 in a few weeks after the onset.[1]

Visual evoked potential (VEP) shows decreased amplitude and delayed latency, while electroretinogram (ERG) is generally normal.[2,3] In LHON, an initial increase and a subsequent decrease in peripapillary retinal nerve fibre layer (pRNFL) thickness were demonstrated on spectral-domain optical coherence tomography (SD-OCT).[4,5]

Curcuminoids is a group of phenolic compounds in which curcumin is the most abundant. It has been shown to possess antioxidant properties and its efficacy has been demonstrated in many free-radical related neurodegenerative diseases.[6] Oral curcumin administration has been shown to improve oxidative stress and antioxidant parameters in serum of chronic pancreatitis and β-thalassemia/Hb E patients.[7] Curcumin was shown to directly react with reactive oxygen species (ROS).[8] Moreover, it has been shown to induce expression of cytoprotective and antioxidant proteins which improved mitochondrial function.[9]

All of the three most common primary LHON mitochondrial DNA (mtDNA) mutations have been shown to impair the biochemical function of the respiratory complex I subunit gene. leading to increased ROS production and oxidative stress during electron transport, and resulting in retinal ganglion cell loss in LHON.[10] As oxidative stress has a leading role in the pathophysiology of LHON, treatments targeted to scavenge ROS would be promising. The previous prospective randomized study by Catarino et al., 2017 suggested the benefit of Idebenone, a short-chain coenzyme Q10 analogue which is an antioxidant, or gene therapy with intravitreal injection of rAAV2/2-ND4 for visual recovery or minimizing severity of LHON.[11-13] Curcumin is another promising antioxidant and was shown to be beneficial in neurodegeneration. Therefore, this study was carried out to determine the effectiveness of curcumin on visual symptoms, electrophysiologic findings and blood oxidative stress and antioxidant parameters in G11778A LHON patients.

Patients and Methods

This was a placebo-controlled, double-blind, randomized trial. The study population consisted of all LHON patients with G11778A mutation from the Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University. The patients were contacted in person or by phone by a neuroophthalmologist (WC). Exclusion criteria included LHON patients with other primary LHON mutation (T14484C or G3460A), pregnant women, patients with known severe systemic underlying diseases, and patients not being able to come for follow-ups. The study protocol was approved by the Siriraj Institutional Review Board (SIRB) and was

registered in clinicalTrials.gov/ NCT00528151. All the participants entered the study with informed consents.

Eligible patients were allocated to either the experimental or placebo group by unpaired random allocation and blinding with proper allocation concealment. After one-month discontinuation of medications which involved optic nerve function including coenzyme Q10, vitamin B, vitamin C, vitamin E and steroids, the subjects received 2 capsules of either curcuminoids or a placebo daily for 12 months. Each capsule was filled with turmeric extract (calculated for 250 mg of curcuminoids, which comprised curcumin, demethoxycurcumin and bismethoxycurcumin in the ratio of 1:0.3:0.1.) and quality controlled under the Good Manufacturing Practices for pharmaceutical products. The amount of curcuminoids in the capsules was tested by the GPO one year after the production and was found to be stable.

Main Outcome Measures

Baseline parameters included visual acuity (VA) by Snellen charts, mean deviation (MD) and pattern standard deviation (PSD) of Humphrey automated visual field (HVF), P100 latency and N75-P100 amplitude in flash VEP, mesopic ERG, blood oxidative stress and antioxidant. The Snellen's VA was expressed as logMAR (logarithm of the minimal angle of resolution). The HVF was performed using Swedish Interactive Threshold Algorithm (SITA) Standard 30-2. The ERG and VEP were performed using Viking Select Master Software V7.1 according to the International Society for Clinical Electrophysiology of Vision (ISCEV). Complete blood count (CBC), liver function, renal function tests and urinalyses were performed to monitor safety. The oxidative stress indicator, malondialdehyde (MDA), was measured in plasma and the antioxidant parameters comprising superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px) and total glutathione (GSH) were measured in red blood cells.

The same examinations and measurements as those at baseline were performed at the 12th, 24th, 36th, and 48th week visit, except for the 36th week visit, in which the oxidative stress and antioxidant parameters were not measured.

Malondialdehyde (MDA)

MDA, a product of lipid peroxidation, was measured in plasma by the method of Asakawa and Matsushita by reacting with thiobarbituric acid in acidic and boiling temperature.[14] After cooling, butanol was added and the fluorescence of the butanol extracts was measured by spectrofluorometer at 515 nm excitation and 553 nm emission.

Superoxide dismutase (SOD)

SOD activity was determined in hemolysate by a modified method based on the ability of SOD to inhibit the reduction of nitroblue tetrazolium (NBT) by superoxide anions generated by xanthine and xanthine oxidase reaction.[15]

Catalase

Catalase activity was determined by a spectrophotometric assay based on the catalytic decomposition of hydrogen peroxide.[16]

Glutathione peroxidase (GSH-Px)[17]

Briefly, the hemolysate was added into 5 mM EDTA sodium salt, 0.1 M GSH and 10 unit/ml

glutathione reductase in Tris-HCl buffer pH 8.0. The enzymatic reaction was started with 7 mM cumene hydroperoxide which served as a peroxide substrate. The rate of decrease of the absorbance at 340 nm measured by a spectrophotometer was directly indicative of GSH-Px activity.

Total glutathione (GSH)

GSH was measured by a modified method based on the GSH recycling method. GSH reacted with 5, 5'-dithiobis-(2-nitrobenzoic acid) (DTNB) to form a yellow color and was measured by a spectrophotometer.

Statistical analysis

An intention-to-treat analysis was performed including all 49 randomized patients analyzed according to group assignment. Missing data were handled using the Last Observation Carried Forward (LOCF) method, in which the last available follow-up data were used in place of the missing data.[18] For visual parameters (VA, HVF, VEP and ERG) all the examined eyes (97 eyes) were included.

Comparisons of continuous data between the curcuminoids and placebo groups were performed using two-way repeated measures ANOVA. For comparison of duration of LHON between the two groups, the Mann-Whitney U test was employed since the data were not normally distributed. Percentage changes in parameters at each visit from baseline values were calculated and compared between the two groups. Within group changes from baseline values of continuous parameters in each visit were tested using one-way repeated measures ANOVA with Bonferroni adjustment. For comparisons of nominal data, Chi-square test was used. $P < 0.05$ was considered significant. Statistical calculations were performed with SPSS for Windows 15 (SPSS Inc, Chicago, IL).

Results

Samples

Eighty-seven patients were assessed during May 2005 to December 2007 for eligibility, (Figure 1). Baseline characteristics between the curcuminoids and placebo groups were comparable (Table 1).

Visual parameters

There were no statistical differences in VA, MD, PSD, ERG amplitude, VEP amplitude and VEP latency between the curcuminoids and placebo groups at baseline and each follow-up visit. The means of percentage change from baseline of each parameter are shown in Table 2. No statistically significant differences in the means of percentage change from baseline of any parameters between the two groups were observed at any follow-up visit.

At 48th week visit, of 53 patients, 12 patients in curcuminoids group and of 44 patients, 12 patients in placebo group had improvement of VA. The proportions of eyes with VA improvement of ≥ 0.2 logMAR were similar between the two groups (P = 0.60, Chi-square test) with the overall frequency of VA improvement at 23.7%. However, in each group, when each follow-up value of the visual parameters was compared to the corresponding baseline value, there were some significant changes in the visual field. The results showed that there was subtle but statistically significant improvement of MD at week 36th (P = 0.027) and 48th week (P = 0.027) in the curcuminoids group, while the values were not significant in the placebo group. The PSD increased significantly at

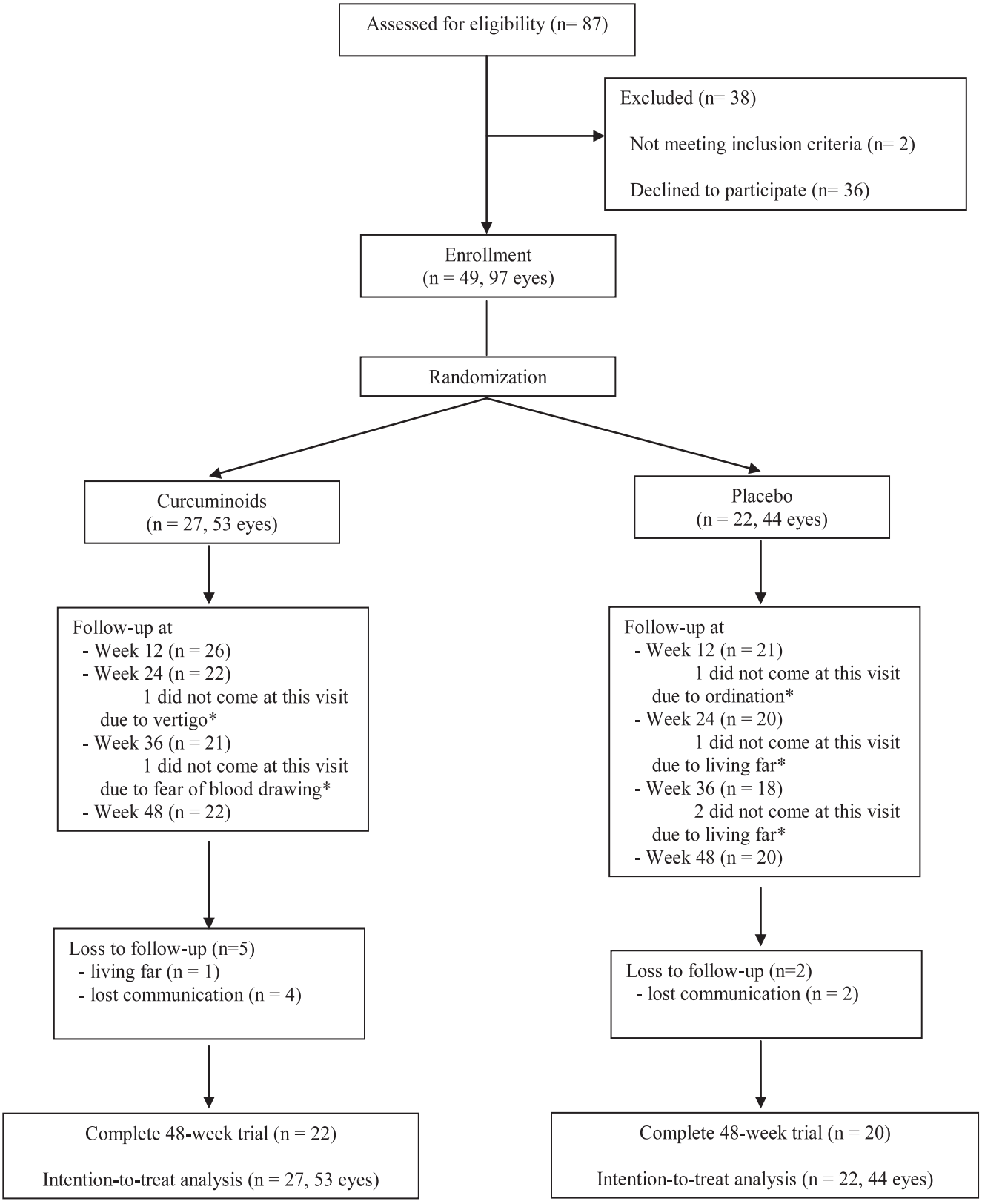

Figure 1 Flow of enrollment and follow-up of participants in the study. *, the trial medications were sent to the subjects by mail.

Table 1 Characteristics of the G11778A LHON patients in the study

Characteristics	Curcuminoids	Placebo	*P*-value
No. of cases	27	22	
No. of eyes	53	44	
Sex			0.97
Male (%)	23 (85)	19 (86)	
Female (%)	4 (15)	3 (14)	
Age (years)			0.88
Mean	32.0	31.4	
SD	14.1	12.9	
Median	27	28.5	
Range	12-67	14-62	
Age of onset (years)			0.55
Mean	22	23.7	
SD	9	10.4	
Median	20	20	
Range	16-44	7-53	
VA at baseline (logMAR)			0.99
Mean	1.85	1.86	
SD	0.76	0.52	
Duration of LHON (months)			0.37
Mean	106.7	87.6	
SD	130.8	105.8	
Median	66	46	
Range	4-475	2-370	

week 36th (P = 0.011) and 48th week (P = 0.021) in the curcuminoids group but not in the placebo group (Figure 2). The median duration of LHON before treatment in eyes that showed improvement of MD was 65 months (range 5-378 months, n = 27) and 76 months (range 2-348 months, n = 31) in the curcuminoids and placebo groups, respectively. The difference was not statistically significant (P = 0.69, Mann-Whitney test). Therefore, it was unlikely that the significant improvement of MD in the curcuminoids group was largely explained by spontaneous visual recovery seen in patients with more recent onset.

Oxidative stress and antioxidant parameters

The oxidative stress parameter, plasma MDA, and antioxidant parameters in red blood cells comprising SOD, catalase, GSH-Px and GSH, were measured before and at 12th, 24th and 48th week after treatment. The effects of curcuminoids on these parameters were not statistically different compared with the placebo (Table 3).

The levels of MDA, SOD, catalase and GSH changed in a similar fashion over time comparing between the two groups but this was not the case for GSH-Px (Figure 2). It was found that GSH-Px showed

Table 2 Means of percentage changes from baseline of each visual parameter between curcuminoids and placebo group at each follow-up visit

Parameters	Week	Mean of % change from baseline			*P*-values
		Curcuminoids	Placebo	Difference (95% CI)	
LogMAR					
	12th	-0.97	3.07	-4.04 (-10.44, 2.36)	0.21
	24th	0.02	3.12	-3.11 (-10.56, 4.34)	0.41
	36th	-4.33	-1.88	-2.45 (-11.63, 6.72)	0.60
	48th	-1.95	-3.03	1.09 (-6.86, 9.03)	0.79
HVF MD (dB)					
	12th	1.58	8.62	-7.04 (-21.00, 6.92)	0.32
	24th	0.05	1.84	-1.79 (-15.55, 11.97)	0.80
	36th	-3.98	1.02	-5.00 (-20.75, 10.75)	0.53
	48th	-3.97	1.66	-5.63 (-20.41, 9.15)	0.45
HVF PSD (dB)					
	12th	5.52	8.39	-2.86 (-14.90, 9.17)	0.64
	24th	7.34	7.78	-0.44 (-13.64, 12.77)	0.95
	36th	15.00	21.66	-6.66 (-22.26, 8.94)	0.40
	48th	14.08	21.77	-7.69 (-21.95, 6.58)	0.29
Flash VEP amplitude (μV)					
	12th	17.56	20.55	-2.99 (-20.34, 14.35)	0.73
	24th	20.75	20.32	0.42 (-17.33, 18.17)	0.96
	36th	25.80	31.55	-5.76 (-30.03, 18.52)	0.64
	48th	30.06	32.12	-2.06 (-31.28, 27.17)	0.89
Flash VEP latency (ms)					
	12th	2.16	-1.01	3.17 (-2.96, 9.30)	0.31
	24th	1.24	-1.51	2.75 (-2.12, 7.62)	0.26
	36th	0.63	1.29	-0.66 (-6.25, 4.92)	0.81
	48th	1.56	1.51	0.05 (-5.73, 5.84)	0.99
Mesopic ERG b-wave amplitude (μV)					
	12th	5.35	1.71	3.64 (-9.19, 16.47)	0.57
	24th	4.53	6.78	-2.25 (-14.57, 10.06)	0.72
	36th	8.44	4.36	4.08 (-19.74, 27.90)	0.73
	48th	9.23	5.44	3.79 (-12.06, 19.63)	0.64

LogMAR, logarithm of the marginal angle of resolution; ERG, electroretinogram; HVF, Humphrey visual field; MD, mean deviation; PSD, pattern standard deviation; VEP, visual evoked potential

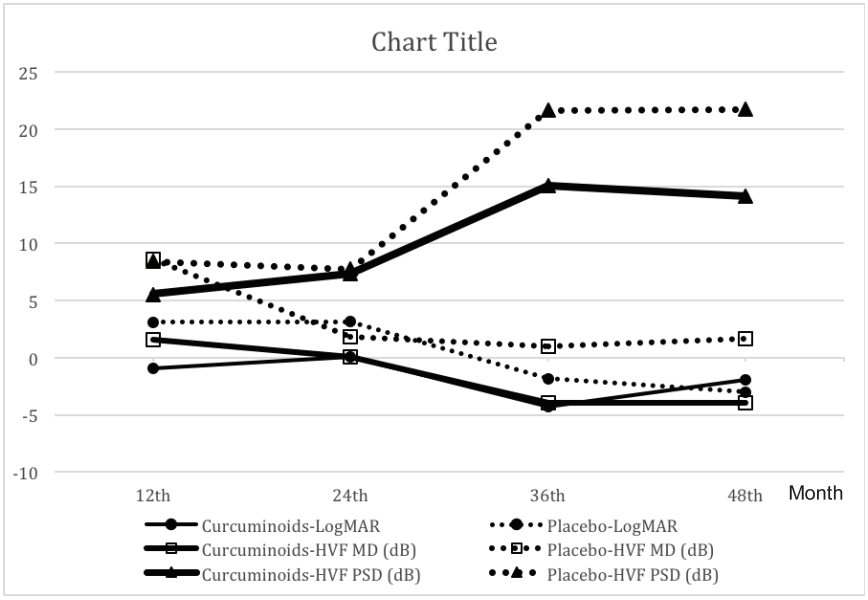

Figure 2 Shows visual acuity, visual field mean deviation (MD) and pattern standard deviation (PSD) overtime in the curcuminoids and the placebo groups. The proportions of eyes with visual acuity improvement of ≥ 0.2 logMAR were similar in the curcuminoids and the placebo groups. There was subtle but statistically significant improvement of MD and the PSD increased significantly in the curcuminoids group but not in the placebo group.

