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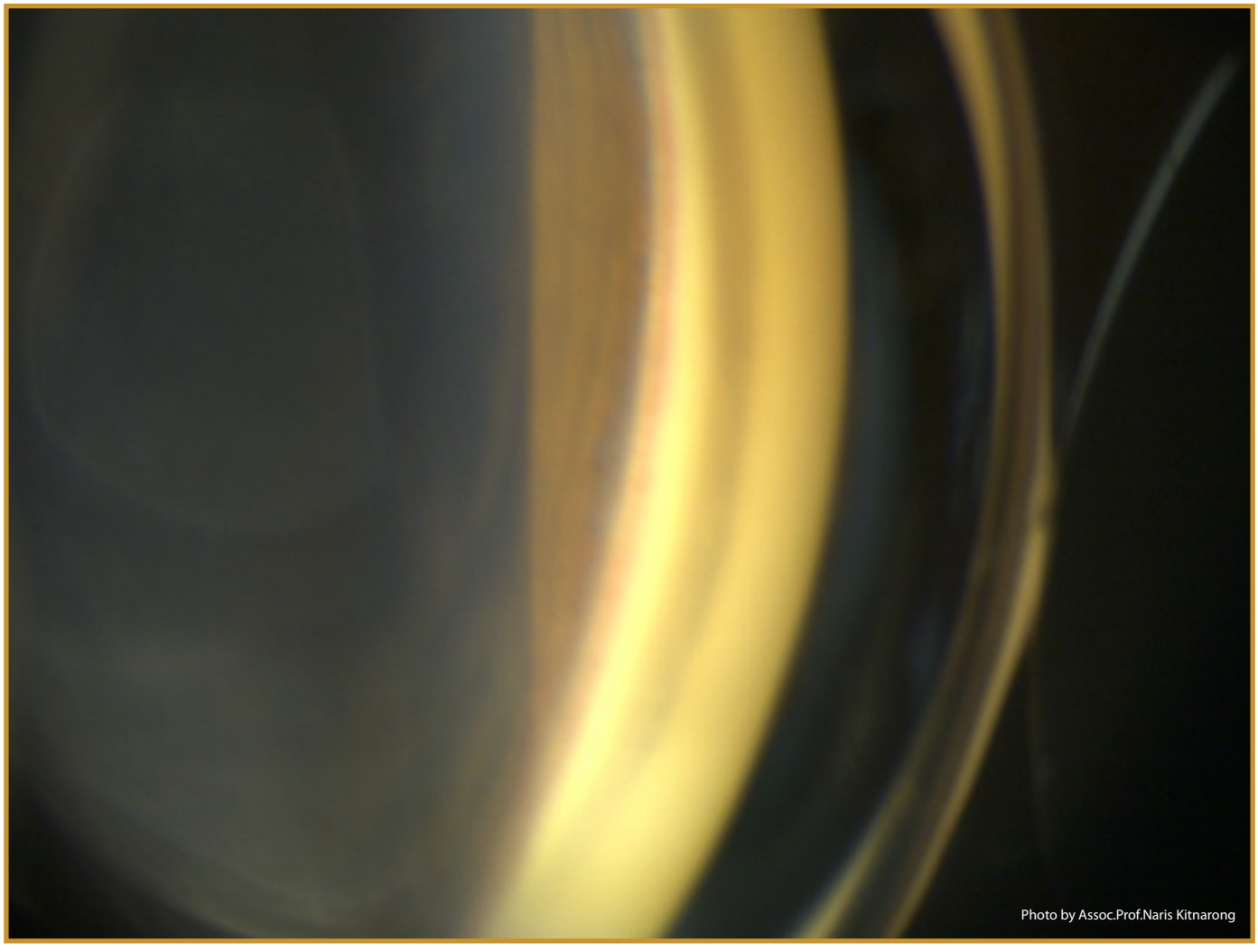

Photo by Assoc.Prof.Naris Kitnarong

This image shows blood in Schlemm's canal, an unusual finding that may indicate elevated episcleral venous pressure. The presence of blood suggests potentially linked to conditions like Sturge-Weber syndrome, thyroid eye disease or carotid-cavernous fistula. Gonioscopy allows for the detailed visualization of this abnormality, aiding in the diagnosis and management of underlying ocular or systemic disorders.

Anuwat Jiravarnsirikul, MD

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E-mail: sijournal92@gmail.com

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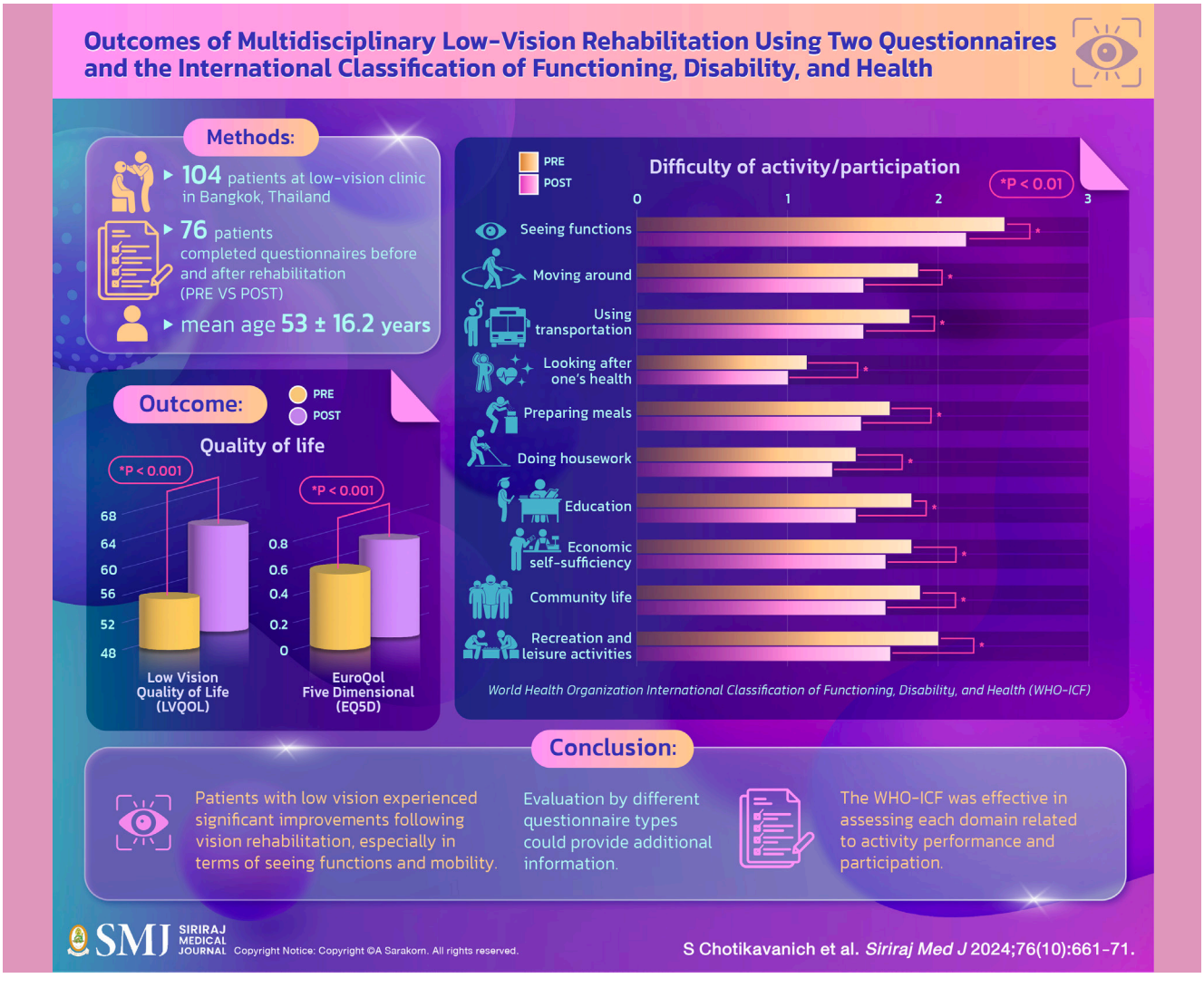
Office: His Majesty the King's 80th Birthday Anniversary 5th December 2007 Building (SIMR), 2nd Fl., Room No.207
Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand Tel: 02-419-2888 Fax: 02-411-0593
E-mail: sijournal92@gmail.com

Outcomes of Multidisciplinary Low-Vision Rehabilitation Using Two Questionnaires and the International Classification of Functioning, Disability, and Health

Suksri Chotikavanich, M.D.[1], Akarawit Eiamsamang, M.D.[1,*], Thanaporn Layangool, M.D.[1], Wichuda Krutthong, MA[1], Siriwan Loket, B.Ed.[1], Rungtip Yingyong, BSW[1], Somthin Dongngam, B.Sc.[1], Waree Nujoi, BS[1], Jaruwan Jai-ai, BS[1], Nattapon Sarinak, B.Sc.[1], Ekpipat Eksupapan, B.Sc.[1], Saranya Sagan, BPH[1], Peeraya Chaowalitwong, MA, B.Sc.[2]

[1]Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Human Research Protection Unit, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.



*Corresponding author: Akarawit Eiamsamang
E-mail: cokejoon13@hotmail.com
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ORCID ID:http://orcid.org/0009-0002-6073-8106
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ABSTRACT

Objective: To evaluate the effectiveness of a low-vision service by using three tools and to identify the specific outcomes obtained from each instrument.

Materials and Methods: Patients consecutively visiting the low-vision clinic at Siriraj Hospital, Bangkok, Thailand, were enrolled. The impact of the prescribed rehabilitation on patient quality of life was measured using three tools: the Low-Vision Quality-Of-Life Questionnaire (LVQOL); the generic EuroQol Five-Dimensional Questionnaire (EQ-5D); and the World Health Organization International Classification of Functioning, Disability, and Health (WHO-ICF).

Results: Out of the 104 patients recruited, 76 patients (mean age, 53 ± 16.2 years) completed the questionnaires before and after rehabilitation, which was assessed after 5.8 ± 2.0 months. Post-rehabilitation, the time of follow-up, patients had significant improvements in the mean scores of both the LVQOL scores and mean EQ-5D scores compared to before rehabilitation ($P < 0.001$), with Cohen's effect sizes of 0.85 and 0.67, respectively. Subgroup analyses by age, severity, and cause of visual impairment also showed significant improvements in the LVQOL ($P < 0.05$), but not the EQ-5D score in the blindness severity subgroup. The ICF scores also showed significant improvement in most domains, including seeing functions, mobility across different locations, transportation use, meal preparation, economic self-sufficiency, community life, and recreational activities ($P < 0.01$).

Conclusion: Patients with low vision experienced significant improvements following vision rehabilitation, especially in terms of seeing functions and mobility. Evaluation by different questionnaire types could provide additional information. The WHO-ICF was effective in assessing each domain related to activity performance and participation.

Keywords: International classification of functioning disability and health; low vision; quality of life; Thailand; vision rehabilitation (Siriraj Med J 2024; 76: 661-671)

INTRODUCTION

Low-vision rehabilitation aims to help patients with visual impairments improve their ability to perform activities of daily living, and thus enhances their well-being and quality of life. Despite encouragement for the integration of low vision care into ophthalmology services within hospitals, this service remains limited in many countries, including Thailand. There is a need to investigate the benefits of such interventions in real-life settings to facilitate their integration into health policies.

Since there is no gold standard to evaluate the outcomes of the service, most studies rely on quality-of-life questionnaires. These questionnaires have predominantly been vision-specific[1-4], and includes the Low-Vision Quality-Of-Life Questionnaire (LVQOL),[1] which has demonstrated improvements in quality of life following rehabilitation. Some studies also utilize generic questionnaires like the EuroQol Five-Dimensional Questionnaire (EQ-5D).[5,6] However, based on our review of English-language literature, there is a lack of research investigating outcomes of low-vision rehabilitation in Thailand. It is important to recognize that cultural and geographical differences may influence well-being of patients and potentially yield varying outcomes in different contexts.

Interestingly, the International Classification of Functioning, Disability and Health (ICF),[7] one of the World Health Organization's (WHO) Family of International Classifications, aims to define the health status issued from functioning and disability, rather than solely relying on disease diagnoses as with the International Classification of Diseases.[8] One key advantage of ICF is its ability to assess and code patients' capabilities in terms of "activities" and "participation", which are dimensions that align closely with quality of life measures that can be enhanced through rehabilitation interventions. Additionally, the ICF offers a comprehensive overview of functional domains with clearly defined scales of grading, unlike traditional quality of life questionnaires. Moreover, the ICF is recognized for providing a universal language internationally, thereby facilitating better communication among multidisciplinary health professionals and policymakers. In line with Thailand's health policy to focus on individuals with disabilities, a national committee recreated the ICF into Thai language,[9] an initiative that was endorsed by the Strategy and Planning Division, Ministry of Public Health in 2012.

Previous publications have only described the utility of ICF in assessing the health of patients with visual impairment,[10,11] however, there has been no

prior publication, to our knowledge, utilizing the ICF to examine outcomes of low-vision rehabilitation service. Meanwhile, the ICF has been applied to evaluate quality-of-life outcomes across other services, such as post-acute stroke rehabilitation,[12] computerized cognitive training in acquired brain injury,[13] and upper-limb tetraplegia surgery.[14]

The primary objective of this study was to assess outcomes of a hospital-based, low-vision rehabilitation service using different tools, namely, the LVQOL and EQ-5D self-reported quality of life questionnaires, and the WHO-ICF. The secondary aim was to evaluate characteristics of results obtained from these tools within the same population.

MATERIALS AND METHODS

Ethics approval and subjects

The study was conducted according to the principles of the Declaration of Helsinki. Approval for the research was obtained from the Committee for the Protection of Human Participants in Research at the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (approval number:349/2556[EC3]). Furthermore, the study was registered as quasi-experimental research in the Thai Clinical Trials Registry (identification number: 20171013002). Recruitment occurred between August 2015 and May 2017, with consecutive new patients attending the low-vision rehabilitation clinic at Siriraj Hospital, which is one of the largest tertiary referral centres. Patients were enrolled if they had difficulty performing activities because of visual loss (visual acuity [VA] and/or visual field loss) at any severity level.[15] However, ophthalmologists had referred most of the patients when they had abnormal visual function defined as "low vision" or "blindness".[16] Some patients with near-normal vision still attended the clinic when they had difficulties performing their activities because of visual problems (such as decreased contrast acuity, which makes reading very small newsprint very difficult and night blindness, which makes travelling at night difficult).

The inclusion criteria for this study were an age of 18 or older, and being able to respond to a face-to-face questionnaire-based interview. The exclusion criteria were subjects who had undergone previous low-vision rehabilitation elsewhere. The patients also needed to be willing to comply with the protocol, which included at least two follow-up visits, and to provide written informed consent before enrolment.

Rehabilitation services

After a review of the ocular pathology and medical history of the patients, assessments of their visual functions were made, including visual acuity (VA) using the Early Treatment of Diabetic Retinopathy Study VA chart; visual field evaluation through the Goldmann or Humphrey perimetry; trial frame refraction; and identification of the preferred retinal locus for seeing (eccentric viewing) using the clock-face method. Additionally, the functional history was evaluated by gathering information from both patients and their caregivers regarding the specific challenges encountered in activities such reading, daily activities, safety, and psychosocial well-being. After providing rehabilitation counselling, service objectives were set for each individual patient. These objectives took into account the expectations of each patient, but they were modified to reflect the realistic possibility for rehabilitation as assessed by the service provider. Once the service goals were finalized based on discussions between the patient and service provider, rehabilitation services were executed. The clinic was staffed by a multidisciplinary team that included an ophthalmologist, rehabilitation teachers, orientation and mobility instructors, and social workers.

The services available at the low-vision rehabilitation clinic included the prescribing of, and training in the use of, optical and non-optical devices (mostly supported by Sirindhorn National Medical Rehabilitation Institute, Ministry of Public Health). Basic activities-of-daily-living training was also provided in personal hygiene, meal preparation, and house cleaning. Additionally, orientation and mobility training for independent travel was available (partly supported by Ratchasuda College, Mahidol University, and the National Health Security Office). Examples of the items covered by the 80-hour orientation and mobility program were route and orientation training, long-cane training, sighted guide training, and the use of visual substitutes training. The use of a video magnifier, a closed-circuit television system or vision-assistive technology could be suggested. Participation in support groups and referral for further occupational or educational rehabilitation could be endorsed. If necessary, a patient was prescribed multiple services.

The clinic offered free services to patients with a recognized legal visual disability, and assistance with registration for Thai visual disability status was available for eligible individuals. To qualify, a patient's VA had to be below 6/18, or their visual field had to be narrower than 30 degrees in the better eye. Legal visual disability was further classified into two categories: low vision, defined as VA worse than 6/18 to 3/60, and blindness, characterized by VA worse than 3/60 to no light perception.

Questionnaires

The study incorporated two distinct categories of self-reported quality-of-life questionnaires, including the EQ-5D, a broadly applicable, non-disease-specific quality-of-life questionnaire. This questionnaire was utilized in its Thai version, which was validated and received approval from the EuroQol group.[17,18] The EQ-5D consists of five questions covering the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension was scored on one of three levels of severity. The utility scores applied in this research were based on preference scores from the Thai population for EQ-5D health states, determined through a Time Trade-Off (TTO) method[18] from a random sample of the general population in Thailand. The final EQ-5D score is a single-index value, where higher scores indicate a better quality of life.

The second quality-of-life questionnaire used in this study was the vision-specific LVQOL questionnaire, developed by Wolffsohn and Cochrane.[1] This study used a validated Thai version of the LVQOL, consisting of 22 questions spanning areas such as reading and fine work, distance vision and mobility, and activities of daily living and adjustment.[19] Responses were scored on a scale from 5 (no difficulty due to vision impairment) to 1 (significant difficulty), with an option for 0 (unable to perform the activity). An "irrelevant" option was also available for items not pertinent to the respondent's daily life, ensuring that individuals marking more items as irrelevant did not receive a disproportionately lower overall score, which could suggest a poorer quality of life.[1] The LVQOL's final score is a single-index value, with higher scores indicating a better quality of life.

The third instrument employed was the Thai version of the WHO-ICF (Supplement 1)[9], with a focus on the "activity and participation" component for those with visual disabilities. This included scoring performances across 10 domains of visual functions, such as mobility, transportation use, personal health care, meal preparation, housework, education, economic self-sufficiency, community life, recreation, and leisure. Table 1 shows the ICF qualifier scale for each domain category, where a higher score denotes greater difficulty. The scale uses "8" to indicate "not specified" which is applicable when there is insufficient information to accurately rate a difficulty level. For example, this was applied when patients did not know there is a problem with an activity or if the degree of that problem is mild or severe. The numeric scale "9" was assigned to indicate "not applicable" and was used when an activity was not performed for reasons unrelated to visual difficulties. An example is when patients did not perform an activity because they disliked it or felt that I was not necessary to do rather than due to visual difficulties.

Two interviewers (T.L. and V.K.) who had no prior exposure to the services received by the patients during the study, conducted face-to-face interviews using those questionnaires at both pre- and post-rehabilitation appointments. Given the individual nature of the rehabilitation service plans, some patients underwent multiple follow-up visits throughout the rehabilitation process, with intervals ranging from one to six months between visits. To reduce inconvenience for the patients, both questionnaires were administered during their regular clinic visits. The pre-rehabilitation questionnaire was filled out before starting rehabilitation, and the post-rehabilitation questionnaire was conducted during the first visit after the conclusion of all prescribed rehabilitation services, and verification of completion, as confirmed by patient accounts and hospital medical records.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). The quality-of-life scores from the LVQOL and EQ-5D questionnaires, both before and after rehabilitation, were reported as means and medians. The distribution normality of the data across the entire sample and within each subgroup was assessed using the Kolmogorov–Smirnov test. Score changes were analyzed using paired t-tests or the non-parametric Wilcoxon signed-rank test for data a not adhering to normal distribution.