Table 3 Means of percentage changes from baseline of each oxidative stress and antioxidant parameters in blood between curcuminoids and placebo group at each follow-up visit

Parameters	Week	Mean of % change from baseline			*P*-values
		Curcuminoids	Placebo	Difference (95% CI)	
MDA (nmole/mL)					
	12th	2.91	8.69	-5.78 (-20.50, 8.93)	0.43
	24th	13.68	17.99	-4.31 (-23.91, 15.29)	0.66
	48th	23.74	27.92	-4.18 (-26.27, 17.90)	0.70
SOD (U/g Hb)					
	12th	-12.38	-11.35	-1.03 (-16.47, 14.42)	0.89
	24th	-2.37	-5.95	3.58 (-12.84, 19.99)	0.66
	48th	0.54	-0.12	0.66 (-21.81, 23.12)	0.95
Catalase (kU/g Hb)					
	12th	14.70	5.74	8.96 (-4.93, 22.86)	0.20
	24th	19.78	19.00	0.78 (-18.93, 20.49)	0.94
	48th	19.58	15.69	3.89 (-13.39, 21.17)	0.65
GSH-Px (U/L)					
	12th	-13.76	-0.41	-13.34 (-34.38, 7.70)	0.21
	24th	-8.23	14.46	-22.69 (-50.12, 4.75)	0.10
	48th	-10.93	4.27	-15.20 (-39.03, 8.62)	0.21
GSH (µmole/ g Hb)					
	12th	28.30	26.30	2.00 (-20.14, 24.14)	0.86
	24th	21.50	20.68	0.82 (-16.56, 18.19)	0.93
	48th	17.85	10.83	7.02 (-6.18, 20.22)	0.29

MDA , malondialdehyde; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; GSH, glutathione; Hb, hemoglobin

a trend of declination over time in the curcuminoids group but not in the placebo group (Figure 3). The decreased was almost significant at 12th week (P = 0.069).

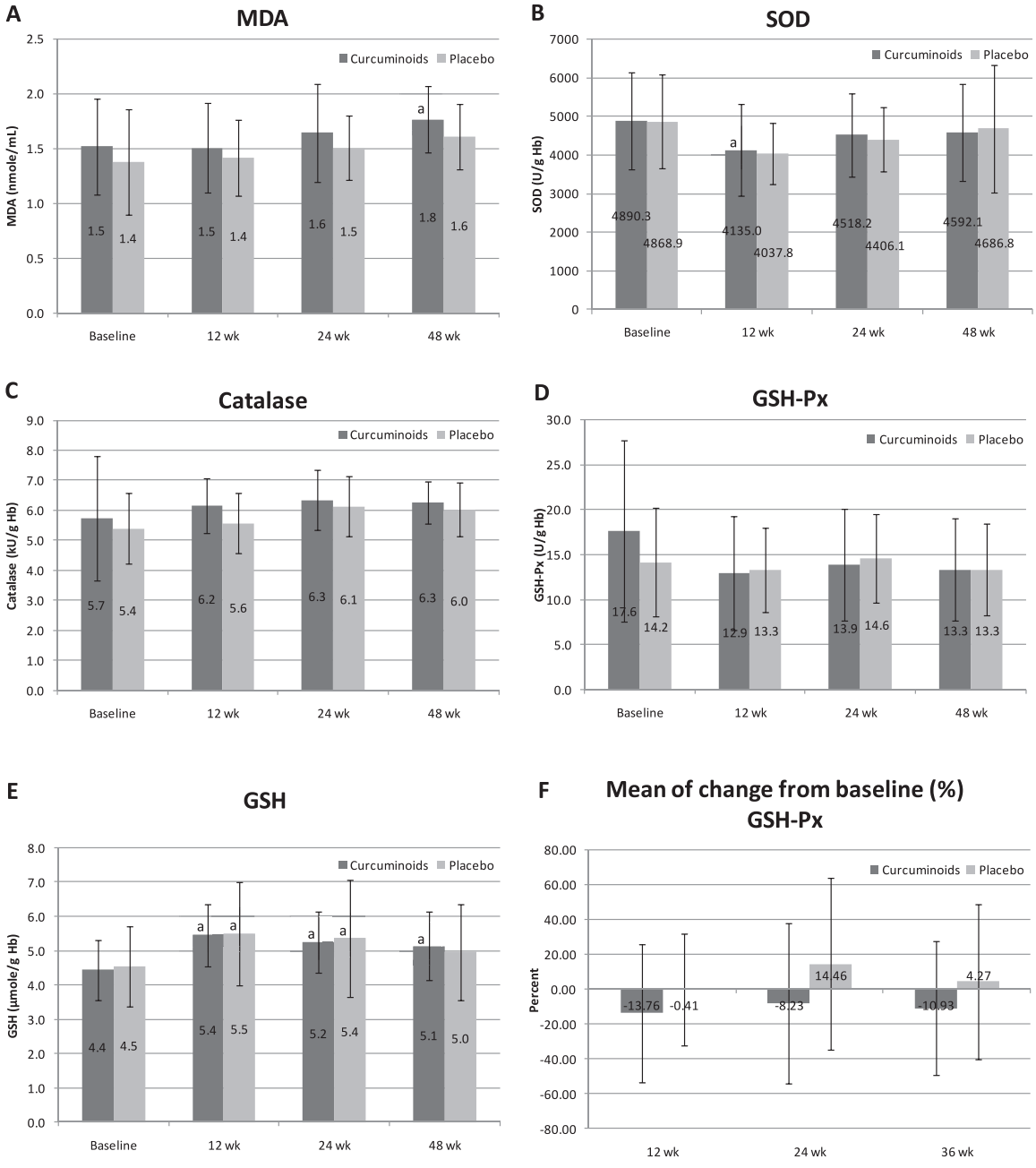

Figure 3 Bar charts showing oxidative stress and antioxidant parameters in blood of the patients in curcuminoids (n = 27) and placebo group (n = 22) at each visit. Each bar represents a mean with a standard deviation as shown by an error bar. Malondialdehyde (MDA) (A) was measured in plasma. Superoxide dismutase (SOD) (B), catalase (C), glutathione peroxidase (GSH-Px) (D) and glutathione (GSH) (E) were measured in hemolysate. The effects of curcuminoids on these parameters were not statistically different compared with the placebo. GSH-Px reduced from baseline level in the curcuminoids group but not in the placebo group (F). Hb, hemoglobin; a, statistically significant compared to baseline, using one-way repeated measures ANOVA with Bonferroni adjustment.

Compliance

Among 42 patients who completed the follow-up visit at 48th week, 22 were in the curcuminoids group and 20 were in the placebo group. All 22 patients in the curcuminoids group had more than 85% compliance to the trial medication and 77% (17/22) showed more than 95% compliance (range 87.5%–100%). In the placebo group, all 20 except 2 patients had more than 93% compliance (range 71%-100%).

Adverse effects

Dizziness, dyspepsia, diarrhea, constipation, thirst and increased appetite were reported by some subjects. There were no statistical differences in any blood parameters between the curcuminoids and placebo groups at any follow-up visits.

Discussion

Growing amount of experimental evidence revealed that increased ROS production and oxidative stress involved in the pathophysiology of LHON, secondary from the oxidative phosphorylation defect caused by the primary LHON mutation in the respiratory complex I subunit gene.[19] Thus, this study described, for the first time, the role of curcuminoids, whose antioxidant property is well-known, in LHON patients with the G11778A mutation.

This study did not find a significant effect of curcuminoids on the clinical parameters including VA, VF, VEP and ERG in G11778A LHON patients as compared with the placebo (Table 2). Similar proportions of patients in the curcuminoids and the placebo groups demonstrated some degrees of VA improvement. The overall proportion of the patients with visual improvement was 23.7%, which was in accordance with Spruijt et al., reporting 22% of G11778A LHON patients showing partial recovery of vision, and the prospective randomized study indicating the benefit of Idebenone, an antioxidant, in visual recovery[11,20] Interestingly, HVF analysis revealed a slight improvement of MD from baseline and the difference became statistically significant at 36th and 48th week in the curcuminoids group. Although there were some limitations in the HVF we performed due to the poor vision of the patients, the confirmatory fields were undertaken to minimize the variability in measuring visual function. The improvement of MD was also observed in the placebo group but it did not reach the statistically significant level. Conversely, PSD gradually increased from the baseline level and the difference became statistically significant at 36th and 48th week in the curcuminoids group, corresponding to the decrease of MD. This finding may reflect the fenestration of central scotoma, the pattern of visual recovery previously reported in LHON and curcuminoids may potentiate this improvement of vision.[11]

Oxidative status in LHON patients was investigated in blood. MDA is an indicator of oxidative stress since it is generated following oxidation of polyunsaturated fatty acids.

The results showed that curcumin did not have significant effect on plasma MDA compared to placebo. Alizadeh et al demonstrated that curcumin could be effective in reducing MDA levels but not found in our study.[21]

This was also not in agreement with a previous study in β-thalassemia/Hb E patients which showed a decrease in red blood cell MDA in the patients after treatment with 500 mg curcuminoids daily for 12

months (the same dose used in this study).[6] This might be explained by differences in the mechanism of ROS generation in thalassemia and LHON. In thalassemia, one of the major factors contributing to free radicals generation is excess iron, which is not in the context of LHON. Apart from being a free radical scavenger, curcumin possesses iron-chelating ability and thus lowering ROS in thalassemia.[22] Moreover, although G11778A is present in blood, the oxidative status in blood might not well correlate with that in the affected but inaccessible tissue, the optic nerve. This was demonstrated by the baseline level of plasma MDA of LHON patients in this study (1.46 ± 0.46 nmole/mL), which was comparable to that in healthy Thai subjects.

The antioxidant status in LHON patients were investigated by measurement of cytoprotective enzymes, namely, SOD, GSH-Px and catalase, and the endogenous cellular antioxidant GSH in red blood cells. Curcuminoids treatment for 48 weeks did not show statistically significant effects on these parameters as compared to a placebo. However, in the group treated with curcuminoids, we found some effect of curcuminoids in lowering the activity of GSH-Px which was not observed in the placebo group (Figure 2). GSH-Px and catalase are enzymes that catalyzed toxic hydrogen peroxide to oxygen and water. The increase of ROS is associated with upregulation of GSH-Px and the antioxidant ability of curcuminoids may decelerate this process, resulting in the decreased activity of GSH-Px.[23-25]

This effect of curcuminoids on GSH-Px was also reported by a study by Lao et al.[26] In the brain, GSH-Px but not catalase is active, thus, the antioxidant effect of curcuminoids in lowering GSH-Px in LHON patients in this study might have implications in the optic nerve tissue. The level of GSH-Px in healthy Thai subjects was 13.9 ± 1.05 kU/g Hb. Interestingly, the LHON patients with higher GSH-Px (higher than 14 kU/g Hb) seemed to respond better to curcuminoids as shown by their greater reduction in the GSH-Px than that of the patients with lower GSH-Px (data not shown). This suggested the effect of curcuminoids in normalization of the GSH-Px.

There might be some limitations in VA measurement in the study. In particular, the baseline VA of most of the patients in this study was quite severe (around finger count). The scale of improvement from hand motion to finger count to 20/200 was rather vague and rough. Therefore, in clinical practice, it would be rather difficult to accurately detect VA improvement from severely impaired VA baseline, if the magnitude of VA was unremarkably improved. Other limitations of the study included the inclusion of patients with longterm visual loss, patients with previously treated visual loss and the lack of follow-up beyond 48 weeks.

The administration of curcuminoids at the dose of 500 mg/day for 48 weeks in this study did not show clinically significant toxic effects as demonstrated by hematological profiles, renal function and liver function tests. The safety of curcumin has also been supported in other studies using the dose of 8,000 mg/day for up to 3 months or the high single dose of 12,000 mg.[25,26] The drop out rate in the curcumin group (18.5%) compared to the placebo group (9.1%) could affect the results of the toxicity of the treatment but we employed intention to treat analysis to minimize this bias. The adverse symptoms of the patients were minor and were distributed similarly in both curcumin and placebo groups.

In conclusion, with 500 mg/day of curcuminoids

for 48 weeks, we could not find significance effects of curcuminoids on the clinical parameters, visual electrophysiological parameters, and blood biochemical oxidative parameters in G11778A LHON patients as compared with the placebo. Nevertheless, we did find significant changes from baseline values of HVF-MD, and HVF-PSD in the curcuminoids group which may reflect subtle fenestrated scotoma visual filed improvement. The antioxidant effect of curcuminoids lowering GSH-Px in red blood cells was observed. Given the safety of curcuminoids, higher dose, longer duration, or larger trials would be likely to reveal more evident effects.

In addition, the role of curcumin as a neuroprotective agent has emerged and this might be of benefit in preventing visual loss in asymptomatic LHON mutation carriers or improving retinal ganglion cell function shortly after the onset of symptoms. Curcumin may be used as an adjunct to treatment of neurological disease with oxidative stress. A long-term prospective cohort of asymptomatic LHON mutation carriers will be needed to prove this role of curcuminoids.

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Original Article/นิพนธ์ต้นฉบับ

Long-Term Outcomes and Measuring Vascularisation of Three-Dimensional Printed Porous Polyethylene Orbital Implant in Enucleation and Evisceration

ผลการศึกษาระยะยาวและการวัดปริมาณหลอดเลือดของลูกตาเทียมชนิดโพลีเอธิลีนที่ขึ้นรูปจากเครื่องพิมพ์สามมิติเพื่อใช้ในการผ่าตัดเอาตาออกแบบทั้งลูกและแบบเหลือตาขาว

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Abstract

Objective: To report the long-term outcome in terms of safety and efficacy of a new three-dimensional printed polyethylene (3DP-PE) orbital implant in patients who required orbital reconstruction after eye removal and to measure area of fibrovascular ingrowth in the orbital implant by using ImageJ software.

Methods: Prospective, consecutive selection in 21 patients which met the criteria. Each case had evisceration, enucleation, or secondary orbital implant performed by one of three oculoplastic surgeons. A gadolinium-enhanced, 1.5-Tesla MRI scan was performed at least 6 months after surgery. The follow-up time was at least 12 months. Safety was measured in terms of infection and tissue reaction to the implant. Efficacy was measured in terms of exposure rate, grades of fibrovascular ingrowth and postoperative results in long-term follow-up. Comparison of vascularisation of first and second MRI scans was measured by subjective technique and ImageJ software.

Results: The mean age was 40.4 ± 15.3 years old (range, 18-73 years old). 57.1% of patients had evisceration procedures. The mean follow-up time was 64.0 ± 37.4 months (range, 18-128 months). No postoperative infection was reported. The exposure rate was 19%. A total of four patients had two MRI scans and 75% of patients had increased enhancement at the second MRI scan, using subjective technique and ImageJ software. The correlation in interpretation of enhancement techniques between subjective technique and ImageJ software was 50%.

Conclusion: A 3DP-PE orbital implant is safe in terms of infection rate in long term follow-up.