For evaluating changes in in the difficulty rating within each WHO-ICF category domain before and after rehabilitation, the non-parametric Wilcoxon signed-rank test was employed. This analysis was limited to ICF qualifier scales ranging from 0 to 4, as outlined in Table 1. Qualifiers scored as 8 and 9 were treated as missing data. A p-value of < 0.05 was considered statistically significant.

RESULTS

Subject demographics and characteristics

Out of 104 patients who were initially enrolled, 76 successfully completed the questionnaires both before and after undergoing rehabilitation. The gender distribution showed a slight female predominance (52.6%) over males (47.4%), with an average age of patients being 53.4 ± 16.2 years (range: 18-78 years). Detailed demographic data, characteristics of the patients' visual impairments, and rehabilitation services provided are outlined in Table 2. The average duration between the initial and post-

TABLE 1. World Health Organization International Classification of Functioning, Disability and Health Qualifier Scales.

Numerical scale		Percentage (%)
0	NO problem/difficulty (none, absent, negligible, . . .)	0–4
1	MILD problem/difficulty (slight, low, . . .)	5–24
2	MODERATE problem/difficulty (medium, fair, . . .)	25–49
3	SEVERE problem/difficulty (high, extreme, . . .)	50–95
4	COMPLETE problem/difficulty (total, . . .)	96–100
8	Not specified	
9	Not applicable	

rehabilitation assessment was 5.8 ± 2.0 months (range: 1-12 months).

Most patients had low vision rather than blindness. The most common severity of visual impairment identified was a VA worse than 6/18 but not exceeding 6/60 and a visual field of less than 30 degrees (46.1% and 68.4%, respectively). The primary causes of visual impairment were retinitis pigmentosa (38.2%), glaucoma (26.3%), and various macular diseases, including age-related macular degeneration, macular scar and macular dystrophy (18.4%).

The top three rehabilitation services provided to the patients included reading devices (82.9%), orientation and mobility training (81.6%), and basic activities of daily living training (72.4%). It was common for patients to receive more than on type of service tailored to their needs.

Changes in LVQOL scores

The LVQOL scores, both before and after rehabilitation, demonstrated a normal distribution and showed a significant shift towards higher mean quality-of-life scores (Table 3). There was a notable improvement in the mean LVQOL score, increasing from 55.2 ± 9.2 before rehabilitation to 63.9 ± 11.5 after rehabilitation, with the difference being statistically significant ($P < 0.001$).

Given that the quality of life can be influenced by various factors such as working age or retired, the severity of visual impairment (categorized as low vision or blindness), or the underlying cause of visual impairment (e.g.; retinitis pigmentosa, glaucoma, macular disease, or other conditions), analyses were conducted across patient subgroups. Notably, significant improvements in LVQOL scores were observed in all subgroups, regardless of age, severity of visual impairment, and type of ocular disease, with all showing $P < 0.05$. To assess the meaningfulness of these improvements, Cohen's effect sizes were calculated, which measure the magnitude of differences in mean scores relative to the pooled standard deviation across these groups. According to Cohen's guidelines, effect sizes are considered small if between 0.2 to 0.3, medium at 0.5, and large at ≥ 0.8.[20,21] For this study, the overall effect size was large (Cohen's effect size = 0.85), indicating substantial improvements in quality of life for most patient subgroups.

Changes in EQ-5D scores

The EQ-5D scores before and after rehabilitation, as well as their respective changes, are shown in Table 4. There was a significant improvement in the mean EQ-5D quality-of-life score, rising from 0.549 ± 0.195 before rehabilitation to 0.680 ± 0.197 following rehabilitation, with a $P < 0.001$. Significant improvements in the EQ-5D scores were also observed across all patient subgroups when categorized by age and ocular disease responsible for visual impairment ($P < 0.05$). When analyzing subgroups based on the severity of visual impairment, significant improvements were only observed in the low-vision subgroup, where VA was not worse than 3/60. This occurred despite the quality-of-life scores having improved for the overall levels of visual impairment.

Changes in ICF ratings

For the ICF ratings, the difficulty scales for activity and participation components before and after low-vision rehabilitation are presented in Fig 1. After excluding

TABLE 2. Demographic data, characteristics of visual impairment, and rehabilitation services provided to patients

Information	Total 76 (100%)
Unemployed	44 (57.9%)
Income ≤5,000 THB/month	40 (52.6%)
No/inadequate financial support	50 (65.8%)
No/inadequate transportation support	30 (39.5%)
Living alone	9 (11.8%)
Multiple disability: visual and hearing loss	1 (1.3%)
Visual acuity	
Equal to or better than 6/18 (normal or near normal)	16 (21.1%)
Worse than 6/18 to 6/60 (low vision)	35 (46.1%)
Worse than 6/60 to 3/60 (low vision)	9 (11.8%)
Worse than 3/60 to 1/60 (blindness)	9 (11.8%)
Worse than 1/60 to PL (blindness)	7 (9.2%)
Visual field	
Central scotoma	8 (10.5%)
Visual field of less than 30 degrees	52 (68.4%)
Normal/visual field of 30 degrees or larger	15 (19.7%)
No data	1 (1.3%)
Ocular diseases	
Retinitis pigmentosa	29 (38.2%)
Glaucoma	20 (26.3%)
Macular diseases†	14 (18.4%)
Others	13 (17.1%)
Services	
Reading devices	63 (82.9%)
Orientation & mobility training	62 (81.6%)
Basic activities of daily living training	55 (72.4%)
Assistive technology	2 (2.6%)
Referral for education/occupation	7 (9.2%)

PL, perception of light

† Macular diseases include age-related macular degeneration, macular scar and macular dystro

TABLE 3. Changes in scores of low-vision quality of life questionnaire before and after low vision rehabilitation.

	Pre-rehabilitation		Post-rehabilitation	*P* value	Cohen's
	Mean ± SD	Median (P25, P75)	Mean ± SD	Median (P25, P75)	effect size
Total (n = 76)	55.2 ± 9.2	55.0 (49.1, 59.0)	63.9 ± 11.5	62.0 (57.0, 70.3)	< 0.001*	0.85
Subgroups: Age						
< 60 years (n = 44)	53.2 ± 7.8	54.0 (48.0, 57.8)	62.3 ± 9.5	60.5 (57.0, 67.8)	< 0.001*	1.05
≥ 60 years (n = 32)	57.8 ± 10.4	56.1 (51.0, 63.0)	66.2 ± 13.5	62.3 (57.0, 77.0)	*< 0.001**	–
Subgroups: Visual impairment						
Equal to or better than 6/18 (n = 16)	57.4 ± 8.5	56.0 (53.3, 63.5)	62.6 ± 10.4	61.5 (55.5, 70.0)	0.036*	0.57
Worse than 6/18 to 6/60 (n = 35)	56.5 ± 9.4	56.0 (50.0, 60.0)	65.6 ± 12.5	62.0 (58.0, 75.0)	*< 0.001**	–
Worse than 6/60 to 3/60 (n = 9)	51.3 ± 9.5	48.7 (45.0, 56.0)	60.2 ± 10.8	58.0 (51.5, 62.5)	*0.007**	–
Worse than 3/60 to 1/60 (n = 9)	55.0 ± 7.9	55.0 (49.0, 63.0)	64.1 ± 11.1	63.0 (55.5, 69.0)	0.024*	0.93
Worse than 1/60 to PL (n = 7)	48.4 ± 8.4	53.0 (38.0, 56.0)	63.1 ± 10.9	61.0 (55.9, 73.0)	0.002*	1.96
Subgroups: Ocular disease						
Retinitis pigmentosa (n = 29)	55.1 ± 8.2	55.0 (51.00, 58.5)	65.2 ± 12.7	63.0 (58.0, 73.0)	*< 0.001**	0.94
Glaucoma (n = 20)	56.6 ± 8.6	56.0 (53.3, 62.8)	64.1 ± 9.9	62.5 (57.0, 69.8)	*0.001**	–
Macular diseases (n = 14)	55.2 ± 13.3	53.0 (45.8, 59.3)	65.5 ± 13.6	60.3 (56.8, 75.8)	*0.009**	–
Others (n = 13)	52.9 ± 7.6	51.0 (47.9, 58.0)	59.1 ± 7.3	58.0 (53.0, 64.5)	*0.008**	0.83

SD, standard deviation; P25, 25th percentile; P75, 75th percentile; PL, perception of light

* *P* value is considered statistically significant by a paired t-test or nonparametric Wilcoxon signed-rank test (italicised *P* values)

TABLE 4. Changes in mean scores of EuroQol Five-Dimensional Questionnaire before and after low-vision rehabilitation.

	Pre-rehabilitation		Post-rehabilitation		*P* value	Cohen's effect size
	Mean ± SD	Median (P25, P75)	Mean ± SD	Median (P25, P75)		
Total (n= 76)	0.549 ± 0.195	0.513 (0.398, 0.645)	0.680 ± 0.197	0.677 (0.560, 0.766)	< 0.001*	0.67
Subgroups: Age						
< 60 years (n = 44)	0.586 ± 0.206	0.543 (0.428, 0.707)	0.737 ± 0.184	0.693 (0.591, 1.000)	*< 0.001**	–
≥ 60 years (n = 32)	0.498 ± 0.170	0.484 (0.392, 0.618)	0.602 ± 0.190	0.626 (0.463, 0.693)	0.001*	0.58
Subgroups: Visual impairment						
Equal to or better than 6/18 (n = 16)	0.563 ± 0.199	0.513 (0.425, 0.642)	0.667 ± 0.203	0.672 (0.524, 0.748)	0.01*	0.74
Worse than 6/18 to 6/60 (n = 35)	0.537 ± 0.192	0.573 (0.392, 0.677)	0.688 ± 0.200	0.677 (0.573, 0.766)	*< 0.001**	–
Worse than 6/60 to 3/60 (n = 9)	0.583 ± 0.269	0.513 (0.380, 0.854)	0.705 ± 0.201	0.666 (0.574, 0.883)	0.012*	1.08
Worse than 3/60 to 1/60 (n = 9)	0.561 ± 0.199	0.513 (0.409, 0.656)	0.639 ± 0.185	0.634 (0.483, 0.726)	0.091	0.64
Worse than 1/60 to PL (n = 7)	0.517 ± 0.121	0.513 (0.392, 0.618)	0.692 ± 0.229	0.645 (0.556, 1.000)	0.071	0.83
Subgroups: Ocular disease						
Retinitis pigmentosa (n = 29)	0.556 ± 0.182	0.513 (0.431, 0.656)	0.686 ± 0.177	0.677 (0.573, 0.739)	*< 0.001**	–
Glaucoma (n = 20)	0.561 ± 0.164	0.535 (0.435, 0.645)	0.679 ± 0.172	0.677 (0.564, 0.756)	0.001*	0.70
Macular diseases (n = 14)	0.459 ± 0.156	0.421 (0.392, 0.564)	0.585 ± 0.199	0.625 (0.392, 0.726)	0.021*	0.70
Others (n = 13)	0.613 ± 0.279	0.618 (0.380, 0.883)	0.772 ± 0.246	0.766 (0.543, 1.000)	*0.008**	–

SD, standard deviation; P25, 25th percentile; P75, 75th percentile; PL, perception of light

* *P* value which is considered statistically significant by a paired t-test or nonparametric Wilcoxon signed-rank test (italicised *P* values)

Activity and participation	n (%)†		Difficulty 0 1 2 3 4	*P* value	Difficulty n (%) 8	Difficulty n (%) 9
1. Seeing functions	76 (100%)	Pre-rehabilitation		<0.001*	-	-
	74 (97.4%)	Post-rehabilitation			-	2 (2.6%)
2. Moving around different locations	75 (98.7%)	Pre-rehabilitation		<0.001*	1 (1.3%)	-
	75 (98.7%)	Post-rehabilitation			1 (1.3%)	-
3. Using transportation	75 (98.7%)	Pre-rehabilitation		0.001*	1 (1.3%)	-
	75 (98.7%)	Post-rehabilitation			1 (1.3%)	-
4. Looking after one's health	76 (100%)	Pre-rehabilitation		1.222	-	-
	75 (98.7%)	Post-rehabilitation			-	1 (1.3%)
5. Preparing meals	57 (75.0%)	Pre-rehabilitation		0.008*	3 (3.9%)	16 (21.1%)
	61 (80.3%)	Post-rehabilitation			-	15 (19.7%)
6. Doing housework	66 (86.9%)	Pre-rehabilitation		0.073	3 (3.9%)	7 (9.2%)
	66 (86.9%)	Post-rehabilitation			2 (2.6%)	8 (10.5%)
7. Education	13 (17.1%)	Pre-rehabilitation		0.18	9 (11.8%)	54 (71.1%)
	10 (13.2%)	Post-rehabilitation			3 (3.9%)	63 (82.9%)
8. Economic self-sufficiency	73 (96.1%)	Pre-rehabilitation		0.006*	2 (2.6%)	1 (1.3%)
	76 (100%)	Post-rehabilitation			-	-
9. Community life	66 (86.9%)	Pre-rehabilitation		0.001*	3 (3.9%)	7 (9.2%)
	71 (93.4%)	Post-rehabilitation			1 (1.3%)	4 (5.3%)
10. Recreation and leisure	69 (90.8%)	Pre-rehabilitation		0.003*	2 (2.6%)	5 (6.6%)
	73 (96.1%)	Post-rehabilitation			1 (1.3%)	2 (2.6%)

Fig 1. Classification of Functioning, Disability, and Health scales of difficulty before and after low-vision rehabilitation.
The box-plot shows the mean (plus sign), median (dark bar), 25th and 75th percentile (box), range of the scales of difficulty (whisker), and potential outlier (circles) of each domain before and after rehabilitation. The changes in the scales of difficulty for each ICF category domain were analysed by the non-parametric Wilcoxon signed-rank test.
† Remaining number of patients after removing the missing data ("8" and "9")
**P* value which is considered statistically significant.

the ICF qualifiers of 8 and 9 as missing data, the figure indicates the number of patients evaluated. Improvements were noted across all domains in the ICF difficulty scales, with significant enhancements in specific areas such as seeing functions, mobility across different locations, use of transportation, meal preparation, economic self-sufficiency, community life, and recreation and leisure activities ($P < 0.01$). The numerical qualifier 9 was most frequently recorded in domains of doing housework (about 10% of patients), meal preparation, (about 20%), and education (more than 70%).

DISCUSSION

This prospective study was undertaken to assess the outcomes of low-vision rehabilitation practice, using validated tools to quantify the effects. In the absence of a consensus on the most effective assessment tool, three different instruments were utilized to gain a better understanding of the problems and to best evaluate the outcomes. Additionally, the WHO-ICF framework was applied to ensure findings could be understood by personnel working in broader medical and socioeconomic fields related to visual disability.

The study used the vision-specific, self-reported LVQOL questionnaire, and found significant improvements in quality of life that were clinically meaningful. This positive shift in score aligns with outcomes observed in a similar study conducted by a low-vision clinic in Australia, which also employed the tool.[1] Moreover, significant enhancements in LVQOL scores, indicating large clinical significance, were observed across all patient subgroups analyzed. However, the smallest effect size was noted among patients with near-normal VA. This was probably because this subgroup typically experienced only mild problems, leading to less pronounced changes in outcomes.

In assessing the outcomes of the same population with the generic, self-reported EQ-5D questionnaire, a significant improvement in overall EQ-5D quality of life scores was observed, although the effect size was smaller compared to that of LVQOL. Notably, the improvement in EQ-5D scores did not achieve statistical significance for the subgroup classified as blind. These EQ-5D results may reflect less favourable outcomes for this subgroup. These results might be explained by the fact that the EQ-5D had only four out of its five questions that are likely to be influenced by visual impairment, with the remaining item focused on pain or discomfort, a factor

generally unrelated to visual impairment or the outcomes of vision rehabilitation and more connected to broader heath factors. Similarly, a recent report from the US found that EQ-5D was undemonstrative as an outcome measure for low-vision rehabilitation.[5] This suggests that generic questionnaires might not be as sensitive as vision-specific ones in evaluating outcomes.[22] However, a recent Portuguese study reported a strong correlation between EQ-5D and visual ability, suggesting that the EQ-5D could be effective in illustrating the impact of visual impairment.[23] The variation in utility scores derived from population-based preferences in different countries could contribute to the mixed results. Therefore, the suitability of the EQ-5D for measuring outcomes in low-vision rehabilitation remains inconclusive.

Although the WHO-ICF does not consolidate its findings into a single index like the quality-of-life questionnaires, it proved useful for detailed examinations of outcomes within low-vision rehabilitation, specifically within each domain of activity and participation. In this research, the low-vision rehabilitation outcomes in domains such as seeing functions, mobility across different locations, use of transportation, meal preparation, economic self-sufficiency, community life, and recreational activities all showed significant progress. ($P < 0.01$). However, no significant advancements were detected in the areas of personal health care, housekeeping, and education. This lack of perceived improvement in these categories might be explained to patients' pre-existing ability to manage daily tasks within their homes, leading to an underestimation of any change.

The only prior study that utilized a measurement related to the ICF for evaluating rehabilitation outcomes was conducted using the Dutch ICF activity inventory.[2] This tool was based on (rather than a direct translation of) the original WHO-ICF. Instead, the research team developed several unique questions that focused exclusively on the domains of reading, writing, and watching television. Similar to the findings of the current study, the Dutch researchers observed a reduction in difficulty scores in three domains from the baseline.

The "not applicable" response was the most commonly observed in the education category, largely due to the average age of participants being 53.4 ± 16.2 years, with very few in the school-going demographic. Similarly, response of "not applicable" were frequent for tasks related to housework and meal preparation. This trend aligns with the fact that most Thai patients reside with family or friends, and not alone, as shown in Table 2. Hence, they likely received assistance with these activities.

The time frame used to assess the rehabilitation outcomes is another influencing factor in any questionnaire, and the duration has varied in other studies.[24–26] In principle, the follow-up span should be long enough to observe meaningful changes, yet short enough to avoid complications from disease progression or shifts in the patients' environmental or personal circumstances. *Wang et al.* reported an improvement in the quality-of-life scores over a longer period (1 month *vs.* 3 months).[24] Meanwhile, *Stelmack et al.* noted that these effects diminished after a year.[25,26] Interestingly, another recent study found no significant difference between outcomes measured at three months and those at 1 year.[27]

In the current study, the mean follow-up duration was 5.8 ± 2 months (range, 1-12 months). The broad spectrum of follow-up times was a limitation of the study. These variations in duration were due to various patient characteristics, the range of services, and the patients' differing abilities to attend follow-up visits, whether short or long. Further investigation is needed to explore specific patient groups and to continue ongoing evaluations over extended periods to determine if the improvements in the quality-of-life outcomes are sustained. Another limitation was the potential for bias, which could be minimized by employing a control group, such as patients on a clinic waiting list. However, ethical considerations of delaying low-vision rehabilitation also needs to be considered.

CONCLUSION

This study assessed the self-reported quality of life among patients with low vision and blindness, and revealed significant improvements following rehabilitation. Notably, the improvements were most evident in seeing functions and mobility. The use of various questionnaires, including LVQOL, EQ-5D, and WHO-ICF, leveraged their individual strengths and provided additional information about the outcomes.

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DECLARATION

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Author Contributions

S.C., A.E. designed the research; T.L., W.K., S.L., R.Y., S.D., W.N., J.J., N.S., E.E., S.S., P.C. conducted the study; S.C., T.L. wrote the main manuscript text; A.E. approved the final manuscript.