Keywords: Prosthesis, Orbit, Reconstruction, Eye

บทคัดย่อ:

วัตถุประสงค์: เพื่อรายงานผลระยะยาวเกี่ยวกับความปลอดภัยและประสิทธิผลของลูกตาเทียมโพลีเอธิลีนใหม่ที่ขึ้นรูปจากเครื่องพิมพ์สามมิติในผู้ป่วยที่ต้องการผ่าตัดเอาตาออกและวัดพื้นที่การงอกของหลอดเลือดในลูกตาเทียมโดยใช้ซอฟแวร์อิมเมจเจ

วัสดุและวิธีการ: การศึกษาไปข้างหน้า เรียงตามลำดับผู้ป่วยที่เข้าเกณฑ์จำนวน 21 ราย ผู้ป่วยแต่ละรายได้รับการผ่าตัดเอาตาออกแบบเหลือตาขาวไว้ หรือเอาตาออกทั้งลูก หรือผ่าตัดใส่ลูกตาเทียมเป็นครั้งที่สองโดยจักษุแพทย์ตกแต่งและเสริมสร้างหนึ่งในสามคน หลังผ่าตัดทำการตรวจ MRI ที่ระยะเวลาอย่างน้อย 6 เดือน ติดตามผลเป็นเวลาอย่างน้อย 12 เดือน ความปลอดภัยวัดจากการติดเชื้อและปฏิกิริยาของเนื้อเยื่อต่อลูกตาเทียม ประสิทธิผลวัดจากอัตราการโผล่ของลูกตาเทียม เกรดการงอกของหลอดเลือดเข้าไปในลูกตาเทียม และการติดตามผลการผ่าตัดในระยะยาว การเปรียบเทียบการงอกของหลอดเลือดในลูกตาเทียมครั้งแรกและครั้งที่สองใช้วิธีอัตนัยและซอฟแวร์อิมเมจเจ

ผลการศึกษา: อายุเฉลี่ย 40.4 ± 15.3 ปี (ช่วง 18-73 ปี) ได้รับการผ่าตัดเอาตาออกแบบเหลือตาขาว 57.1% ค่ากลางในการติดตามอาการเท่ากับ 64.0 ± 37.4 เดือน (ช่วง 18-128 เดือน) ไม่มีการติดเชื้อหลังผ่าตัด อัตราการโผล่ของลูกตาเทียมเท่ากับ 19% ผู้ป่วยจำนวน 4 รายได้รับการทำ MRI จำนวน 2 ครั้ง และ 75% ของผู้ป่วยมีการเพิ่มของหลอดเลือดในการทำ MRI ครั้งที่สอง โดยการวัดแบบวิธีอัตนัยและซอฟแวร์อิมเมจเจ ความสอดคล้องกันของการแปลผลด้วยวิธีทั้งสองเท่ากับ 50%

สรุป: ลูกตาเทียมชนิดโพลีเอธิลีนที่ขึ้นรูปจากเครื่องพิมพ์สามมิติปลอดภัยไม่มีการติดเชื้อหลังผ่าตัด ในการติดตามผลระยะยาว

Introduction

The aims of the orbital implant insertion after enucleation or evisceration are to restore the volume of the orbit, improve motility and also the external appearance of the patients. The porous or integrated orbital implant has become more common since natural hydroxyapatite orbital implants were introduced in ocular socket reconstruction. The porous orbital implant allows vascular and fibrovascular ingrowth into the implant. This vascularisation promotes implant motility, decreases migration and extrusion.[1] At this time, the materials of porous implants range from synthetic hydroxyapatite, aluminium oxide and polyethylene. There are pros and cons among them. The benefit of polyethylene over synthetic hydroxyapatite and aluminium oxide is that it is possible to suture directly to the implant without the need for any wrapping. However, in our experience, we have found that the current commercially available polyethylene (Medpor, Stryker, Kalamazoo, MI, U.S.A.) is not easy to suture and it also takes time for the implant to uptake antibiotic solution. Moreover, it is not easy for surgeons to shape its surface to refit the orbit.

Three-dimensional printing is a manufacturing technique that has been adopted in many fields of medicine including to produce orbital implants. We adopted this technique to fabricate porous orbital implants by using two-stepped heat treatment process coupled with large-sized polyethylene powder printing so the implant has high porosity and large pore size. The three-dimensional printed polyethylene (3DP-PE) orbital implant has pore sizes ranging from 140 to 830 μm, with porosity of 61.9% which is greater than those of Medpor. These properties allow the 3DP-PE implant to be sutured easily and allow the rapid uptake of antibiotic solution into the implant according to the report by Suwanprateeb J et al.[2] A previous study in animals did not find any infections or adverse systemic reactions using an onlay bone graft in the mandibles of New Zealand white rabbits for 24 weeks.[3] This can confirm the safety of the 3DP-PE implant in animal study.

In this study, we prospectively studied the 3DP-PE orbital implant in a series of patients whose eyeballs had to be removed in consecutive cases. The study aimed to evaluate postoperative infection, exposure rate, to determine the fibrovascular ingrowth in the 3DP-PE orbital implant using MRI of the orbit with Gadolinium uptake, and also long-term postoperative results.

Materials and Methods

We recruited all consecutive patients who met the age and language criteria. Patients who were more than 18 years old, could co-operate and understand Thai language were recruited. These patients had either painless or painful blindness, phthisis bulbi or needed to reconstruct the orbit to fit new prostheses. Patients who had prior eye infections up to 6 months prior to examination, immune suppression, orbital fracture, orbital radiation, chemotherapy or who could not be followed-up for at least 12 months post-surgery were excluded from the study. The operations were performed by three oculoplastic surgeons (authors SS, KL, and ML). Data was collected for patients who had operations between July 2009 and December 2016 and the latest follow-up time was until December 2020. Informed consents were obtained. The study was approved by the Mettapracharak (Wat Rai Khing) Hospital Research Ethics Committee (METTA-REC).

The research adhered to the tenets of the Declaration of Helsinki.

The three-dimensional printed polyethylene orbital implant (3DP-PE)

Porous polyethylene orbital implant (Figure 1) was prepared by the technique as described previously.[2,4] High density polyethylene granules (Bangkok Polyethylene Co., Ltd, Thailand) were obtained and ground down to achieve a mean particle size of 305 mm. Maltodextrin (sourced from Shandong Duqing, Inc., China) and poly (vinyl alcohol) (sourced from Sigma–Aldrich, USA) with a particle size of 80–100 mm. were mixed with the polyethylene granules at the ratio of 20:10:70 % by weight. This mixture was loaded in a three- dimensional printing machine (Z400, Z Corporation, USA) and 16 mm., 18 mm., 20 mm. and 22 mm. spheres were printed using the commercial water-based binder ZB7 (Z Corporation, USA). After fabrication, the specimens were left in the printing machine for 2 hours, then removed and left in the atmosphere for 24 hours. The specimens were then air blown to remove any unbound powder and heat treated by using a wet salt bed technique.[5,6] In brief, the samples were heated at 145°C for 1 hour, sonicated in water and heat treated again in a salt powder bed (using Prungtip salt, Thailand) at 145°C for another 2 hours. All the samples were then cleaned in deionized water, dried and packed in a pouch before being sterilised by ethylene oxide gas. The 3DP-PE orbital implants have been studied for safety in pigs' skulls and no signs of infection were found after implantation for 20 weeks (Khongkhunthian P., unpublished data 2009) and no adverse systemic reactions were reported in the New Zealand study cited above.[3] Compared to the Medpor implant,[2] the 3DP-PE scored well for suturing and shaping ability and also for antibiotic solution uptake.

Figure 1 Three-dimensional printed polyethylene (3DP-PE) orbital implants

Evisceration and Enucleation

Standard eviscerations and enucleations were performed under general anesthesia. For enucleations, the surgeons sutured the four recti muscles to the implants in every case. Posterior sclerotomy or scleral relaxing incision was applied in some cases of evisceration. A 3DP-PE implant was soaked and pores filled with gentamicin (40 mg/ml) solution by negative pressure technique before insertion. In a case with a contracted socket, a buccal mucosal graft was harvested and placed between superior edge of the conjunctiva after enucleation. A fornix deepening suture was used in some cases.

MRI of the orbit

Nine patients were sent to have MRI scans at least 6 months after surgery, of these, five patients underwent a second MRI scan. Of the remaining patients, some declined to have MRI scans and others did not attend their appointments. A whole-body 1.5 Tesla Siemens

Symphony MRI model (Siemens, Erlangen, Germany) was used. T1-weighted (TE/TR=680/11) images were obtained. The imaging sequences had an imaging matrix of 224 × 320 and a field of view of 160 mm. The slice thickness was 3 mm. Axial, coronal and sagittal enhanced T1-weighted images were obtained within 5 minutes of Gadolinium injection. The central part of the implants and areas of fibrovascular ingrowth were marked on the image by a technician and verified by a neuroradiologist. The grades of enhancement of the fibrovascular ingrowth in the 3DP-PE implants were classified (by subjective technique) according to the studies of Klapper SR. et al[7] and Galluzzi P. et al[8]. The percentage of enhancement in the implants of the patients who had two MRI scans were also measured by ImageJ software (NIH, Bethesda, MD).

Measurement the area of enhancement using ImageJ software

Image J software for Windows was downloaded from https://imagej.nih.gov to a personal computer, and the MRI scan image file of the selected implant was opened from the File menu. The Freehand selection tool was used by author (SS) to draw the outline of the implant. To measure the area of enhancement, the author (SS) used the thresholding process to highlight pixels in the image. This was done first by converting the image to grayscale (choosing Image > type > 8-bit) then by chosing the area within the outline by using Duplicate command. By using the Image > Adjust>Threshold tool, the pixels that represent vascularization turned red. We then adjusted until the red areas were very similar to the areas of enhancement in the grayscale photo. We used the Rectangular selection tool, to limit the area of image analysis. In the Analyze > Set Measurement tool, we checked the "Area" and "Limit to Threshold" boxes to measure only the highlighted pixels within the selected rectangular area. The "Measure" analytical tool within the software was used to measure the area in the outline. The author (SS) used the measurement a total of three times, and the average of these measurements was calculated (Figure 2). Lastly, the percentage of enhancement of the implant was calculated on the basis of dividing the average area of enhancement by the average total area of the implant.

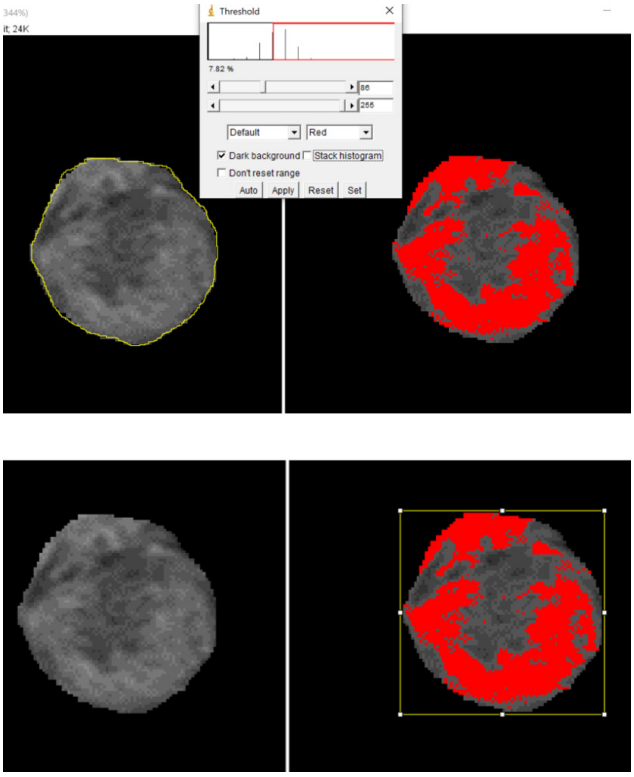

Figure 2 Measurement the area of enhancement using ImageJ software. The Freehand selection tool was used to outline the implant (top left). The author (SS) adjusted until the red areas were very similar to the areas of enhancement in the grayscale photo (top left and right). A rectangular selection was drawn at the border of the implant (bottom right)

Statistical analysis

Descriptive statistics were presented using mean ± SD for continuous data and percentage for nominal data. All statistical data analyses were performed by SPSS for Windows, version 28.0 (IBM, Armonk, NY, U.S.A.).

Results

A total of 21 patients met the criteria. The male patients (52.4%) were slightly predominant. The mean age was 40.4 ± 15.3 years old (range, 18-73 years old). The left eyes (71.4%) were more prominent. The primary diagnoses were painful blindness (47.6%), anophthalmic socket (19.0%), blindness (14.3%), phthisis bulbi (14.3%), and microphthalmos (4.8%) respectively. Trauma was the most common cause of blindness in this study (61.9%). The mean follow-up time was 64.0 ± 37.4 months (range, 18-128 months). Among types of operation, evisceration was the most common procedure (57.1%) (Figure 3) and one patient had secondary orbital implant insertion. The two most common implant sizes were 18 (47.1%) and 20 mm. (41.1%). No postoperative infections were found. The main implant-related complication was implant exposure (19.0%) (Table 1). The exposed implants were not sent for culture. Time between operation and implant exposure was between 1 to 2 months. The period of follow-up after the last surgery ranged from 61 to 128 months. No further implant exposures were reported.

Nine patients had an MRI scan of the orbit after the first operation. The mean period between operation and first MRI scan was 8.0 ± 2.0 months (range, 6.0-12.0 months). These were assessed by the subjective technique.[7,8] Accordingly, two (22.2%) patients were classified as having grade 2 enhancement, five (55.6%) patients were classified as having grade 3 enhancement and two (22.2%) patients were classified as having

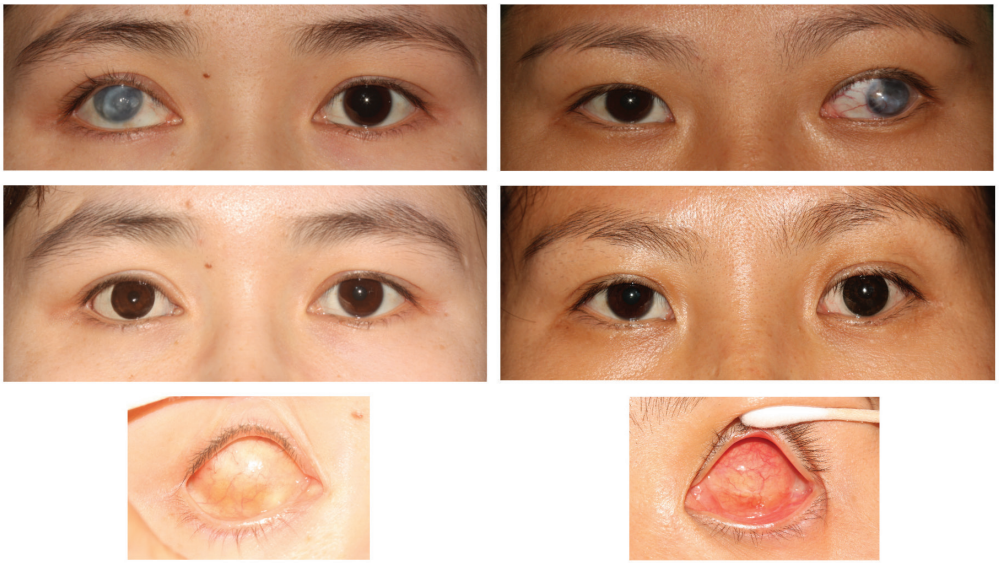

Figure 3 Preoperative (top), postoperative (middle) photos and the sockets (bottom). (left) The eviscerated patient (at 17 month-follow-up) had levator advancement in right upper lid one year after evisceration. (right) The enucleated patient (at 30 month-follow-up) had no additional surgeries.

Table 1 Four patients with exposed implants

Patient No. /sex/side	Diagnosis	Operation	Implant size (mm.)	Time between operation and implant exposure (mo.)	Treatment of implant exposure	Follow-up time after treatment (mo.)
1/F/OS	Blindness	Evisceration	20	2	Enucleation with 3DP-PE implant	97
2/M/OS	Phthisis bulbi	Evisceration	18	1	Enucleation with 3DP-PE implant	128
3/M/OD	Phthisis bulbi	Enucleation with buccal graft	20	1	Dermis fat graft	100
4/M/OS	Painful blindness	Enucleation	20	2	Dermis fat graft	61

M, male; F, female; OD, right eye; OS, left eye

grade 4 enhancement at first MRI scan (Figure 4).

The mean period between operation and second MRI scan was 27.0±3.0 months (range, 21.0-30.0 months). Five out of the nine (55.6%) patients had a second MRI scan. One case was excluded due to poor image quality from shadow of the prosthesis (Table 2). Of the remaining four cases in this group, using the above subjective technique, three were assessed to have increased enhancement in the orbital implant at the second MRI scan, while the first case was assessed to have the same enhancement at both first and second MRI scans. Subsequent measurement by ImageJ

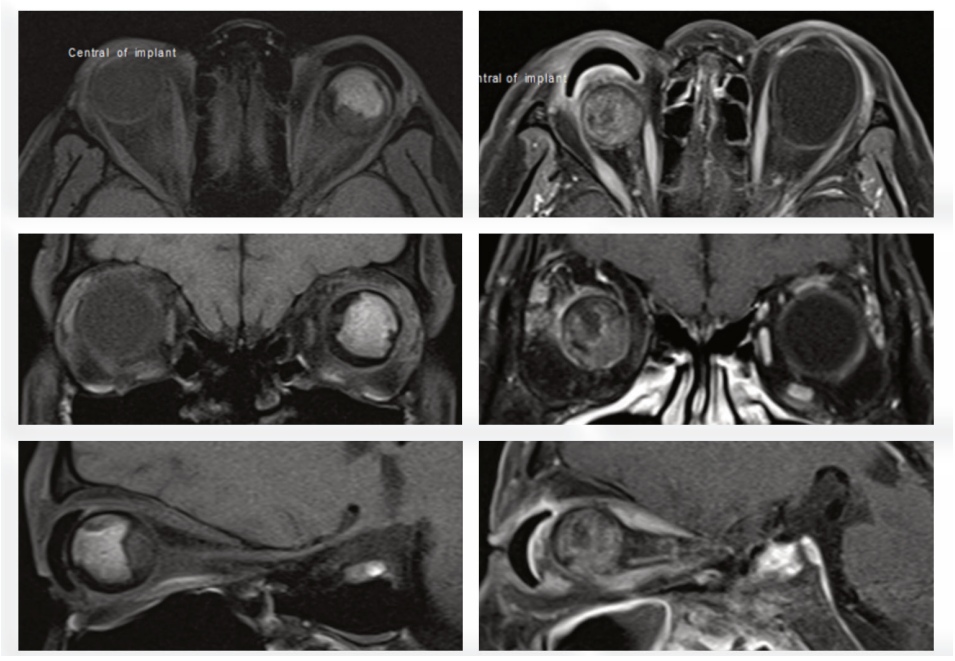

Figure 4 Post contrast T1-weighted 1.5 Tesla MRI in evisceration (left) and enucleation (right) patients. Each patient was tested in axial (top), coronal (middle) and sagittal (bottom) planes. The areas of enhancement were marked by a technician and verified by a neuroradiologist

software also showed that three out of four cases in this group had increased enhancement in the orbital implant at the second MRI scan, while the fourth case was assessed to have the same enhancement at both first and second MRI scans, the two types of measurements were not correlated in two cases (Table 2).

Table 2 Four patients who had first and second MRI orbit with Gadolinium tests.

Patient (sex/side)	Diagnosis	Operation	Time between surgery and MRI test (mo.)	
			1st MRI (MRI grade) (% of enh.)	2nd MRI (MRI grade) (% of enh.)
F/OS	Painful blindness	Evisceration	7 (3) (63.8)	27 (3) (76.5)
F/OS	Painful blindness	Evisceration	6 (3) (59.7)	21 (4) (95.9)
F/OD	Anophthalmic socket	Enucleation	8 (3) (78.8)	28 (4) (91.0)
F/OD	Microphthalmos	Enucleation with buccal graft	6 (3) (75.0)	27 (4) (74.0)

F, female; OD, right eye; OS, left eye;
MRI, magnetic resonance imaging;
MRI grade, MRI grade by subjective technique;
% of enh, percentage of enhancement measured by ImageJ software

Discussion

Orbital implant is an important factor in ocular socket reconstruction whether by enucleation, evisceration or secondary implant insertion. The first generation of orbital implants were non-integrated or non-porous orbital implants. They were made of thin and light glass, silicone and polymethylmethacrylate (PMMA), etc. The second generation was the integrated or porous orbital implant. Natural hydroxyapatite was introduced as a material for ocular implants in orbital reconstruction after enucleation and evisceration in 1985 and was approved by the US Food and Drug Administration for orbital implantation in 1989.[9] After that, other medical grade materials such as polyethylene and aluminium oxide were available. Porous orbital implants were widely used in many countries[10-17] because porous implants can promote fibrovascular ingrowth into the implant and improve implant motility, decrease migration and extrusion.[1] Among the three available materials of porous implant, porous polyethylene is the only implant that can be sutured directly on its surface without any wrapping material. The authors have experienced difficulties in suturing to the Medpor implant, also in antibiotic solution uptake and shaping the implant.

We have developed a new porous polyethylene orbital implant from a three-dimensional printed technique which has become common for fabricating many implants in the human body including the orbit. The three-dimensional printed polyethylene (3DP-PE) orbital implant was fabricated by a novel two-stepped heat treatment, coupled with large-sized PE powder printing to produce porosity and large pore size ocular implant that facilitates suturing and antibiotic impregnation.[2] Suwanprateeb et al[2] reported that using a scanning electron microscope (SEM), the 3DP-PE

implant (pore sizes ranging from 140 to 830 μm) had much greater porosity compared to Medpor (pore size ranging from180 to 570 μm). According to an earlier study by Suwanprateeb J et al,[2] the larger the pore size, the better the fibrovascular ingrowth. The 3DP-PE had less density and greater porosity compared to the Medpor (384.3 vs 494.3 kg/m^3 and 61.9 vs 48.4%), hence with the same dimensions, the 3DP-PE is lighter than the Medpor. It was also found that 1% methylene blue solution was taken up more rapidly and in greater quantity by the 3DP-PE than the Medpor[2].

Compared to other clinical studies relating to the Medpor implant, the mean age of patients in our study was 40.4 ± 15.3 years old (range, 18-73 years old), older than the study of Huang D. et al[18], Tabatabaee et al[17] and Naik et al.[19] There were no postoperative infections in all cases. This confirms the safety of 3DP-PE implant. For the efficacy of the 3DP-PE implant, we studied 21 patients who had operations ranging from evisceration, enucleation with or without buccal grafts and secondary orbital implant insertion. For those in the enucleation group, three patients had enucleation with buccal grafts and one patient had enucleation with buccal graft and fornix fixation. Only one patient had secondary orbital implant insertion. All patients except two in the evisceration group recovered well after the operations between 18 and 128 months. Meanwhile all patients except two in the enucleation group recovered well after the operations between 23 and 123 months.

The exposure rate in our study was 19.0% with the mean follow-up time of 64.0 ± 37.4 months (range, 18-128 months). Among our three surgeons, two surgeons had one patient with implant exposure and one surgeon had two patients with implant exposure. Among the four patients who experienced implant exposures (Table 1), two patients had evisceration operations and two patients had enucleation operations. For the evisceration group, the time between surgery and implant exposure was 2 months and 1 month respectively. The exposed implant of the first patient was removed and enucleation with a new 3DP-PE implant was carried out successfully. This patient was followed up for at least 97 months without postoperative implant exposure. The second patient had implant exposure one month after the operation. An enucleation with a new 3DP-PE implant was carried out. This patient (male) was followed-up for at least 128 months without any implant exposure. The authors consider that the reason for the implant exposure in these two eviscerated cases was because the implants were not placed in the posterior tenon space properly, because both of them exposed in the early phase after operations. Currently, traditional techniques in evisceration surgery have been replaced in favour of a four-petal technique. For the enucleation group, two patients experienced implant exposure at 1 month and 2 months respectively. The third patient (Table 1) with a history of phthisis bulbi of unknown causes, had enucleation with buccal graft (implant size 20 mm.). He had an exposed implant at one month after the operation. The patient had a small ocular socket so the surgeon had to harvest a buccal graft. The authors consider that the cause of early implant exposure may be the result of high tension on the anterior surface of the implant. Then the surgeon decided to remove the implant and harvest dermis fat for an orbital graft. The patient recovered well for at least 100 months. The fourth patient (Table 1) was diagnosed with traumatic painful blindness. He had implant exposure at two months after operation. The surgeon removed the implant and harvested dermis fat

for an orbital graft. The patient recovered well after the operation for at least 61 months. The authors consider that the causes of implant exposure in this case might be from poor vascularisation due to old age and traumatic in origin.

Karesh et al[20] reported no implant exposure in 21 patients who received enucleation, evisceration and secondary implant insertion with the mean follow-up time of 19 months (range, 7-43 months). Naik et al[19] compared the fibrovascular ingrowth between Medpor and Medpor-Plus implants. The exposure rate in their study was 10% with the mean follow-up time of 36.7 months (range, 18-43 months). Huang et al[18] reported no implant exposure in 21 patients who underwent modified evisceration techniques. The mean time between the implantation and MRI scan in this study was 24.1 ± 19.3 months (range, 1.5-69 months). Lin CW et al[21] found that the exposure rate was 76.5% of 17 patients who had Medpor implants and the mean time to exposure was 73.4 ± 51.2 months. The exposure rate in our study is lower than Lin et al but higher than the other studies cited above. However, a direct comparison may not be possible. Our study differs from studies with a lower exposure rate in two ways. Our study had longer follow-up times. Secondly, implant exposure occurred shortly after operation, suggesting surgical factor rather than implant factor. In our study, three surgeons were included, with differing experience. Had the study only included the most experienced surgeon, the exposure rate would have been less than 19%.

The fibrovascular ingrowth into the implant was confirmed by MRI of the orbit with Gadolinium uptake. De Potter P. et al[22] reported that areas of enhancement showed as early as 1.5 months after enucleation. In this study, the first MRI scans were conducted at least 6 months after operation because it is assumed that the implant would have vascularisation within 6 months, and to limit the need for patients to be subjected to multiple MRI scans. For the results of the first MRI scan, 77.8% of patients were assessed to have a gadolinium enhancement of at least grade 3 and more than half of the patients who had second MRI tests had grade 4 enhancement (Table 2), that is the fibrovascular ingrowth into the implant increased over time for at least 28 months. A study by Huang et al[18] found that the mean interval between the evisceration and the MRI scan was 24.14 ± 19.26 months (range, 1.5-69 months).[18] He also found that the longer the time interval between the evisceration and the MRI test, the greater the increase in the grade of fibrovascular ingrowth in Medpor. This was also supported by other studies.[20,22,23] Naik et al[19] found that the mean area of vascularisation of the Medpor at 1.5 months, 3 months and 4.5 months was 58%, 70% and 75% respectively. The 3DP-PE implant did not differ from other porous polyethylene implants in terms of fibrovascular ingrowth. Measurement by ImageJ software showed that three out of four cases who had two MRI scans had an increase in enhancement in the orbital implant between the first and second MRI scans. The correlation in interpretation of enhancement techniques between subjective technique and ImageJ software was 50%. This is the first study to use ImageJ software to measure area of enhancement in the orbital implant. Further study with a larger sample size is needed.

This is a case-series study, aimed to determine the outcomes of the new 3DP-PE orbital implant described in this study in various eye removal operations and also the vascularisation into the implant after surgery. From the results of the study, on the basis of long-

term follow-up, we can be sure about the safety of the implant. In terms of efficacy, the 3DP-PE implant can be used successfully in evisceration, enucleation with or without buccal graft and fornix fixation, and also in secondary orbital implant insertion. The exposure rate is acceptable compared to other studies. The fibrovascular ingrowth of the implant after operation is also acceptable. Vascularisation may be more accurately measured using ImageJ software. The limited number of patients who had MRI scans in this study makes it difficult to draw firm conclusions about the efficacy. Another limitation of the study was that many surgeons were included in the study, which meant that it was not possible to control the surgical factors from different surgeons. In future, a larger study with a comparison group is needed.

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Original Article/นิพนธ์ต้นฉบับ

Corneal Astigmatism Changes After Ptosis Correction in Two Age Groups of Patients with Congenital Ptosis

การเปลี่ยนแปลงค่าสายตาเอียงจากกระจกตาภายหลังการผ่าตัดแก้ไขหนังตาตกตั้งแต่กำเนิดระหว่างสองกลุ่มอายุ

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Abstract

Purpose: To evaluate postoperative corneal astigmatism changes after ptosis correction in groups of young and older patients with congenital ptosis.

Patients and Methods: A prospective cohort study of 28 patients (56 eyes) with congenital ptosis enrolled at Ramathibodi Hospital was performed from April 2018 to June 2019. Within this group of patients there were 6 cases of bilateral congenital ptosis and 22 unilateral cases of congenital ptosis forming a total of 34 individual ptotic eyes for the study. The patients were categorized into two groups: early-age group (aged ≤5 years,) comprising of 14 eyes and older-age group (aged >5 years) comprising of 20 eyes. The preoperative visual acuity, amblyopic status, ptosis severity, and refractive error of both groups were evaluated prior to ptosis correction. All patients underwent ptosis correction with either levator resection or frontalis sling. Following the correction, the refractive error was measured after a follow-up period of at least 6 months. The astigmatism results were classified into three subgroups: with-the-rule, against-the-rule and oblique astigmatism.

Results: The mean age at diagnosis was 8.91 ± 7.05 years. From the study group, amblyopia was found in 13 out of 28 patients (46.4%). The most common type of astigmatism was with-the-rule astigmatism, making up 26 out of 34 ptotic eyes (75.6%). A postoperative astigmatism change of >0.50 diopters was found in 4 out of14 eyes (28.6%) in the early-age group and in 6 out of 20 eyes (30.0%) in the older-age group (Rate ratio, 1.43; 95% CI, 0.34–6.07).

Conclusion: Astigmatism was reduced following ptosis correction, with no statistically significant difference in the amount of reduction between the two age groups. Surgical correction may be deferred in patients of all age groups with anisometropic amblyogenic ptosis until appropriate surgical planning is possible.

Keywords: congenital ptosis, corneal astigmatism, refractive error, amblyopia, blepharoptosis

บทคัดย่อ:

วัตถุประสงค์: เพื่อศึกษาการเปลี่ยนแปลงค่าสายตาเอียงจากกระจกตาภายหลังการผ่าตัดแก้ไขหนังตาตกตั้งแต่กำเนิดระหว่างกลุ่มอายุน้อยกว่าหรือเท่ากับ 5 ปีและกลุ่มอายุมากกว่า 5 ปี

วิธีการศึกษา: การศึกษาไปข้างหน้าของผู้ป่วยหนังตาตกตั้งแต่กำเนิดจำนวน 28 ราย โดยแบ่งผู้ป่วยเป็น 2 กลุ่มอายุ คือ กลุ่มอายุน้อยกว่าหรือเท่ากับ 5 ปี จำนวน 14 ตา และกลุ่มอายุมากกว่า 5 ปี จำนวน 20 ตา โดยชนิดการผ่าตัดของผู้ป่วย คือ การผ่าตัดแบบ Levator resection หรือ Frontalis sling โดยมีการวัดค่าสายตา ระดับการมองเห็น ตาขี้เกียจ ระดับของหนังตาตกก่อนและหลังการผ่าตัด

ผลการศึกษา: อายุเฉลี่ยในงานวิจัย คือ 8.91 ± 7.05 ปี ผู้ป่วยมีภาวะตาขี้เกียจ 13ใน 28 ราย คิดเป็นร้อยละ 46.4 โดยพบว่า ตาที่มีหนังตาตกแต่กำเนิด มีค่าสายตาเอียง with-the-rule astigmatism จำนวน 26 ใน 34 ตา คิดเป็นร้อยละ 75.6 ภายหลังการผ่าตัดแก้ไขหลังหนังตาตก ค่าสายตาเอียงที่เปลี่ยนแปลงมากกว่า 0.50 ไดออปเตอร์ พบว่ามีจำนวน 4 ใน 14 ตา คิดเป็นร้อยละ 28.6ในกลุ่มผู้ป่วยอายุน้อย และมีจำนวน 6 ใน 20 ตา คิดเป็นร้อยละ 30.0 ในกลุ่มอายุมาก (Rate ratio, 1.43; 95% CI, 0.34–6.07)

สรุป: ค่าเปลี่ยนแปลงสายตาเอียงลดลงภายหลังการผ่าตัดแก้ไขหนังตาตกในสองกลุ่มอายุ ไม่มีความแตกต่างนัยสำคัญทางสถิติ การผ่าตัดแก้ไขหนังตาตกแต่กำเนิดในกลุ่มอายุน้อยที่มีตาขี้เกียจจากภาวะค่าสายตาผิดปกติ อาจจะสามารถชะลอการผ่าตัดได้ โดยคำนึงถึงความพร้อมผ่าตัดของผู้ป่วยแต่ละราย

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Introduction

Congenital ptosis is a condition in which the upper eyelid falls to a lower-than-normal position. This condition usually presents at birth or within the first year of life.[1] The development of congenital ptosis originates from the dystrophic, fat-infiltrated and fibrous tissue of the levator palpebrae superioris muscles. In severe cases, the drooping eyelids cover the cornea and pupil, resulting in visual deprivation. Moreover, drooping eyelids can impact corneal astigmatism, refractive error and amblyopia, which subsequently causes permanent visual loss.[1–7] Some studies[3–4] have reported that high corneal astigmatism is frequently associated with congenital ptosis because eyelid ptosis modifies the anterior corneal surface.