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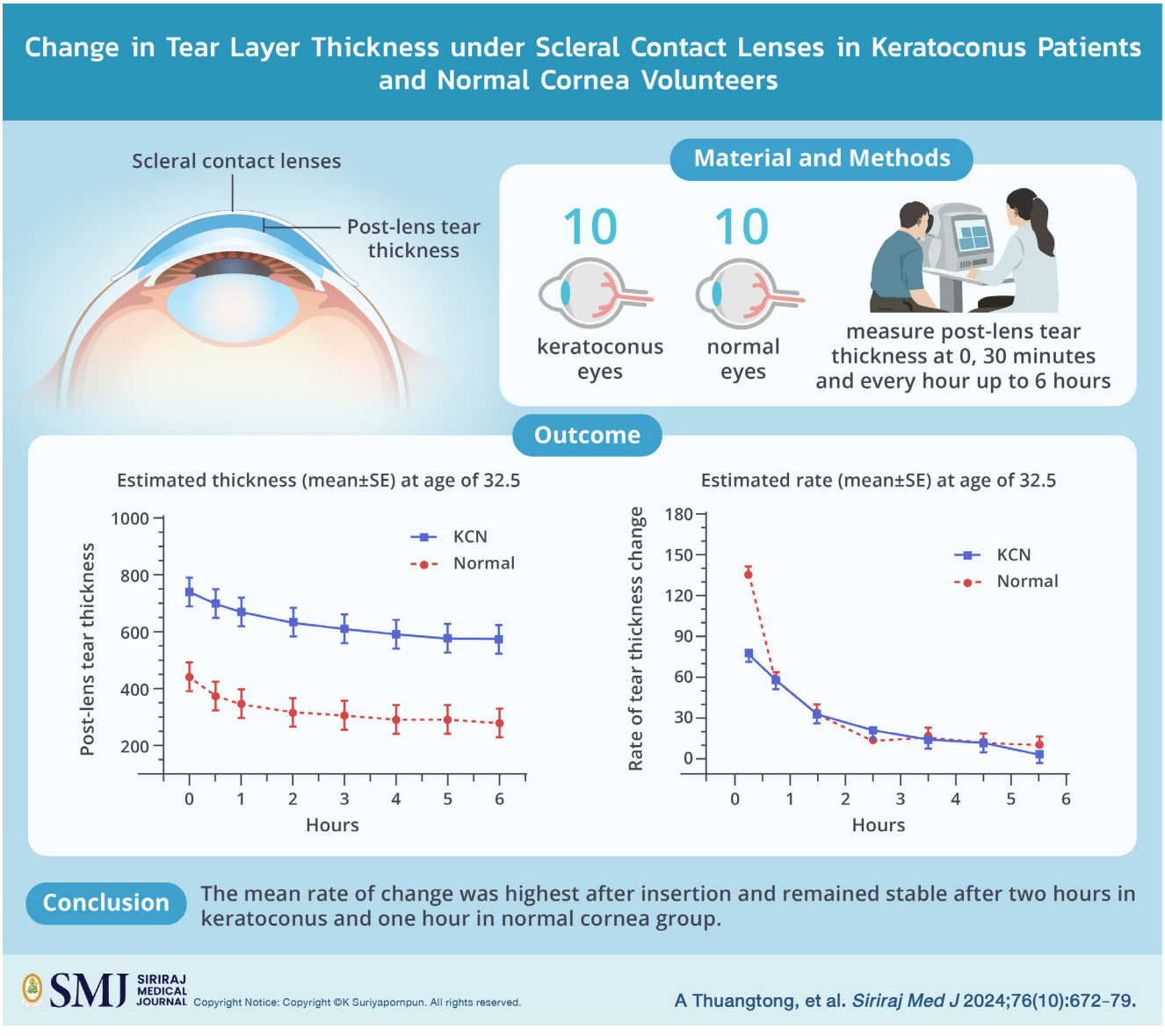
Change in Tear Layer Thickness under Scleral Contact Lenses in Keratoconus Patients and Normal Cornea Volunteers

Atiporn Thuangtong, M.D., Nuttacha Taetrongchit, M.D.*, Rung Kemahayung, MST

Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.



*Corresponding author: Nuttacha Taetrongchit
E-mail: girtnuttacha@gmail.com
Received 2 February 2024 Revised 20 May 2024 Accepted 29 May 2024
ORCID ID:http://orcid.org/0000-0003-0676-7272
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ABSTRACT

Objective: To quantify rate of post-lens tear thickness change under scleral contact lenses in keratoconus patients and normal cornea volunteers.

Materials and Methods: We conducted a prospective observational study where semi-scleral lenses were fitted to 20 eyes (5 subjects, 10 eyes in each group). After insertion, post-lens tear thickness was measured at 0, 30 minutes and every hour up to 6 hours using Anterior Segment OCT. To analyze post-lens tear thickness and its rate of change at each time point, both within and between groups, a linear mixed model was used.

Results: The initial mean post-lens tear thickness (μm) was 742 ± 50 and 440 ± 50 in keratoconus and normal cornea group, respectively. The mean rate of change (μm/hr) was highest in the first 30 minutes in both groups (80.8 ± 8.7, 132.2 ± 8.8 in keratoconus and normal cornea group). Following the first four hours in keratoconus and the first hour in normal cornea group, the reduction rate in post-lens tear thickness exhibited no statistically significant difference from the rate of change observed during the 5-6 hour period. The mean percentage of total change over 6 hours after lens insertion was higher in normal cornea compared to keratoconus group (36.6% vs 22.5%).

Conclusion: The reduction in post-lens tear thickness follows a nonlinear pattern. The mean rate of change was highest after insertion and remained stable after four hours in keratoconus and one hour in normal cornea group. The percent change over the 6-hour period was greater in normal cornea group.

Keywords: Keratoconus; scleral contact lenses; post-lens tear layer thickness; anterior segment OCT (Siriraj Med J 2024; 76: 672-679)

INTRODUCTION

Scleral contact lenses are becoming popular for treating diverse ocular surface diseases, particularly corneal ectasia, such as keratoconus.[1,2] Unlike traditional rigid gas permeable contact lenses, which make direct contact with the corneal surface, scleral contact lenses are uniquely designed to vault over the cornea and limbus and rest on the sclera instead. This creates a space between the corneal surface and the lens, forming a tear reservoir. This design has proven effective and stable in improving visual performance in individuals with corneal ectasia, especially keratoconus, due to its ability to cover the entire cornea and neutralize both regular and irregular corneal astigmatism. Additionally, the tear reservoir prevents direct contact between the lens and the apical corneal surface.[3,4]

Currently, there is a lack of consensus on the optimal amount of corneal clearance or post-lens tear thickness required to achieve an ideal fit for scleral contact lenses.[5] Recommendations for corneal clearance range between 100 and 400 μm, with variations depending on the lens design and diameter.[4,6-8] If the post-lens tear thickness is too low, there is a risk of mechanical damage to the corneal epithelium and consequent patient discomfort. This is particularly critical in cases of corneal ectasia like keratoconus where the progression of the condition can reduce post-lens tear thickness, which increases the likelihood of contact between the lens surface and the cornea. Conversely, excessive post-lens tear thickness can negatively impact optical quality and reduce oxygen transmission to the cornea.[4,6]

Due to the compressible nature of the conjunctival and tenon tissues, coupled with the pressure exerted by the eyelids, the clearance of scleral contact lenses decreases over time following the initial insertion.[4,7,9,10] The exact time it takes for a scleral lens to fully settle on the eye remains unknown. Factors like the lens diameter and the length of time it is worn are thought to affect the extent of settling of scleral lenses.

Fitting scleral contact lenses is a time-consuming process and requires practitioners to dedicate a significant amount of time to find ideal lens that provide optimal visual performance and comfort, while also being safe for the ocular surface, especially in the patients with advanced corneal ectasia. The sole type of design for scleral contact lenses utilized at Siriraj Hospital is the semi-scleral design (Onefit®). Previous studies have not reported on the settling of semi-scleral lenses and the rate at which post-lens tear thickness stabilizes in conditions of corneal ectasia compared to non-ectatic conditions.

This study aims to quantify the rate of change of post-lens tear thickness beneath scleral contact lenses (semi-scleral design) in keratoconus patients and normal cornea volunteers.

MATERIALS AND METHODS

In this pilot prospective observational study, we enrolled 10 subjects (20 eyes) aged over 18 years from the Department of Ophthalmology, Siriraj Hospital, between January 2022 and May 2023. The study included two groups: the keratoconus group comprising 10 eyes from 5 subjects previously diagnosed with keratoconus (Rabinowiz Criteria), and the normal cornea group, which consisted of 10 eyes from five volunteers with normal corneal curvature, as indicated by corneal topography (Oculus Pentacam). We excluded patients with active ocular disease and/or infections, those using eye drops during the study, and individuals for whom scleral contact lenses were contraindicated.

Prior to enrollment, all subjects gave their consent and signed an informed consent form. This study adhered to the principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the Siriraj Institutional Review Board (SIRB) at Siriraj Hospital, Mahidol University in Bangkok, Thailand, under IRB number 767/2022. The clinical trial was registered with the identifier TCTR20221208004 at www.clinicaltrial.gov.

All subjects were fitted with Onefit SC® semi-scleral lenses, each with a diameter of 14.7 mm (Blanchard Contact Lens, Inc) using non-preservative artificial tears (Tear Naturale Free®).

To measure post-lens tear thickness, we used anterior segment optical coherence tomography (CASIA2) at eight different time points after lens insertion: 0 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, and 6 hours. A single researcher[5] conducted these evaluations to minimize interobserver variability. At each time point, three images were captured along both the steep and flat axes of the cornea. We utilized a software program to draw a line connecting the scleral spurs on either side of the anterior chamber angle. A perpendicular line was then drawn from the midpoint of this line, passing through the cornea and post-lens tear to the surface of the lens. The measurement of post-lens tear thickness was conducted manually on this perpendicular line as shown in Fig 1. The post-lens tear thickness measurements were conducted by a single researcher (NT) who calculated the average thickness at the center of both the steep and flat cornea from three images at each timepoint.

Statistical analysis

Quantitative data were summarized using means and standard deviations. Since post-lens tear thickness and the rate of its change were observed in both eyes for each subject and at eight different time points (0, 0.5, 1, 2, 3, 4, 5 and 6 hours after lens insertion), a multilevel linear mixed model was applied with level 1 of time, level 2 of eye and level 3 of subject. Subject and eye were random effects whereas time was repeated. Independent variables of group (KCN, normal), time (as a categorical variable), group*time interaction and age were fixed effects. Age was included in the mixed model due to a clinically significant higher mean age in the normal than KCN group and age might affect the outcome. Bayesian information criterion (BIC) was used to choose covariance structure and the best fitted model.

Data analysis was performed using IBM SPSS 30.0 (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant.

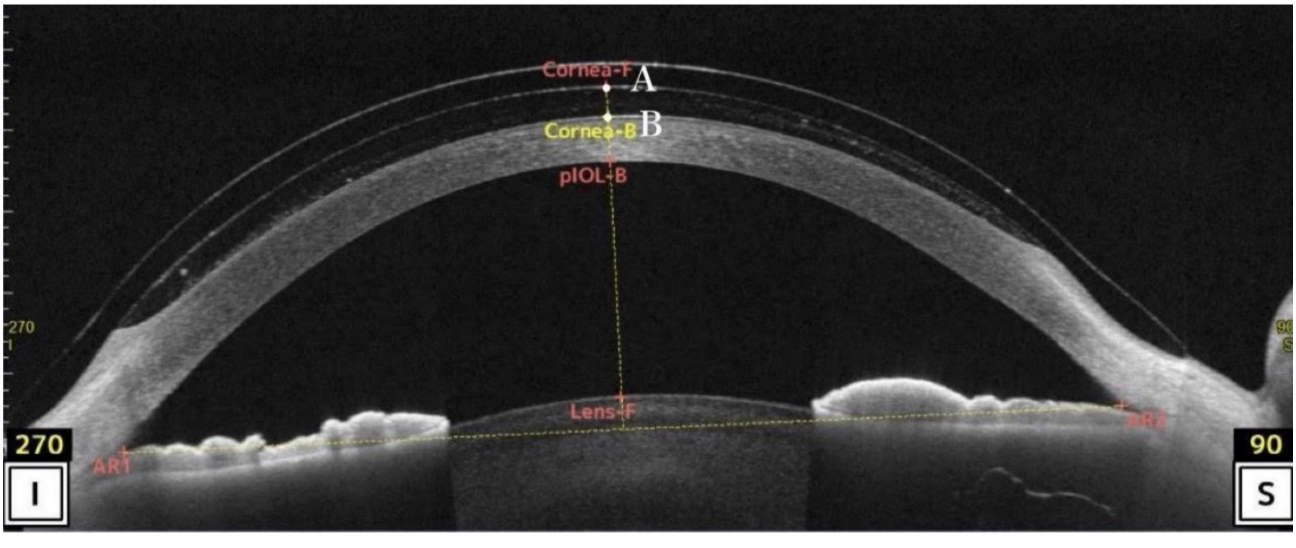

Fig 1. Measurement of post-lens tear thickness using the AS-OCT. Post-lens tear thickness is represented as distance from point A to point B.

RESULTS

In this study, a total of 20 eyes from 10 subjects (5 subjects in each group) were examined. In the keratoconus group, there was one female participant, while the normal cornea group consisted of five female subjects. Subjects in the normal cornea group were 8 years older than those in the keratoconus group, with a mean ± SD of 36.8 ± 8.0 and 28.6 ± 5.7 respectively (p=0.100). Due to only five subjects in each group, the difference in age of eight years was not statistically significant but clinically important. Among the 10 eyes diagnosed with keratoconus, the mean keratometry readings at the steepest and flattest axes were 54.26 ± 7.92D and 49.59 ± 6.95D respectively. In contrast, the 10 eyes in the normal cornea group showed mean keratometry readings of 43.93 ± 0.97D and 43.18 ± 0.96D, respectively. In keratoconus group, according to ABCD keratoconus grading system, 1 patient was grade 1, 4 patients were grade 2, 2 patients were grade 3 and 3 patients were grade 4 keratoconus.

Fig 2A illustrates the spaghetti plot of post-lens tear thickness against time for each subject's eye, by group (KCN, normal), while Fig 2B presents the observed mean ± SD by group and time. In the keratoconus group, the mean post-lens tear thickness (μm) at baseline and 6 hours post-lens insertion were 720 ± 166 and 553 ± 160, respectively, compared to 463 ± 91 and 303 ± 75 in the normal cornea group. The post-lens tear thickness was different in both groups. Over time, post-lens tear thickness in both groups decreased. Notably, at each time point, a post-lens tear thickness the keratoconus group was roughly 230-283 μm greater than that of the normal cornea group.

To account for correlated eyes and 8 repeated measures over time, a multilevel linear mixed model of post-lens tear thickness was applied. Based on the fitted mixed model, the post-lens tear thickness was estimated using the average age among 10 subjects. Mixed model reveals that the keratoconus group had consistently thicker post-lens tear than normal cornea group at every time point, with an average difference of 309 μm (Fig 2, Table 1). Within-group comparisons indicated that post-lens tear thickness decreases over time in both groups but stabilizes after 3 hours. In the keratoconus group, post-lens tear thickness decreased from 743 μm (0-30 minutes) to 614 μm (at 3 hours) and remained relatively stable at roughly 584 μm during the 4-6 hour period. Conversely, in the normal cornea group, it decreased from 441 μm (0-30 minutes) to 305 μm (3 hours) and was roughly stable at 287 μm after 3 hours. According to Table 1, the percentage change in post-

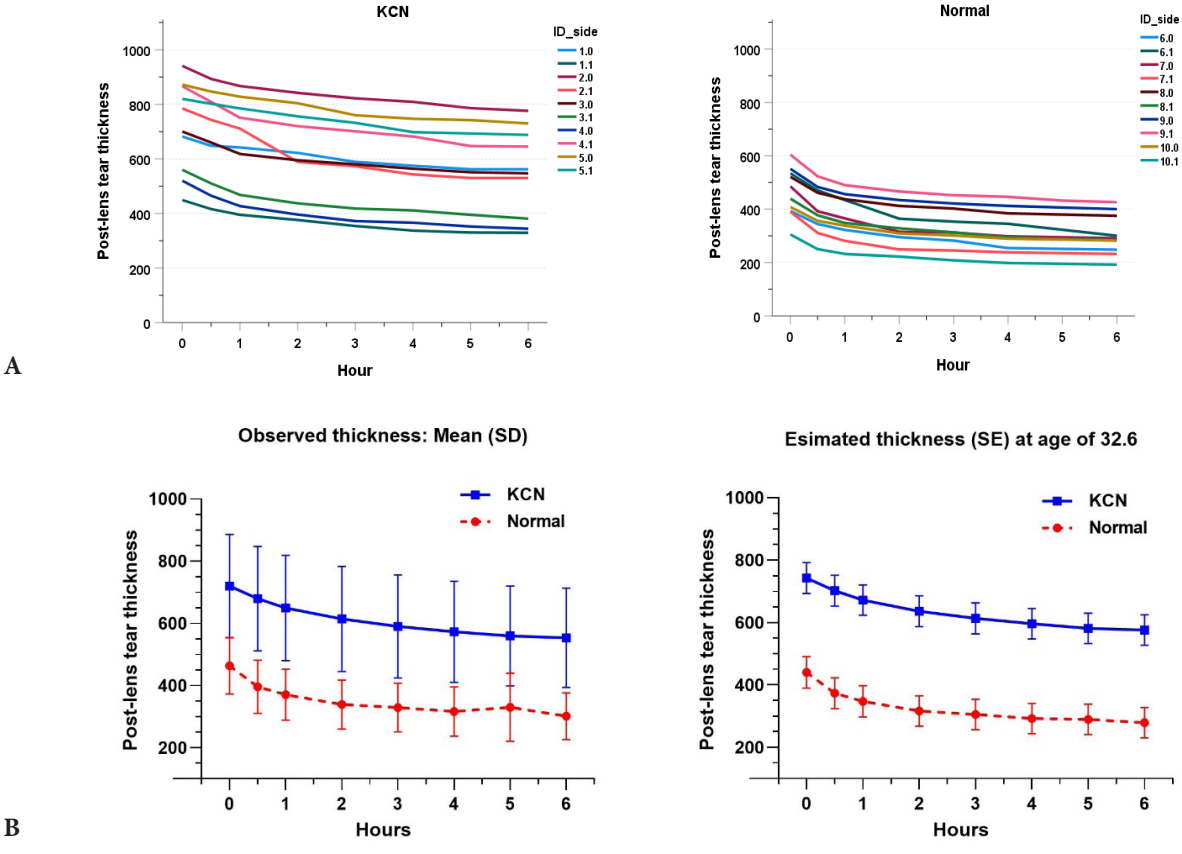

Fig 2. A spaghetti plot of the post-lens tear thickness in each eye over time by group (A), observed and predicted mean from mixed model (B).

TABLE 1. Estimated post-lens tear thickness (μm) at each time point in the keratoconus and normal cornea group.