Treatment options for congenital ptosis are patching regimens, spectacles or surgical correction. Indication for surgical correction is required to reduce visual deprivation. Anisometropic amblyopia is another relative indication for surgical correction in order to modify the anterior corneal surface and to restore corneal symmetry and corneal astigmatism.[4]

In Southeast Asia, there have been no reports regarding the characteristics of patients with congenital ptosis, such as their refractive status and astigmatism type, and how the timing of surgical intervention affects refractive changes between young and older-age groups. Our study aims to evaluate postoperative corneal astigmatism changes after ptosis correction in different age groups of patients with congenital ptosis in Thailand.

Material and Methods

This prospective cohort-study was approved by the Human Research Ethics Committee, Faculty of Medicine of Ramathibodi Hospital, Mahidol University, and adhered to the tenets of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki. Written informed consent was obtained from all participants and their guardians for their clinical records to be used in this study.

Patients

The diagnosis of congenital ptosis was based on the presence of drooping eyelids since birth or within the first year of life. Amblyopia was defined as best corrected visual acuity (BCVA) less than 20/40 and greater than two Snellen chart lines of difference in BCVA between the two eyes. Amblyopia in young children was defined by the patient's lack of fixation or their inability to follow objects in the ptotic eye during the induced tropic test compared with the normal eye. The exclusion criteria included ocular surgery (except for refractive surgery), paralysis, strabismus, trauma or neurological diseases.

Twenty-eight patients (56 eyes) of various ages, with either unilateral or bilateral congenital ptosis, were scheduled for ptosis-correction surgery from April 2018 to June 2019 and were enrolled in our study. Patients were divided into two groups: an early-age group (aged ≤ 5 years) comprising of 14 eyes, and an older-age group (aged > 5 years) comprising of 20 eyes, forming a total of 34 individual eyes for the study.

All patients underwent complete ophthalmic examinations. BCVA was measured by age-appropriate methods which include the preferential-looking test, Allen chart or Early Treatment of Diabetic Retinopathy (ETDRS) chart. The results were noted in Snellen fraction (feet) and were converted to Log of the minimum angle of resolution (LogMAR). Cycloplegic

refraction was recorded after administering two drops of 1% cyclopentolate, 10 minutes apart, in all patients and then a third drop was administered 10 minutes after the second drop if the pupil size was less than 6 mm. Refractive error was measured using standard retinoscopy. The spherical equivalent (SE) was calculated as the sum of the dioptric power of the sphere and one-half of the cylinder power. Myopia was defined as negative SE of more than −0.50 diopters (D) and hyperopia was defined as positive SE of more than +0.50 D. Astigmatism was classified as with-the-rule (WTR) when the steeper meridian was close to 15° from the vertical meridian (90°) and against-the-rule (ATR) when the steeper meridian was close to 15° from the horizontal meridian (180°). Oblique astigmatism (OA) was classified when the steeper meridian was not close to either side of the vertical or horizontal meridian.

Marginal reflex distance 1 (MRD1) was used to classify ptosis severity into mild (MRD1 ≥ 2 mm), moderate (0 ≤ MRD1 < 2 mm) or severe (MRD1 < 0 mm). Levator function was classified as poor (≤ 4 mm), fair (5–9 mm) or good (≥ 10 mm).

Each patient underwent ptosis correction: by levator resection, if levator function was good, fair or their ptosis was moderate-to-severe; or by frontalis sling, if levator function was poor or their ptosis was severe. Refraction tests were performed 6 months after surgery to compare corneal astigmatism changes in the different age groups.

Statistical analysis

All results and data are summarized as mean ± standard deviation. Categorical and continuous variables were compared using the chi-squared test and one-way analysis of variance, respectively. Differences with $p < 0.05$ were considered statistically significant. To compare postoperative astigmatism changes between the early and older-age groups, we used the incidence rate ratio and 95% confidence interval for the rate ratio. All analyses were performed using SPSS software (version 25.0 for Windows).

Results

Of the 28 patients (56 eyes) included in this study, the congenital ptosis was bilateral in 6 patients (21.4%) and unilateral in 22 patients (78.6%). The mean age of diagnosis was 8.91 ± 7.05 years old, with a male: female ratio of 1.33: 1. The preoperative clinical presentations in the ptotic eyes are demonstrated in Table 1 with no statistical difference between the two age groups. WTR astigmatism was the most common type and was found in 26 out of 34 ptotic eyes (76.5%). Twenty-one cases had severe ptosis, i.e., MRD1 < 0 mm, and 50% had fair levator function, i.e., 5–9 mm. More importantly, the ptosis had caused preoperative amblyopia in up to 13 of 28 patients (46.4%). Following the ptosis-correction surgery, there was improvement in astigmatism in both groups as shown in Table 2. In the early-age group, a postoperative astigmatism change of more than 0.50 D was found in 4 of 14 eyes (28.6%). Similarly, this was observed in 6 of 20 eyes (30.0%) in the older-age group. However, the change was not statistically different between the two age groups (incidence rate ratio of 1.43; 95% confidence interval of 0.34–6.07).

Table 1 Clinical presentations of the ptotic eye

	Ptotic eyes	
	early-age group N=14	older-age group N=20
Visual acuity (logMAR)	0.33 ± 0.32	0.34 ± 0.28
Amblyopia (patients)	5	8
- Deprivation	3	4
- Refractive error	2	4
Marginal reflex distance 1 (mm)	0.53 ± 1.26	0.28 ± 1.60
Ptosis severity		
- Mild (MRD1 ≥ 2 mm)	2	3
- Moderate (0 ≤ MRD1 < 2 mm)	4	4
- Severe (MRD1 < 0 mm)	8	13
Mean levator function (mm)	4.85 ± 2.61	5.27 ± 2.71
Levator function		
- Poor (≤ 4 mm)	1	2
- Fair (5-9 mm)	7	10
- Good (≤ 10 mm)	6	8
Operation		
Frontalis sling (patients)	7	10
Levator resection (patients)	7	10

Table 2 Comparison of refractive and astigmatism changes before and after ptosis correction surgery

Number of eyes	Ptotic eye prior operation		Ptotic eye post operation	
	early-age group (N=14)	older-age group (N=20)	early-age group (N=14)	older-age group (N=20)
Spherical equivalent refraction (diopters)	-1.34 ± 5.13	-1.08 ± 5.60	0.46 ± 6.03	-0.17 ± 5.63
Astigmatism (diopters)	-1.73 ± 0.76	-1.73 ± 0.85	-1.37 ± 0.60	-1.32 ± 0.95
Astigmatism type (eyes)				
- With the rule	9	17	9	18
- Against the rule	1	1	1	0
- Oblique astigmatism	4	2	4	2

Discussion

Refraction-associated congenital ptosis has been investigated in previous studies.[2–4] Eyelid ptosis affects the anterior corneal surface, which then induces refractive changes because of corneal refractive error and astigmatism.[4] Huo et al[8] found that unilateral ptosis was associated with myopia. Paik et al[2] reported that ptotic eyes had higher amounts of astigmatism, with the OA and WTR types being the most common. Consistent with previous studies,[2–4,8] we found a higher amount of astigmatism in the ptotic eyes compared with the fellow eyes, and WTR astigmatism was the most common type of astigmatism in ptotic eyes (76.5%) in Table 3.

Table 3 Clinical presentations of the ptotic eye and the fellow eye

	Ptotic eye	Fellow eye
Number of eyes	34	22
Visual acuity (logMAR)	0.34 ±0.29	0.20 ±0.17
Amblyopia (patients)	13 (46.4%)	-
Spherical equivalent refraction (diopters)	-1.19 ±5.33	-0.99 ±4.33
Astigmatism (diopters)	-1.40 ±0.86	-1.01 ±1.27
Astigmatism type (eyes)	34	22
- With the rule	26 (76.5%)	16 (72.7%)
- Against the rule	2 (5.9%)	1 (4.5%)
- Oblique astigmatism	6 (17.6%)	5 (22.7%)
Marginal reflex distance 1 (mm)	1.0±1.5	3.5±0.7
Ptosis severity		
- Mild (MRD1 ≥ 2 mm)	5 (14.7%)	22 (100%)
- Moderate (0 ≤ MRD1 < 2 mm)	8 (23.5%)	-
- Severe (MRD1 < 0 mm)	21 (61.8%)	-
Levator function (mm)	8.0±2.7	12.1±2.2
Levator function		
- Poor (≤ 4 mm)	3 (8.8%)	-
- Fair (5-9 mm)	17 (50%)	2 (9.1%)
- Good (≥ 10 mm)	14 (41.1%)	20 (90.9%)

Amblyopia has also been found to be higher in those with congenital ptosis compared to the general population.[2,7] According to one study, childhood-ptosis-associated amblyopia was reported in about 7.9 per 100,000 births.[9] Other previous studies[2,7,9,10] found that the incidence of amblyopia was between 14% and 21%. Our study showed a higher incidence of amblyopia (46.4%) in the Thai patients under this study. This resulted from more than half of our cases (62.8%) demonstrating severe ptosis and 53.9% from the visual deprivation. The main etiology of amblyopia was occlusion of the visual axis, which is similar to the results of Grinpentrog et al,[9] who reported that half of ptosis-associated amblyopia cases were the result of visual deprivation. Another cause of amblyopia was the correlation between the amounts of anisometropia. Ptotic eyes showed higher amounts of both SE and astigmatism, compared with the fellow eyes. Previous studies[3,7] also reported that more than half of amblyopia cases came from refractive error, which is not different from our study (46.2%).

There has been controversy regarding the benefit of the timing for correction of ptotic eyes, in terms of anisometropic amblyogenic ptosis. Surgical intervention at an earlier age might provide benefits in terms of early refractive change to the cornea, better visual outcome and less emotional trauma associated with the surgery. Conversely, waiting to perform surgical correction at an older age allows patients to be more cooperative with examinations, producing better anatomical results and refractive stability. Wu et al[11] reported that there was no significant visual

benefit from surgical correction of congenital ptosis in patients at 2 years or younger, compared with patients operated upon between 2 to 5 years of age. Based on a retrospective chart review of 62 patients, Cadera et al[12] reported that changes in cylinder were not statistically significant between patients in their younger and older-age groups (< 4 years old and ≥ 4 years old, respectively). A recent study[2] in an Asian population also reported no significant change in the magnitude of astigmatism between age groups after surgical correction, but a significant increase OA in postoperative eyes.

Our study is the first prospective study, apart from that by Kumar et al,[13] to include all ages of patients with congenital ptosis, especially those under the age of 5. We compared the astigmatic change after surgical correction between early-age and older-age groups. After ptosis correction, there was an improvement in SE and astigmatism in the ptotic eyes in both groups. However, the improvement in astigmatism did not significantly differ between the two groups. Thus, early surgical intervention might not produce significant benefits in terms of astigmatic change. Surgical correction might be delayed in cases of anisometropic amblyopic ptosis until appropriate surgical planning is done.

The limitation of our study was the small number of congenital ptosis cases,since the numbers might not have been enough to demonstrate statistical significance. Another limitation was that we did not include corneal topography, to examine the characteristics of corneal astigmatism before and after surgery because we tested children under 5 years old and because of the associated research costs.

Conclusion

Following ptosis-correction surgery, there was an improvement in SE and astigmatism. However, the change was not different between the two age groups, so surgical correction might be delayed in patients with anisometropic amblyogenic ptosis. Proper management, including cycloplegic refraction, spectacles, patching and surgical planning, and a follow-up plan should be developed to prevent amblyopia and subsequent permanent visual loss.

Informed consent

Informed consent was obtained from all individual participants included in the study. Ethical approval was waived by the Human Research Ethics Committee Faculty of Medicine Ramathibodi Hospital, Mahidol University and adhered to the tenets of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Disclosure

The authors report no conflicts of interest in this work.

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Footnotes and Financial Disclosures

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A Rare Case of Larval Tick Infestation at the Conjunctiva
รายงานผู้ป่วยที่หายากจากตัวอ่อนของเห็บบนเยื่อตา

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Abstract

This is a case report of a middle-aged man without underlying disease presented with acute pain in his left eye. Ocular examination showed an insect-like foreign body attached on his left lower palpebral conjunctiva. The foreign body was removed gently by non-toothed forceps and a cotton tip applicator. It was further identified as the larval form of *Amblyomma americanum* tick. A topical combination steroid-antibiotic medication was prescribed. It was further identified as the larval form of *Amblyomma americanum* tick. In summary, a thorough eye examination is necessary for the early recognition of this rare condition.

Keywords: *Amblyomma americanum*; conjunctiva; lone star; parasite; tick

บทคัดย่อ:

รายงานผู้ป่วยชายวัยกลางคนไม่มีโรคประจำตัวมาด้วยอาการปวดตาซ้ายแบบเฉียบพลัน ตรวจตาพบสิ่งแปลกปลอมคล้ายแมลงติดอยู่ที่เยื่อตาส่วนหนังตาซ้ายล่าง ได้นำสิ่งแปลกปลอมนี้ออกจากตาด้วยคีมคีบชนิดไม่มีเขี้ยวร่วมกับไม้พันสำลี ผู้ป่วยได้รับยาหยอดตาชนิดยาปฏิชีวนะและยาสเตรียรอยด์ เมื่อนำไปตรวจพบว่าเป็นตัวอ่อนของเห็บชนิด *Amblyomma americanum* โดยสรุป การตรวจตาโดยละเอียดจำเป็นต่อการตรวจพบที่รวดเร็วในภาวะที่หายากนี้

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Background

Ticks commonly infest humans but rarely attach to the conjunctiva. Only nine cases have been reported in the literature.[1-8] Furthermore, most cases have been identified in Western countries.[1,2,4,5,8] In this case, we discussed the clinical presentation and treatment of a patient with a tick affixed to the conjunctiva. Herein, we also summarize other cases published in the literature in comparison with our patient.

Patients and Methods

We report a case of conjunctival tick infestation (Amblyomma americana) in A case report was conducted at the Ophthalmology Clinic, Chiang Mai University Hospital. The study protocol was conducted in accordance with the tenets of the Declaration of Helsinki and the protocol was approved by the Ethics committee of the Faculty of Medicine, Chiang Mai University. A waiver of consent was granted based on a retrospective study and anonymized data analysis.

Case Presentation

A middle-aged man presented to the outpatient unit of the Ophthalmology Department of Chiang Mai University Hospital complaining of left ocular pain for one day which worsened with blinking. He also had eye redness, tearing, and foreign body sensation, but the vision was normal. He refused any history of trauma to his eye. Before coming to the hospital, he rinsed his eye with tap water but did not mitigate the symptoms. Further history taking revealed that he has fostered several dogs at his house and had traveled to a dog kennel in Denver, the United States, recently. Otherwise, his past medical history was unremarkable.

His visual acuity was 20/20 in both eyes. On slit-lamp examination, his left bulbar conjunctiva was markedly injected. A red-brown insect-like foreign body was found at the lower palpebral conjunctiva (Figure 1, arrowhead). Thorough examination revealed six movable legs and the buried head under the conjunctiva (Figure 2). The cornea, anterior chamber, and posterior segment exams were normal.

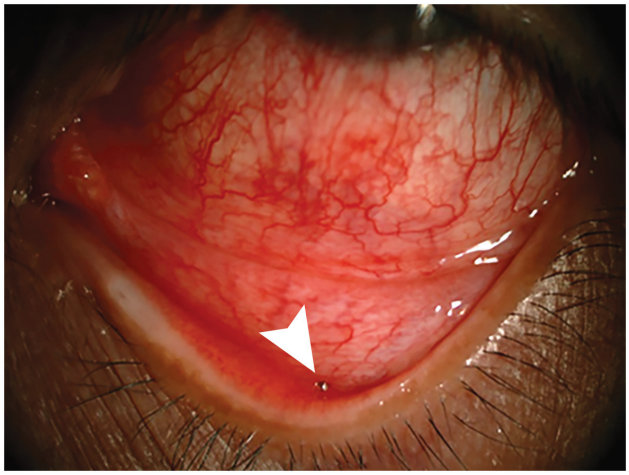

Figure 1 A low magnification image shows an insect-like foreign body found at the injected lower palpebral conjunctiva (arrow head).