	Post-lens tear thickness[#]: Mean ± SE		KCN – Normal:
	KCN	Normal	Mean difference (95% CI)
Time			
0 minute	**742 ± 50**	**440 ± 50**	302 (124 ,481)**
30 minutes	**702 ± 50**	**373 ± 50**	329 (150, 507)**
1 hour	**672 ± 49**	**347 ± 50**	325 (147, 503)**
2 hours	**636 ± 50**	**316 ± 49**	320 (143, 498)**
3 hours	**613 ± 50**	**305 ± 49**	307 (129, 485)**
4 hours	596 ± 49	292 ± 49	303 (126, 481)**
5 hours	581 ± 49	289 ± 49	293 (115, 471)**
6 hours	576 ± 49	279 ± 49	296 (118, 474)**
Comparison with 6 hours: Mean difference (95% CI)			
0 minute	166 (126, 207)***	160 (120, 201)***	
30 minutes	126 (93, 159)***	94 (61, 127)***	
1 hour	96 (67, 125)***	67 (39, 96)***	
2 hours	61 (48, 73)***	37 (24, 49)***	
3 hours	37 (25, 49)***	26 (14, 38)*	
4 hours	20 (7, 33)**	13 (-1, 26)	
5 hours	6 (-9, 20)	9 (-10, 28)	

[#] For subject aged 32.6 years

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

lens tear thickness at 6 hours from baseline was greater in the in normal cornea group than in the keratoconus group (36.6% vs. 22.5%).

The mixed model of the rate of post-lens tear thickness change revealed that the highest rate occurred during the first 30 minutes, with an average of 81 and 132 μm/h in the keratoconus and normal cornea groups (Fig 3, Table 2) and significant difference of 51μm/h ($p < 0.01$). Within each group, the rate of change decreased over time. From 0-30 minutes to 1-2 hours, the rate reduced from 81 μm/h to 36 μm/h in the keratoconus group compared to a reduction from 132 μm/h to 31 μm/h in the normal cornea. After two hours, the rate of change was less than 24 μm/h in both groups. In the keratoconus group, there was no statistically significant difference in the rate of change after 4 hours, whereas in the normal cornea group, significant differences ceased after 1 hour (Table 2).

DISCUSSION

Our study focuses on the variation and rate of change in post-lens tear thickness beneath scleral lenses (14.7 mm in diameter) over a 6-hour period post-lens insertion in eyes with keratoconus and normal corneas. Consistent with previous studies, we observed a decrease in post-lens tear thickness over time in both the keratoconus and normal cornea group. The mean decrease in post-lens tear thickness after 6 hours was 166 ± 50 μm (22.5% from initial thickness) in the keratoconus group and 161± 50 μm (36.6% from initial thickness) in the normal cornea group. Although the reduction in tear thickness in microns was comparable between the two groups, the percentage change from initial to the 6-hour period was greater in the normal cornea group compared to the keratoconus group.

This is comparable to findings of *Caroline et al.*[10] who investigated the fitting of 16.5 mm diameter scleral contact lens in 15 healthy eyes. Their study reported an average decrease in apical corneal clearance of 96 μm (ranging from 70 to 180 μm) after 8 hours of lens wear. This highlights the significant variability in lens settling observed among different subjects.

Varsha M. Rathi et al.[4] conducted a study examining the changes in post-lens tear thickness during a 4-hour scleral lens wear in eyes with corneal ectasia and ocular surface disease. Their results showed a decrease in post-lens tear thickness in 90% of the eyes studied. They also observed a higher percentage of settling in the corneal

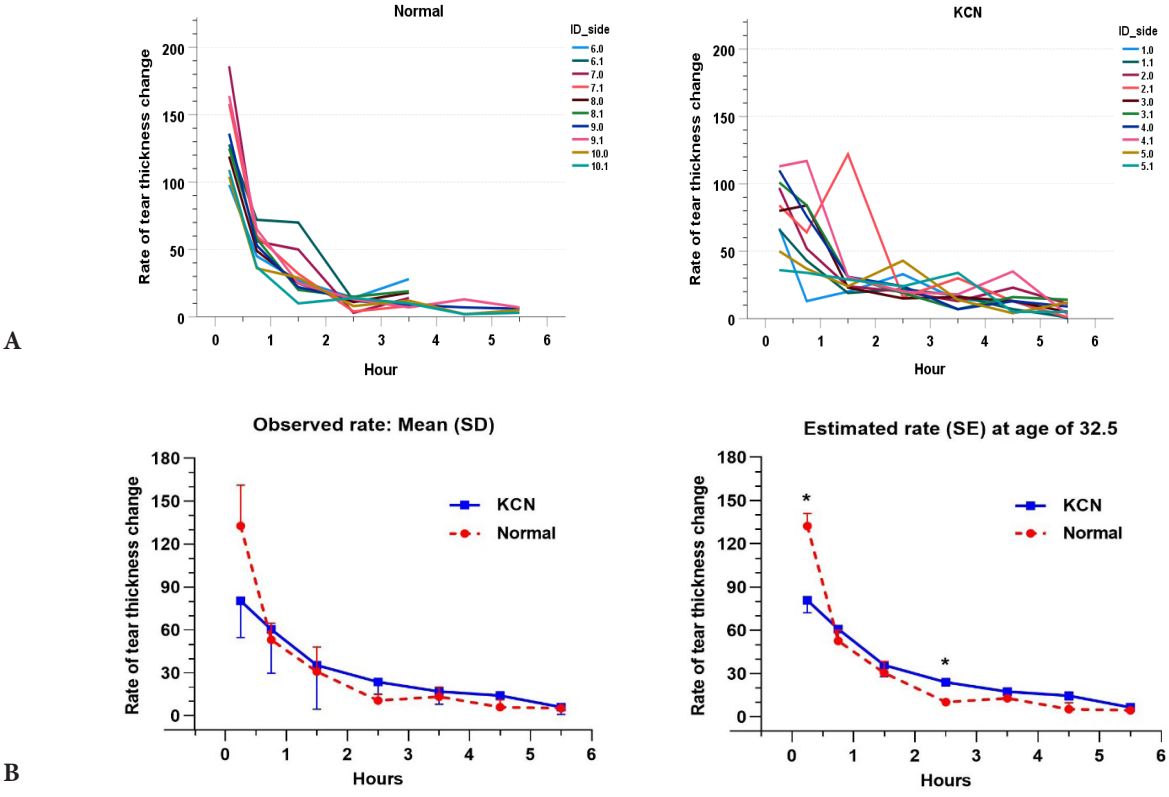

Fig 3. A spaghetti plot of the rate of tear thickness change in each eye over time by group (A), observed and predicted mean from mixed model (B).

TABLE 2. Estimated rate of post-lens tear thickness change (μm/h) at each time point in the keratoconus and normal cornea group.

	Rate of thickness change#: Mean ± SE		KCN – Normal:
	KCN	Normal	Mean difference (95% CI)
Time interval			
0 - 30 minutes	**80.8 ± 8.7**	**132.2 ± 8.8**	-51.4 (-77.4, -25.3)**
30 minutes - 1 hour	60.8 ± 7.4	52.6 ± 7.4	8.2 (-13.9, 30.3)
1 - 2 hours	35.8 ± 7.9	30.5 ± 7.9	5.3 (-18.3, 28.9)
2 - 3 hours	24.0 ± 2.1	10.2 ± 2.1	13.8 (7.4, 20.2)***
3 - 4 hours	17.4 ± 2.5	12.8 ± 2.5	4.6 (-2.9, 12.1)
4 - 5 hours	14.6 ± 2.8	5.3 ± 4.4	9.3 (-2.2, 20.9)
5 – 6 hours	6.5 ± 1.5	4.5 ± 2.4	2.0 (-4.4, 8.4)
Comparison with 5-6 hours: Mean difference (95% CI)			
0 – 30 minutes	74.3 (43.2, 105.4)***	127.7 (96.3, 159.1)***	
30 minutes – 1 hour	54.3 (27.9, 80.7)***	48.1 (21.3, 74.9)***	
1 – 2 hours	29.3 (1.1, 57.5)*	26.0 (-2.5, 54.5)	
2 – 3 hours	17.5 (9.2, 25.8)***	5.7 (-4.6, 16.0)	
3 – 4 hours	10.9 (1.4, 20.4)*	8.3 (-2.8, 19.4)	
4 – 5 hours	8.1 (-3.0, 19.2)	0.8 (-16.8, 18.3)	

For subject aged 32.6 years

*** p < 0.001, ** p < 0.01, * p < 0.05

ectasia group (17.25%) compared to the ocular surface disease group (13.9%). In their research, scleral lenses of various diameters, ranging from 16 mm to 18.5 mm, were used. The differences in settlings observed between the two types of corneal disease may have been influenced by the variations in lens design. In contrast, our study utilized a consistent semi-scleral lens design with a uniform diameter of 14.7 mm for all participants. Our results showed a decrease in post-lens tear thickness in all eyes across both groups, with a statistically significant difference in the percentage of settling between the two groups. Notably, the normal cornea group exhibited a significantly higher percentage of settling (36.6%) compared to the keratoconus group (22.5%).

Kauffman et al.[11] investigated the settling behavior of three different scleral lens designs (diameters of 14.3, 15.8, and 18.2 mm) in individuals with normal eyes. Their research, conducted over an 8-hour period, found variations in lens settling across these different designs. Additionally, they noted that 70% of total lens settling occurred within the first 2 hours following lens insertion. In our study, using 14.7 mm diameter scleral lenses, we noted a non-linear pattern in lens settling in both the normal cornea and keratoconus group. The most significant decrease in the average rate of post-lens tear thickness was observed in the first 30 minutes after lens insertion, followed by a gradual reduction noted over subsequent time periods in both groups. The reduction rate in post-lens tear thickness during the initial 30 minutes was statistically higher in the normal cornea group (132 μm/hr) compared to the keratoconus group (81 μm/hr). Consistent with the findings from *Kauffman's* study, our results in the normal corneal group indicated that 76.5% of the total lens settling over the 6-hour period occurred within the first 2 hours following lens insertion.

Previous studies have indicated that variations in scleral lens design and diameter impact settling behavior.[4,7,11] According to our results, using the same lens design and diameter (semi-scleral lens, diameter 14.7 mm), we observed that the degree and rate of settling vary between eyes with keratoconus and those without corneal ectasia. These findings underscore the importance of considering the settling behavior of scleral lenses in the context of different corneal diseases before finalizing lens orders.