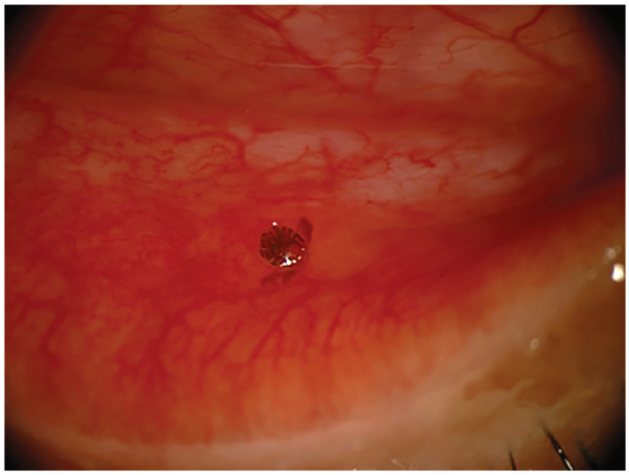

Figure 2 A 100X magnification image shows a rounded body, six-legged insect-like organism with its head burrowed under the lower palpebral conjunctiva.

Treatment

Topical 0.5% tetracaine anesthetic eye drops were applied before the gentle removal of entire parts of the foreign body by non-toothed forceps and cotton tip applicator. The patient was prescribed 0.1% dexamethasone phosphate in combination with 0.5% neomycin eye drops four times daily for three days, then tapered off. No other systemic medications were used.

Outcome and follow-up

After three days, his left eye returned to normal and no signs of systemic infection such as fever and rash. His serologic tests for the vigilance of associated systemic diseases including complete blood count, liver function test, and erythrocyte sedimentation rate were within normal limits. The specimen was further identified by a parasitologist, affirming a complete removal of the larval stage of the tick. The presence of six legs and morphological structures including a single body region with short, broad, and rounded basis capitulum, short palpi with long hair, and a unique hypostome morphology corresponded to the characteristics of *Amblyomma americanum* larva. Unfortunately, we could not demonstrate the larval picture due to malfunction of hard disc.

Discussion

Amblyomma americanum or a lone star tick is a parasitic arachnid, not an insect, which is a known or presumed vector for several diseases affecting humans.[9,10-12] Its endemic area is in the southeastern and eastern United States (Table 1). The common habitats are meadows, woodlands, and hardwood forests.[10,13] It is one of the most troublesome and economically threatening ticks because of the aggressive and wide host range, any mammals.[9] In Thailand, *Amblyomma* spp. is rarely found in domestic and wild animals. Moreover, *A. americanum* has not been reported.[14,15]

Each female tick produces thousands of eggs deposited under leaves and plant litter.[10] After hatching, it develops through three life stages which are the six-legged larva, eight-legged nymph, and adult. Although, ticks cause irritation and inflammation at the attachment site, they are often overlooked due to their small size and the color that might mimic a conjunctival pigmented lesion.[8] Adult female lone star ticks are reddish-brown and have a distinctive white spot or "star" on the back, making them easily distinguished from other types of tick; however, this is not evident in the larval stage.[10]

Adult ticks are commonly found in humans[9], but the conjunctival infestation of the larval stage of ticks is rare. There have been infrequent reports published in several areas, mostly in the United States.[1-8] The most identified species are *A. americanum* (Table 1). Nymphs and adults are the primary vectors of various diseases such as human monocytotropic ehrlichiosis and human granulocytic ehrlichiosis.[9,13] Hosts bitten by lone star ticks may be infected by various bacteria which could cause a southern tick-associated rash illness; but lone star ticks typically do not transmit *Borrelia burgdorferi* which is the cause of Lyme disease.[10,11,12]

The larval form, in contrast, typically does not transmit diseases because of its inexperience in feeding on any other hosts, having no chance of exposure to bacterial pathogens. Surprisingly, the species identified in our patient was the same as previously reported in the United States.[1,2,4,5,8] It is possible that the patient

Table 1 The summary of case reports of tick infestation of the conjunctiva

Authors, year of publication	Tick		Patient				Removal method
	Species	Stage	Age (year)	Gender	Laterality	Geographic area	
Jensen et al., 1982[1]	*Otobius megnini*	larva	2	M	OS	Arizona, USA	mechanical removal with blunt forceps and cotton tip applicator
Bode et al., 1987[2]	*Amblyomma americanum*	larva	28	M	OD	Texas, USA	conjunctival excision
Meades and Lam, 1991[3]	Unknown	larva	27	F	NI	NI	conjunctival excision
Love et al., 2001[4]	*A. americanum*	NI	5	F	OD	Arkansas, USA	conjunctival excision
	A. americanum	NI	2	F	OS	Arkansas, USA	conjunctival excision
Willen et al., 2011[5]	*A. americanum*	larva	39	M	OD	Alabama, USA	conjunctival excision
Celik et al., 2014[6]	*Ixodes* spp.	NI	36	M	OD	Turkey	mechanical removal with blunt forceps
Teong et al., 2015[7]	*I. holocyclus*	larva	10	M	OD	Sydney, Australia	conjunctival excision
Kuriakose et al., 2016[8]	*I. scapularis*	larva	Late 60s	F	OD	New York, USA	mechanical removal with 30-gauge needle
Current case	*A. americanum*	larva	56	M	OS	Denver, USA/ Chiang Mai, Thailand	mechanical removal with blunt forceps and cotton tip applicator

newly contracted the tick in Chiang Mai or imported an *A. americanum* larva from Denver. The larval tick could have tolerated the similar climate of these two places for several days before infestation.

Ophthalmology consultation is advised in cases with ticks affixed to the ocular regions. Surrounded conjunctival excision, the most effective method of removal, is usually required.[2-5,7] Although our patient was infested by the larval stage which usually does not transmit diseases, total removal of the tick was recommended to relieve symptoms and to minimize the inflammatory reaction.[8] In our case, despite the mouthpart being burrowed under the conjunctiva, we were able to completely remove it with non-toothed forceps and a cotton tip applicator which had been proposed by Jensen et al,[1] Celik et al,[6] and Kuriakose et al.[8] Neither complications nor adverse sequelae occurred after treatment.

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Case Report/รายงานผู้ป่วย

Acute Bilateral Visual Loss in Moyamoya Disease after COVID–19 Vaccination: A Case Report

รายงานผู้ป่วยตามัวลงทั้งสองข้างในโรคโมยาโมยาหลังฉีดวัคซีนป้องกันโรคโควิด–19

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Abstract

Purpose: To report a Moyamoya patient who presented with acute bilateral visual loss after covid – 19 vaccination.

Case presentation: A 39-year-old Thai man presented with bilateral visual loss three days after the first dose of COVID-19 vaccination (inactivated vaccine - Coronavac or Sinovac). Eye examination revealed total visual field defects in both eyes. The MRI showed acute infarction in the left occipital cortex and old infarction in the right occipital cortex and other areas of the cerebral hemisphere. MRA showed severe narrowing of both ICAs and both MCAs, with collateral supplied with forming a puff of smoke appearance, representing Moyamoya's disease.

Conclusion: Acute bilateral visual loss caused by occipital infarction in Moyamoya's disease after COVID–19 vaccination. It may be a coincidence or triggered by COVID-19 vaccine, Corona Vac.

Keywords: bilateral visual loss, Moyamoya disease, COVID-19 vaccination

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บทคัดย่อ

วัตถุประสงค์: เพื่อรายงานเคสผู้ป่วยโรคโมยาโมยาที่มีอาการตามัวลงทั้งสองข้าง หลังจากได้รับวัคซีนป้องกันโรคโควิด–19

รายงานผู้ป่วย: ผู้ป่วยชายอายุ 39 ปี มาด้วยอาการตามัวลง 2 ข้างหลังได้รับวัคซีนป้องกันโรคโควิด–19 เข็มแรก (ซิโนแวค) 3 วัน ตรวจพบว่าผู้ป่วยสูญเสียการมองเห็น ทั้ง 2 ข้าง ลักษณะเป็น cortical blindness ผลการตรวจ MRI brain มีสมองขาดเลือดจากหลอดเลือดในสมองตีบเกิดขึ้นใหม่ที่ตำแหน่ง left occipital cortex และสมองขาดเลือดจากหลอดเลือดตีบที่เกิดมานานแล้วที่ตำแหน่ง right occipital cortex และตำแหน่งอื่นๆในสมอง MRA แสดงให้เห็นว่ามีการตีบแคบของ internal carotid artery และ middle carotid artery ทั้งสองข้าง ร่วมกับมีหลอดเลือดฝอยผิดปกติคล้ายหมอกควัน เข้าได้กับโรคโมยาโมยา ผู้ป่วยได้รับการรักษาตามอาการ และหลังติดตามอาการ 1 เดือนผู้ป่วยมีลานสายตาดีขึ้น

สรุป: อาการตามัวในผู้ป่วยโมยาโมยารายนี้เกิดจากหลอดเลือดในสมองตีบตำแหน่ง occipital cortex และ visual pathway การได้รับวัคซีนป้องกันโรคโควิด-19 อาจเป็นตัวกระตุ้นให้เกิดการตีบหรือหลอดเลือดหดตัว หรือเป็นสิ่งที่บังเอิญเกิดขึ้นร่วมกันก็เป็นได้

คำสำคัญ: bilateral visual loss, Moyamoya disease, COVID-19 vaccination

Introduction

Thailand began vaccination against the COVID-19 (Coronavirus disease) infection with the inactivated vaccine (Coronavac or Sinovac) on February 28, 2021. This was later followed by the AZD1222 (AstraZeneca) vaccine on June 7, 2021, and then messenger RNA (mRNA)-based vaccine BNT162b2 (Pfizer/BioNTech) in August 2021.

Multiple side effects have been reported, ranging from mild symptoms, such as swelling and redness at the injection site, low-grade fever, nausea, vomiting, and fatigue, to more severity, including high fever, chills, anaphylactic shock, seizures, and loss of consciousness.[1] In addition, the reports about ophthalmological complications of COVID-19 vaccination also arose. The ocular adverse effects include optic neuritis, facial palsy, cranial nerve palsies including third, fourth, and sixth nerve palsies, acute macular neuroretinopathy, central serous retinopathy, uveitis, multiple evanescent white dot syndrome, Vogt-Koyanagi-Harada disease reactivation, etc.[2,3] There were the reported cases of bilateral transient visual field defect or stroke may be triggered by COVID - 19 vaccine.[4,5] However, there is not enough information on the side effects that may occur following vaccination, is just coincidental or really related to the vaccine.

Moyamoya disease (MMD) or "spontaneous occlusion of the circle of Willis" was first reported in 1969 by Suzuki and Takaku.[6,7] MMD is a rare, chronic progressive disorder of the arteries in the brain. The terminal portion of the internal carotid artery becomes narrow or obstructed and produces abnormal collateral vessels at the base of the brain. Inadequate blood supply can cause ischemic stroke, hemorrhagic stroke, or transient ischemic attacks (TIA). Patients often present with symptoms of limb weakness, hemiparesis, headache, dysarthria, aphasia, cognitive impairment, and seizures. MMD is often diagnosed in children in the first decade, or in adults in their 40s. Females have a higher risk. This arteriopathy occurs on an idiopathic or familial. Many studies show genetic links in Asia.

Suzuki and Takaku classified MMD into 6

stages[7] based on the sequential changes in cerebral angiograms. Stage 1: narrowing of the carotid fork. Stage 2: initiation of Moyamoya collaterals. Stage 3: progressive ICA stenosis with the intensification of Moyamoya collaterals at the base of the brain. Stage 4: minimization of Moyamoya, anterior and middle cerebral artery disappear. Stage 5: reduction of Moyamoya, increase the ECA collaterals. Stage 6: total occlusion of ICA and Moyamoya collaterals disappear, and the brain is supplied from the external carotid or vertebral arterial system.

Moyamoya can be classified as Moyamoya syndrome and Moyamoya disease.[9,11] Patients with the characteristic Moyamoya vasculopathy who also have associated conditions such as Down's syndrome, Neurofibromatosis type I, sickle cell anemia, cranial irradiation, etc. are categorized as the Moyamoya syndrome, whereas patients without associated risk factors are said to have Moyamoya disease. Treatment involves managing symptoms with medicine or improving brain circulation by surgery.

This article aims to report a case of Moyamoya disease with acute bilateral visual loss a few days after vaccination against COVID-19.

Case report

A 39-year-old man presented with acute bilateral visual loss, three days after he received the first dose Sinovac vaccine. The patient was a motorcycle taxi driver who had diabetes mellitus and systemic hypertension. He did not have a history of previous neurological deficits and cardiovascular events. He was not obese and stopped smoking 10 years ago. he did not have a history of COVID-19 infection.

The patient was investigated on the fifth post-vaccination day. Ophthalmological examination revealed visual acuity of hand motion in both eyes. Intraocular tensions were normal. Normal pupillary reaction, clear cornea, and clear lens were manifested bilaterally. Fundus examination showed normal macula and no diabetic retinopathy. the optic disc had clear margin, and neither edema nor pallor was shown. The computerized visual field (CTVF 24-2) appeared totally visual field defect in both eyes (Figure 3). Other neurological deficits were not manifested. Fasting blood sugar was 349 mg%, blood pressure 145/94 mmHg and the syphilis screening was negative. The hemogram was normal.

Brain magnetic resonance imaging (MRI), which was performed on the seventh post-vaccination day, showed multi-stage infarction at both cerebral hemispheres. Acute infarctions at left occipital cortex. Gliotic and encephalomalacia changed at the right temporal lobe, right parietal lobe, right occipital lobe, and left frontal lobe, representing old infarctions. (Figure 1)

Brain magnetic resonance angiography (MRA) showed severe narrowing at cavernous-supraclinoid parts of the right internal carotid artery (ICA), supraclinoid part of left ICA, and M1 segment of both middle cerebral arteries (MCAs), with extensive collateral supplied forming puff of smoke appearance, representing Moyamoya disease. (Figure 2)

The patient was diagnosed with cortical vision loss secondary to occipital stroke. He was hospitalized for a week, under supportive treatment, mainly with aspirin 300 mg and diabetes control. His baseline cortical visual loss persisted, and he still had visual

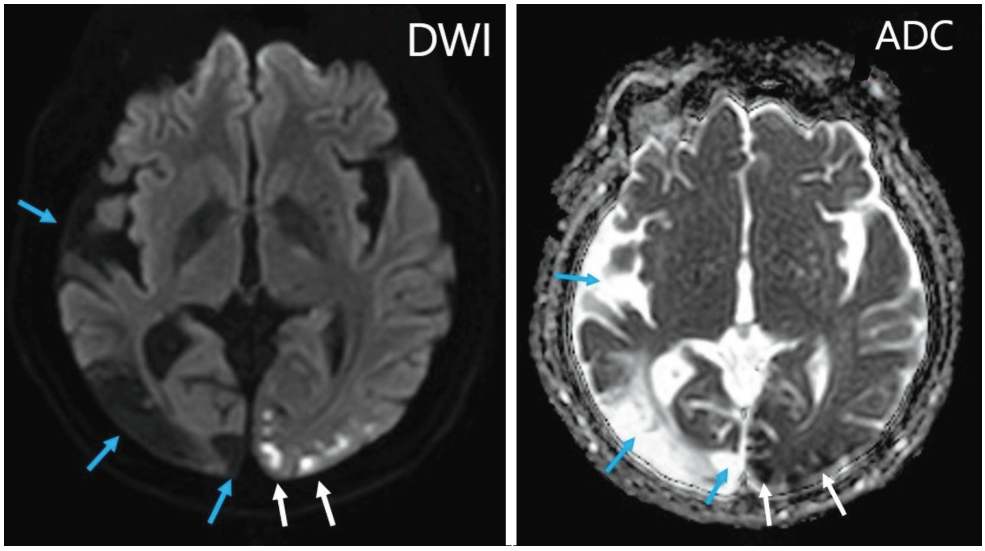

Figure 1 MRI (DWI and ADC): acute infarction at Lt occipital cortex (white arrow). Gliotic and encephalomalacia changed at right temporal lobe and right occipital lobe, representing old infarctions (blue arrow).

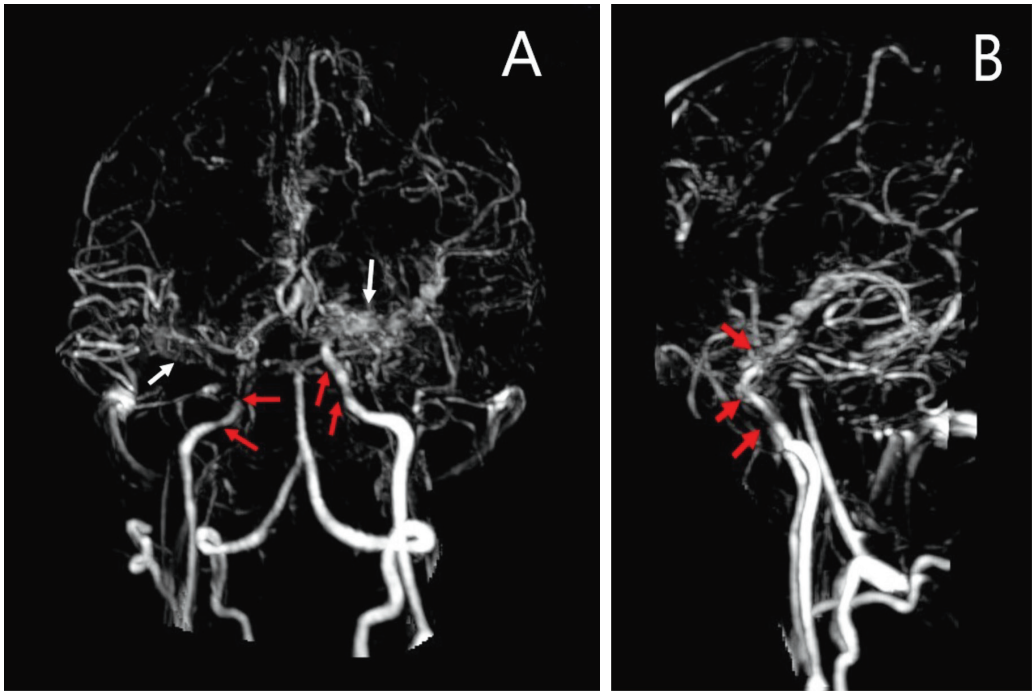

Figure 2 MRA: severe stenosis at bilateral distal internal carotid artery (red arrows) and proximal both middle cerebral arteries. White arrows show extensive collateral vessels.

acuity of hand motion until discharge. He was given aspirin 300 mg, donepezil 5 mg, antihypertensive and diabetic drugs after discharge.

One month later, the vision improved significantly to 20/160 in the right eye and 20/80 in the left eye. CTVF showed bilateral left homonymous hemianopia (Figure 4) the patient rejected the second dose of COVID-19 vaccination and lost follow-up.

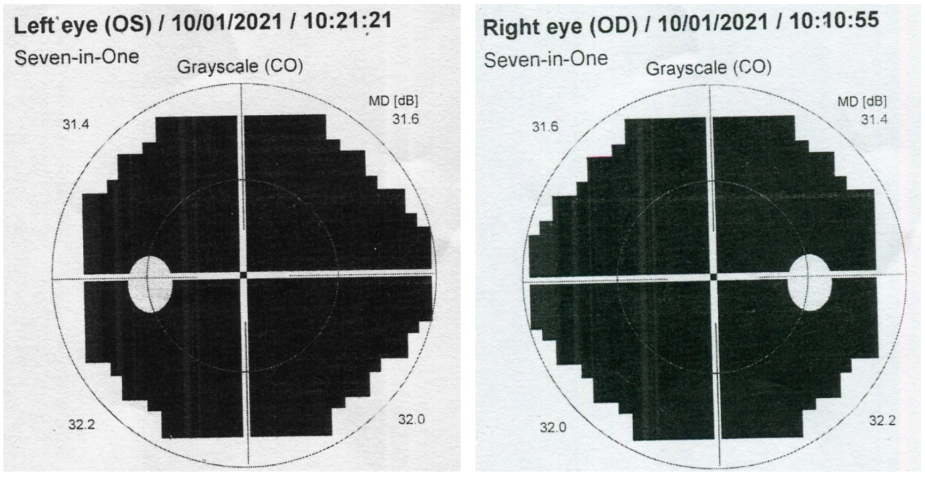

Figure 3 visual field (CTVF 24-2) show total defect in both eyes at first visit.

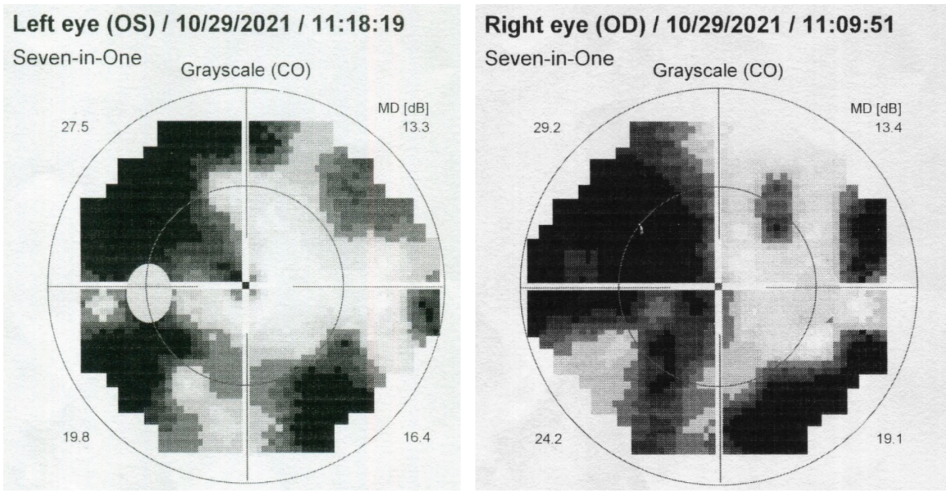

Figure 4 visual field (CTVF 24-2) show improvement at 29 days later (look-like left homonymous incongruous hemianopia and right superior- inferior quadrantanopia).

Discussion

This article reports a patient with Moyamoya disease who had bilateral occipital infarctions resulting in bilateral visual loss after COVID-19 vaccination. Previously, the patient did not have any neurological disorder. Although the old infarction occurred in the right temporal, parietal and occipital cortex causing left homonymous hemianopia, the patient did not aware of his visual problem. Until ischemia in the left occipital lobe leads to loss of vision in the half of the visual field.

"Moyamoya" is a Japanese expression for something hazy just like a puff of cigarette smoke drifting in the air, because the disease produces abnormal net-like vessels at the base of the brain. MMD is a very rare disease, the prevalence appears about 1 per million in Europeans. In Asia, it is more common, especially in Japan and Korea. In Japan, it is found about 1 per 200,000 cases.[8] MMD is chronic, progressive cerebrovascular stenosis characterized by the terminal portion of the internal carotid artery becoming narrow or obstructing and

producing abnormal collateral vessels at the base of the brain. The exact cause is unknown. But it is believed to be caused by genetics or infection.

This abnormal cerebrovascular system can easily lead to ischemic stroke or hemorrhagic stroke. There are two peaks of incidence, the peak in the pediatric group occurs in the first decade and the peak in the adult group occurs at age 30-40 years. TIAs or ischemic strokes are common in children. Whereas most adult patients present with intracranial hemorrhage. Symptoms are associated with the regions of the brain supplied by the internal carotid arteries and middle cerebral arteries, including frontal, parietal, and temporal lobes. Patients may also have syncope, convulsion, visual deficits, or personality changes. The symptoms may be triggered by hyperventilation, exercise, crying, eating hot food, coughing, stress, fever, or dehydration.

No treatment can reverse or prevent cerebrovascular stenosis. The treatment involves managing symptoms and improving blood flow to the brain. Improvement in cerebral blood flow may prevent future ischemic strokes.[9,10] Since MMD affects the internal carotid artery while sparing the external carotid artery, surgical treatment typically uses the external carotid artery as a new source of blood supply to the ischemic areas. There are two methods of revascularization: direct and indirect. Direct revascularization uses a branch of the external carotid artery (usually the superficial temporal artery) directly anastomosed to a cortical artery. This method immediately increases the blood supply to the brain but is often difficult to perform in children because of small vessels. Indirect techniques use vascularized tissue supplied by the external carotid artery (e.g., dura, temporalis muscle) or the superficial temporal artery in direct contact with the brain, in order to stimulate blood vessel growth. This method is less difficult but takes several weeks for the new blood supply.

Medical therapy has been used when the patient has a mild disease or has a high risk for surgery. Antiplatelet agents have been used for stroke prophylaxis. Anticoagulants such as warfarin are rarely used. Calcium-channel blockers may be useful in headaches or migraines, which are common in MMD patients.

This case may have an unusual presentation of MMD such as posterior circulation involvement and only visual loss symptom. The main vascular supply to the occipital cortex is provided by branches of posterior cerebral arteries (PCAs). PCAs originate from posterior circulation (vertebrobasilar system) which is less effective in the early to middle stage of MMD. From MRA, this patient has no stenosis at PCAs, basilar artery, and vertebral arteries. But he may have abnormal vessels that cannot be detected by angiogram (more periphery or very small). He had a previous cerebral infarction without detected symptoms until the new infarction occurred. Many possible mechanisms could explain the cause of this acute infarction such as poor control of blood sugar, stress, and fever after getting the vaccination. The other mechanism that could be related to cerebrovascular stenosis, was triggered by COVID-19 vaccination. Because there were many studies showing the correlation between COVID-19 vaccination and vascular obstruction such as cerebral venous thrombosis[15], stroke[5], or vasospasm[4].

Conclusion

For patients present with occipital stroke in children or middle-aged groups, MMD should be

considered in differential diagnosis although it is a very rare disease. Although MMD usually affects the anterior circulation (ICAs and MCAs), the posterior circulation may also be affected.[12,13,14] MMD patients should be aware when getting vaccination because they can be triggered by stress, crying, fever, or the side effect of the vaccine itself.

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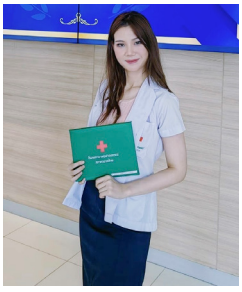
Recurrent Wound Dehiscence after Trabeculectomy in Uveitic Glaucoma: A Case Report

รายงานผู้ป่วยที่มีภาวะแผลแยกซ้ำหลังการผ่าตัดต้อหิน ในผู้ป่วยต้อหินที่เกิดจากโรคม่านตาอักเสบ



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Abstract

Objective: To report an unusual case of recurrent wound dehiscence after trabeculectomy and its management.

Observation: A 47-year-old Thai male with non-granulomatous anterior uveitis of his left eye underwent trabeculectomy with mitomycin C due to uncontrolled intraocular pressure. At postoperative 1 week, conjunctival retraction was observed with the exposure of the base of scleral flap. Conjunctival flap advancement with 10-0 nylon was performed to prevent bleb leakage and risk of intraocular infection. Ten days after conjunctival flap advancement, recurrent conjunctival wound retraction was seen with more amount of scleral flap exposure and positive Seidel test. Conjunctival flap advancement with amniotic membrane transplantation over the scleral flap was performed. A week later, an exposed scleral flap with conjunctival retraction was encountered again. We decided to reconstruct the conjunctival flap with corneoscleral patch graft covering the anterior two thirds of the scleral flap area. At follow up 10 months, corneoscleral patch graft was still in a good position on scleral flap. The intraocular pressure was 10 – 12 mmHg with 0.5% timolol maleate eye drop. No recurrent wound dehiscence occurred.

Conclusion: Recurrent conjunctival dehiscence after trabeculectomy is an unusual complication after trabeculectomy despite multiple surgical corrections with watertight wound closure. The only distinctive personal risk factor that associated with this condition was current smoking. Delay wound healing has been reported in smokers. We assumed that smoking may be a potential cause of poor wound healing in this patient. Conjunctival resuture alone may not enough to handle a large size leakage. Wound reconstruction with biological tissue graft should be considered.

Keywords: Bleb leak, glaucoma, smoking, trabeculectomy, uveitic glaucoma, wound dehiscence

บทคัดย่อ

วัตถุประสงค์: เพื่อรายงานผู้ป่วยที่มีภาวะแผลแยกซ้ำหลังการผ่าตัดต้อหิน และวิธีการรักษา

รายงานผู้ป่วย: ผู้ป่วยชายไทยอายุ 47 ปี ได้รับการวินิจฉัยเป็นโรคม่านตาอักเสบตาและมีความดันตาสูงในตาข้างซ้าย โดยไม่สามารถคุมความดันตาได้ ผู้ป่วยจึงได้รับการผ่าตัดเปิดทางระบายน้ำจากลูกตา หนึ่งสัปดาห์หลังผ่าตัด ตรวจพบเยื่อตาขาวรั้งขึ้นเหนือแผลผ่าตัดที่ตาขาว จึงได้ทำผ่าตัดเย็บซ่อมโดยการเย็บดึงเยื่อตาขาว หลังจากนั้น 10 พบเยื่อบุตาขาวรั้งขึ้น เห็นแผลที่ตาขาวอีกครั้ง จึงได้ทำผ่าตัดเย็บดึงเยื่อตาขาวมาติดที่กระจกตา ร่วมกับการใช้เยื่อหุ้มรกเย็บคลุมอีกชั้นหนึ่ง หนึ่งสัปดาห์หลังจากนั้น เยื่อบุตาขาวยังคงรั้งขึ้น จนกระทั่งเห็นแผลผ่าตัดที่ตาขาวเช่นเดิม จึงได้นำชิ้นส่วนตาขาวและกระจกตา ที่ได้รับบริจาคจากผู้เสียชีวิต มาวางและเย็บปิดบริเวณ 2/3 ด้านหน้าของแผลที่ตาขาว และเย็บเยื่อตาขาวติดกับกระจกตา หลังการตรวจติดตามหลังผ่าตัดครั้งสุดท้าย 10 เดือน ไม่พบการดึงรั้งขอเยื่อตาซ้ำ

สรุป: ภาวะแผลแยกซ้ำหลังผ่าตัดต้อหินเป็นภาวะแทรกซ้อนที่พบได้ไม่บ่อย ผู้ป่วยรายนี้มีประวัติการสูบบุหรี่เรื้อรังที่เป็นปัจจัยเสี่ยงต่อการเกิดแผลแยกซ้ำ การผ่าตัดแก้ไขโดยการเย็บเยื่อตาเพียงอย่างเดียว อาจไม่สามารถปิดแผลที่เกิดจากการดึงรั้งได้ การเย็บแผลร่วมกับการใช้เนื้อเยื่อกระจกตาและตาขาวหรือเนื้อเยื่ออย่างอื่น สามารถช่วยเพิ่มความแข็งแรงของการสมานแผลได้

คำสำคัญ: Bleb leak, glaucoma, smoking, trabeculectomy, uveitic glaucoma, wound dehiscence

Introduction

Trabeculectomy is the most frequent glaucoma filtering surgery to lower the intraocular pressure (IOP) when maximal glaucoma medications are not enough to control the IOP. However, many postoperative complications are encountered. Bleb leakage is a common complication after trabeculectomy and occurs more in fornix-based conjunctival flap compared to limbal-based fashion[1,2]. The causes of wound leakage are wound dehiscence, incomplete conjunctival closure, and the use of adjunctive anti-metabolites. The risk factors that interfere wound healing are elderly, diabetes, immunocompromised condition, obesity, smoking, alcohol consumption and stress[3]. Treatment modalities for wound leak depends on the extent and severity of the leakage. For small bleb leak, aqueous suppressant, soft bandage contact lens with topical antibiotic is sufficient to close the leak[4]. If the conservative treatment is not enough, surgical interventions are indicated. Additional indications for surgical interventions are prolonged hypotony, recurrent wound leakage, and repeated episodes of bleb-related infection. We report a case of recurrent conjunctival wound dehiscence after trabeculectomy with a reconstruction method.

Case report

A 47-year-old Thai male presented with non-granulomatous anterior uveitis of his left eye. Eye examination revealed normal eye exam in the right eye. Left eye examination revealed microcystic edema without keratic precipitate. Anterior chamber cell can't be evaluated due to corneal edema. Anterior chambers were deep in both eyes. His intraocular pressure was 16 and 60 mmHg, right and left eye, respectively. Cup to disc ratio was 0.3 in the right eye and 0.4 in the left eye. Fundus examination was unremarkable in both eyes. He took oral acetazolamide 250 mg four times a day, a fixed combination of 0.2% brimonidine tartrate and 0.5% timolol maleate ophthalmic solution three times a day. Diagnostic anterior chamber paracentesis showed positive for Epstein-Barr virus (EBV) by polymerase chains reaction-based method and positive quantiferon-TB Gold. Vitreous sample was not collected for investigation. Hypertensive viral-associated anterior uveitis was suspected. His uveitis condition was treated with 800 mg oral acyclovir five times a day. The inflammation was continuously controlled by topical prednisolone acetate 1% every two hours. A week later, he was sent to glaucoma clinic because of persistent IOP elevation. At first presentation, his visual acuity in the left eye was 20/50 with IOP of 50 mmHg. Cornea revealed mild microcystic edema without cell in the anterior chamber. Gonioscopy was grade 3 in all mirrors without any pigment or peripheral anterior synechiae. Cup to disc ratio was 0.5. Due to persistent IOP elevation, filtering surgery had been scheduled.

He underwent trabeculectomy with mitomycin-C in the left eye by a glaucoma expert (AM). After subconjunctival injection of 2% Xylocaine, superior conjunctival flap was made in a fornix-based fashion. A wet-field bipolar cautery was applied to stop bleeding over the scleral flap area. Then we applied sponges soaked with mitomycin-C 0.3 mg/ml into subconjunctival space. Care was taken to avoid the mitomycin-C to touch the edge of conjunctival wound. After 3 minutes, all sponges were removed, followed by copious irrigation. Superior trapezoid scleral flap was created. Sclerostomy was made with Kelly Descemet punch and iridectomy was done to

prevent an obstruction of iris at the sclerostomy site. The scleral flap was then closed with 10-0 nylon. The scleral flap sutures were adjusted for adequate drainage. Conjunctiva was closed by 10-0 nylon and checked for watertight wound closure at the end of the surgery. There was no intraoperative or immediate postoperative complications. The patient was prescribed with topical prednisone acetate every 2 hours during the daytime and topical levofloxacin four times a day.

On the first postoperative day, his best corrected visual acuity was 20/20. The bleb was moderately diffuse with negative Seidel test. IOP was 17 mmHg with formed anterior chamber and no choroidal detachment. One week later, the conjunctival retraction was observed with the exposure of the base of scleral flap. The Seidel test was negative. The IOP was 24 mmHg with formed anterior chamber. No choroidal detachment was detected. Consequently, conjunctival flap advancement and resuture with 10-0 nylon was performed. Ten days after that, recurrent conjunctival wound retraction was seen with more amount of scleral flap exposure (Figure 1). The Seidel test was positive. The IOP was 14 mmHg with low bleb. Anterior chamber was deep without choroidal detachment. Conjunctival flap advancement in combination of amniotic membrane transplantation over the scleral flap was performed. We covered the conjunctiva flap with two-layer amniotic membranes and suture with 10-0 nylon. On the first postoperative day, the bleb was moderately diffuse with negative Seidel test. The conjunctiva was sutured securely without dehiscence (Figure 2). A week later, an exposed scleral flap with conjunctival retraction was encountered again with positive Seidel test (Figure 3). The IOP was 5 mmHg, deep anterior chamber without choroidal detachment. We decided to reconstruct the conjunctival flap with corneoscleral patch graft. We placed the donor corneoscleral graft to cover the anterior two thirds of

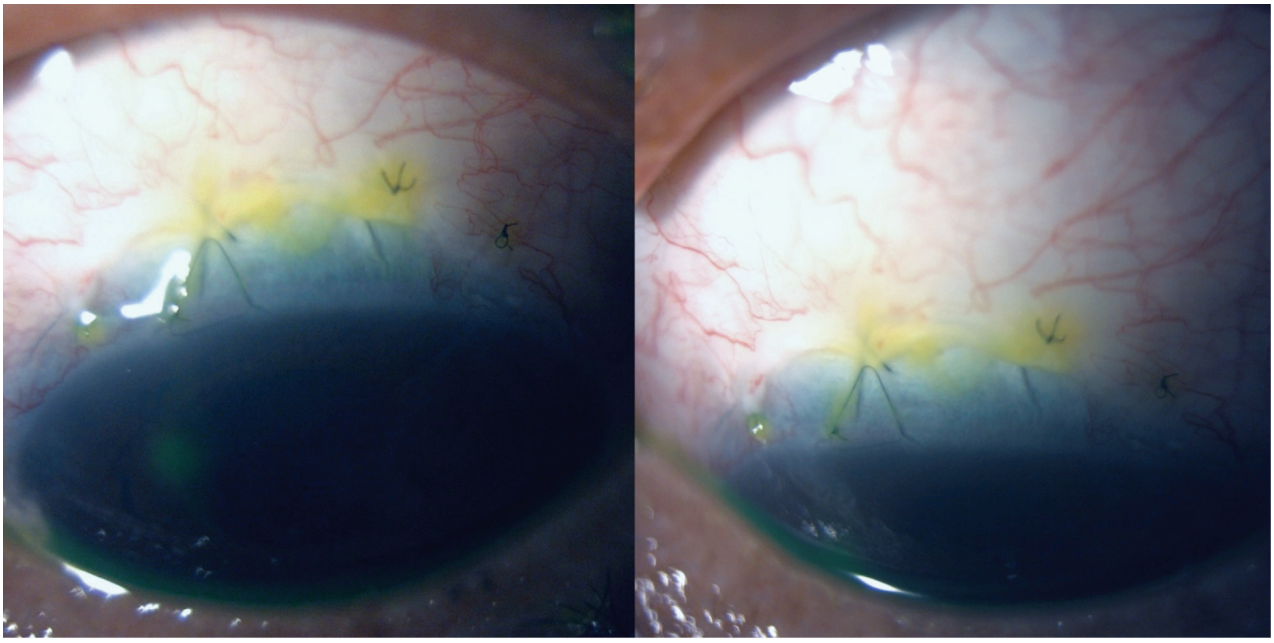

Figure 1 Conjunctival wound retraction with expose scleral flap after conjunctival flap advancement and resuture.

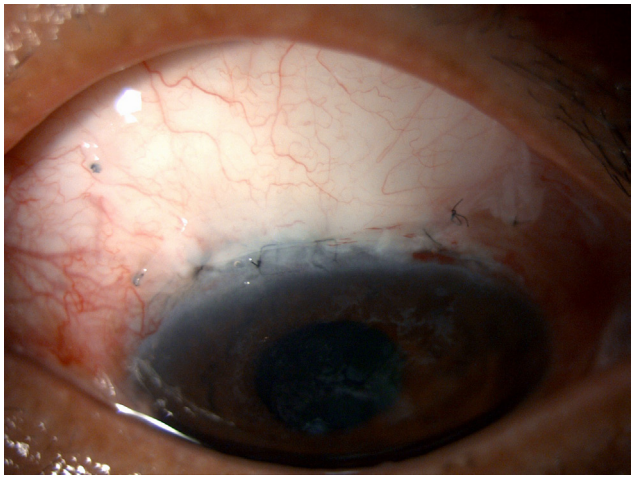

Figure 2 Conjunctival flap advancement with amniotic membrane transplantation.

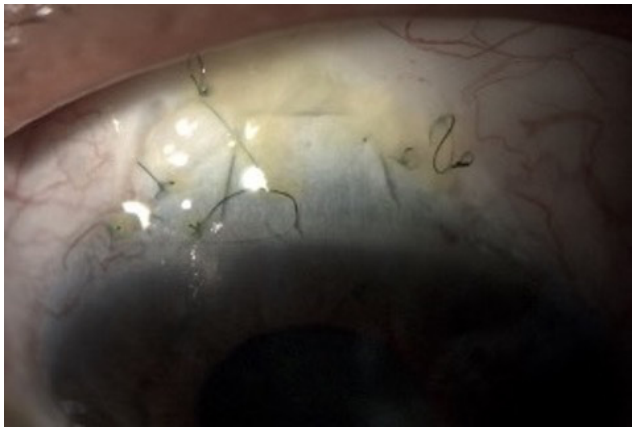

Figure 3 Exposed scleral flap with conjunctival retraction after conjunctival flap advancement with amniotic membrane transplantation.

the scleral flap area and check for adequate aqueous leakage. The conjunctiva was sutured securely with no leakage was seen. One week after the last operation, best corrected visual acuity was 20/25. The IOP was 7 mmHg, formed anterior chamber without choroidal detachment. The bleb was moderately diffuse. The Seidel test was negative. Corneoscleral patch graft was still in a good position on scleral flap without wound dehiscence (Figure 4). After the last procedure, the conjunctival retraction was still observed but because of the integrity of the corneoscleral graft, the leakage was not occurred (Figure 5). Best corrected visual acuity was 20/20 with IOP between 10 and 13 mmHg in the first three months. After that, the IOP was 14 mmHg with cup to disc ratio of 0.7, 0.5% timolol maleate twice a day was prescribed. After that, the IOP was between 10 and 12 mmHg until 10 months after the last operation.

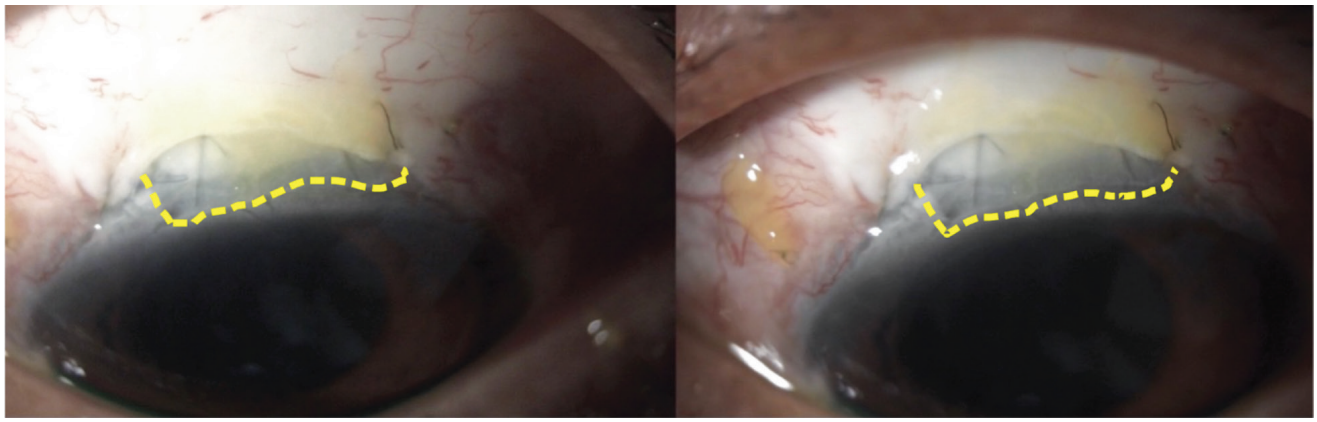

Figure 4 One week after conjunctival flap resuture with corneoscleral patch graft.

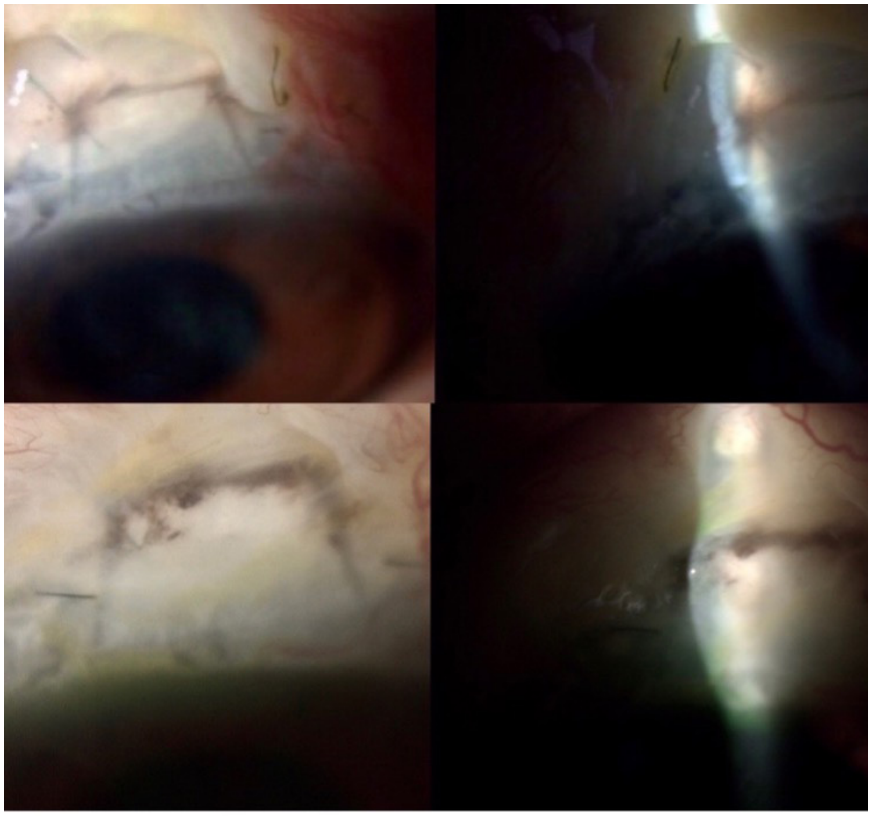

Figure 5 Conjunctival wound findings after conjunctival flap suture with corneoscleral patch graft (Top row: 1 month after surgery, Bottom row: 10 months after surgery).

Discussion

Conjunctival wound leak is a common complication in trabeculectomy. In this patient, conjunctival wound retraction was the cause that led him to multiple conjunctival reconstruction procedures after filtering surgery. Initially, conjunctival flap advancement had been done alone. However, scleral flap exposure was still presented. Conjunctival repair with amniotic membrane transplantation was performed as a second procedure. After that, wound dehiscence rediscovered. Finally, conjunctival restoration with corneoscleral patch graft was done without recurrent episode of wound dehiscence.

There were two interesting points in this case. Firstly, we present a case with recurrent wound dehiscence that is not common after trabeculectomy. During the trabeculectomy surgery, his wound was sutured securely, and no wound leak was detected. Besides, the duration of the surgery was within an hour. During all follow up visits, there was no sign of infection such as blebitis or conjunctivitis. We thought over the causes of poor wound healing in this case. The only distinctive personal history in this patient was continuous smoking prior to surgery. Tobacco smoker patients required higher surgical intervention such as bleb revision, repeat trabeculectomy, tube implant, and cyclophotocoagulation within one year after trabeculectomy compared to non-smokers. In addition, one-year success rate of trabeculectomy was significantly lower in smokers than non-smokers[5].

Good wound healing required delicate balance from inflammation and wound fibrosis. It consists of three phases: inflammation, proliferation and fibrosis[4]. Smoking delayed wound healing by several mechanisms. Tissue oxygenation was reduced, and inflammatory cells were suppressed. Also, proliferative phase was impaired by decreased fibroblasts and down regulated collagen synthesis. Smoking impaired neutrophil activities affecting oxidative bactericidal mechanism which required for eradicating surgical pathogen. Besides, smoking and nicotine significantly disturbed tissue perfusion and oxygenation due to endothelial dysfunction and vasoconstriction beyond the tolerable level of normal tissue. Smoking also had an impact on oxidative stress causing low levels of antioxidants and deteriorated collagen mechanism resulting in damage of tissue components[6]. As smoking greatly affected on inflammation, including wound proliferation and remodeling, we assumed smoking convincingly affected poor wound healing in this patient. One of the local risk factors of wound leak is the application of antimetabolite4. In the case, we used mitomycin-C 0.3 mg/ml which is in the recommended concentration of 0.2–0.4 mg/ml. The duration of application was 3 minutes which was not prolonged. The patient strictly applied medications as prescribed.

The second issue is the reconstruction method. According to trabeculectomy wound leakage, various biological grafts such as amniotic membrane, scleral graft, corneal graft either in full thickness or partial thickness, pericardium, buccal membrane, fascia lata can be considered[7]. The advantage of all materials is to strengthen the wound, however, depends upon availability. Multiple failures by using the same material are associated with lower success rate[11]. Therefore, in this case, we started with conjunctival advancement alone, followed by adjunct with amniotic membrane. Amniotic membrane has been used to repair bleb leakage, including cystic bleb[8,9]. However, the leakage in our case is because of the conjunctival retraction. The extension of leakage may be too board to heal with amniotic membrane alone. Recently, Laspas, et al. reported the benefit of corneoscleral graft to repair hypotony with scleral melting. The IOP was control after 6 months after surgery[10]. In our case, we successfully secure the wound with corneoscleral graft. To prevent obstruction of the aqueous drainage, we covered the corneoscleral graft only the anterior two-thirds of the scleral flap height. The IOP at 10 months after the last reconstruction procedure was 12 mmHg.

Conclusions

Bleb leakage in combination with conjunctival wound dehiscence is an unusual complication after trabeculectomy. The only distinctive personal risk factor that associated with this condition was current smoking. Conjunctival resuture alone may not enough to handle a large size leakage. Wound reconstruction with biological tissue graft should be considered.

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