A notable limitation of this pilot study is its relatively small sample size. Although we included both eyes of each participant in our analysis, we employed a linear mixed model with random intercept for both subject and eye. To the best of our knowledge, no prior study has examined the extent and settling rate of semi-scleral design contact lenses (specifically those with a diameter of 14.7 mm) and compared them between keratoconus and normal corneas. Therefore, further research with a larger sample size to assess the settling pattern in both ectatic and non-ectatic eyes is necessary to minimize scleral lenses fitting duration.

CONCLUSION

The degree and speed of post-lens tear change beneath a scleral lens varies among different corneal conditions. A decrease in post-lens tear thickness follows a non-linear trend. The most significant rate of change in tear thickness occurs within the first 30 minutes after lens insertion, followed by a gradual decrease over time. The rate of post-lens tear thickness reduction after four hours (in the keratoconus group) and after one hour (in the normal cornea group) exhibits no statistically significant difference from the rate observed between 5-6 hours. The overall percentage change in post-lens tear thickness over a 6-hour period is higher in the normal cornea group than in the keratoconus group.

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Author Contributions

A.T. designed and directed the project. R.K. performed the experiments. N.T. collect the data, analyzed of the results and wrote the manuscript in consultation with A.T.

DECLARATIONS

Conflicts of interest

None

Thai Clinical Trials Registry

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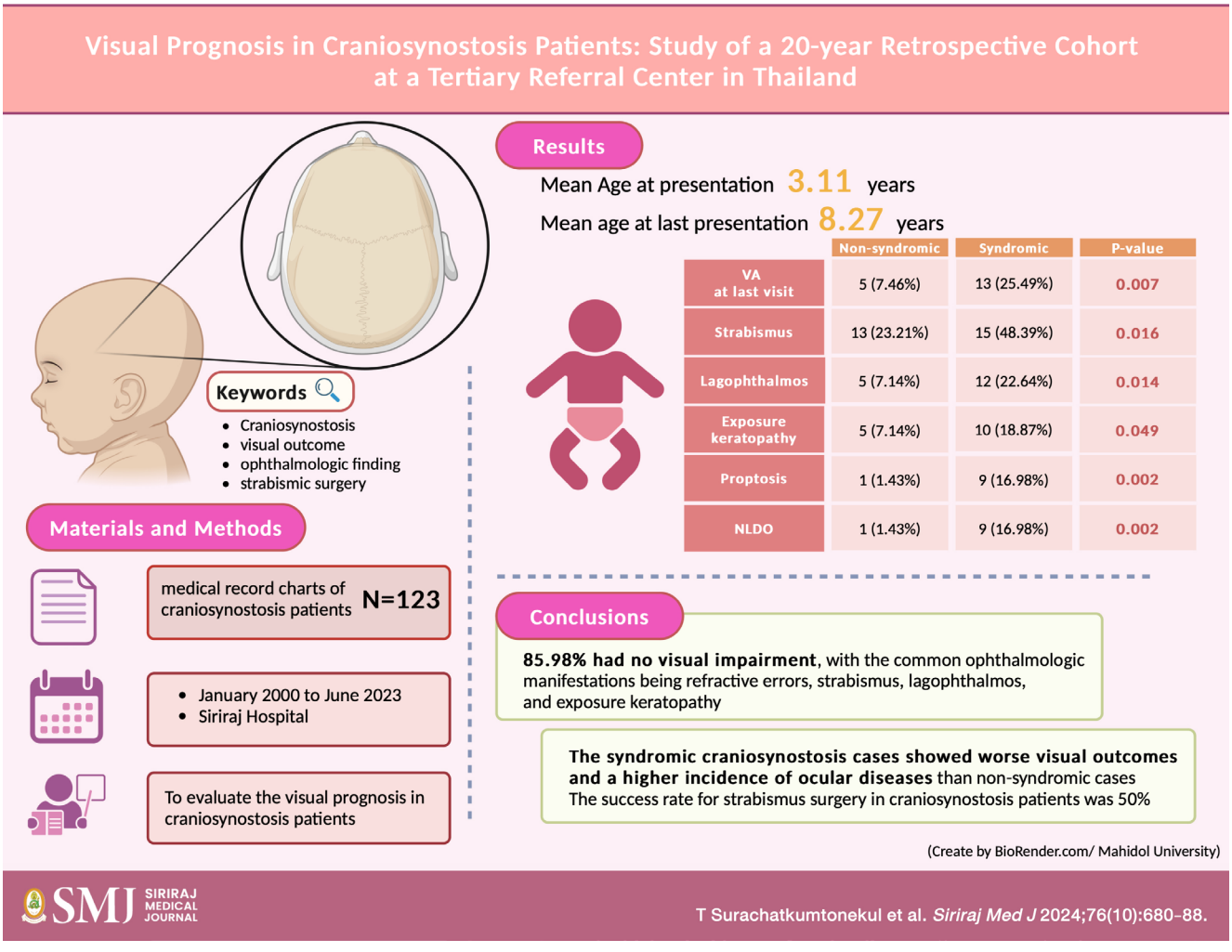
Visual Prognosis in Craniosynostosis Patients: A 20-year Retrospective Cohort Study at a Tertiary Referral Center in Thailand

Subongkoch Subhadhirasakul, M.D., Wasawat Sermsripong, M.D., Thammanoon Surachatkumtonekul, M.D.*

Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.



*Corresponding author: Thammanoon Surachatkumtonekul
E-mail: si95thim@gmail.com
Received 6 June 2024 Revised 28 July 2024 Accepted 7 September 2024
ORCID ID:http://orcid.org/0000-0002-0037-6863
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ABSTRACT

Objective: This study aims to evaluate the visual prognosis in craniosynostosis patients in order to identify ophthalmologic manifestations in craniosynostosis patients and strabismus surgery outcomes in these patients.

Materials and Methods: The medical records craniosynostosis patients were reviewed retrospectively from January 2000 to June 2023. All the relevant patient data, such as age, sex, visual acuity, ophthalmologic examinations, and strabismus surgery outcomes were recorded.

Results: In total, 123 patients were included in the study, among whom 65 (52.84%) were male. Overall, there were 70 cases (56.91%) of non-syndromic craniosynostosis, and 53 cases of syndromic craniosynostosis, comprising Crouzon syndrome (15 cases), Apert syndrome (8 cases), Pfeiffer syndrome (2 cases), and other syndromes (28 cases). The mean age at first examination was 3.11 years old. Out of 107 cases with visual impairment at the first visit, 92 (85.98%) showed no visual impairment at the last visit. Among the 87 patients with strabismus, 28 (32.18%) had strabismus at the primary position, with exotropia being the most common type (18 cases). Eight cases underwent strabismus surgery, and 4 cases achieved success (deviation < 10 prism diopters). Other ophthalmologic manifestations were lagophthalmos (17 cases, 13.82%), exposure keratopathy (15 cases, 12.2%), ptosis (11 cases, 8.94%), proptosis (10 cases, 8.13%), and nasolacrimal duction obstruction (10 cases, 8.13%). The syndromic group exhibited higher rates of visual impairment, strabismus, lagophthalmos, exposure keratopathy, proptosis and nasolacrimal duct obstruction compared to the non-syndromic group.

Conclusion: Among the craniosynostosis cases, 85.98% had no visual impairment, with the common ophthalmologic manifestations being refractive errors, strabismus, lagophthalmos, and exposure keratopathy. The syndromic craniosynostosis cases showed worse visual outcomes and a higher incidence of ocular diseases than non-syndromic cases. The success rate for strabismus surgery in craniosynostosis patients was 50%.

Keywords: Craniosynostosis; visual outcome; ophthalmologic finding; strabismus surgery (Siriraj Med J 2024; 76: 680-688)

INTRODUCTION

Craniosynostosis is a medical condition marked by the premature fusion of one or more cranial sutures. There are two main types: non-syndromic craniosynostosis and syndromic craniosynostosis. Syndromic craniosynostosis is associated with other anomalies, especially bone irregularities in the hands and feet.[1] Crouzon, Apert, and Pfeiffer syndromes are the most common syndromic craniosynostosis types from autosomal dominant inheritance. Non-syndromic craniosynostosis, which is more common, typically presents with a defect in a single growth stream, or suture. Normally, non-syndromic craniosynostosis is not associated with other anomalies.[2] The prevalence of craniosynostosis was reported to be 5.2–5.9 per 10,000 live births.[3]

Hinds AM et al. found in their study that 76.7% of patients had normal visual acuity but that amblyopia, refractive error, and strabismus were common in syndromic craniosynostosis.[4] Khan et al. found that craniosynostosis patients had visual impairment in almost 40% of cases.[5] Moreover, Rafique Ali AA et al. reported that the other ophthalmologic manifestations in craniosynostosis included ptosis, proptosis, lagophthalmos, exposure keratopathy, papilledema, and optic atrophy.[6] Infantile nystagmus syndrome and cataract were also reported in some craniosynostosis patients.[7]

Craniosynostosis has not been comprehensively studied in Asia or South-East Asia yet, and there is a lack of research on this condition in Thailand. Consequently, the primary objective of this study was to assess the visual prognosis of craniosynostosis in a Thai population. Additionally, we aimed to evaluate ocular deviation, the results of strabismus surgery, and other ophthalmologic manifestations associated with craniosynostosis.

MATERIALS AND METHODS

This study was approved by the Siriraj Institutional Review Board (Certificate of Approval no. Si 714/2023). In this retrospective descriptive cohort study, the medical records of craniosynostosis patients treated at Siriraj Hospital between January 2000 and June 2023 were reviewed retrospectively. Eligible patients for inclusion were those diagnosed with craniosynostosis, confirmed by computed tomography (CT) scans evaluated by a radiologist and clinical examination. Patients were included if an ophthalmologic examination was available. Conversely, those without an ophthalmologic examination were excluded from the study. All of the included patients

underwent ophthalmologic examination at least once. The collected data included the first and last age of ophthalmologic examination, sex, the classification of craniosynostosis (syndromic or non-syndromic), best-corrected visual acuity (BCVA), intraocular pressure, refraction, ocular alignment, and eye movement.

Other recorded ocular findings comprised ptosis, proptosis, nasolacrimal duct obstruction, nystagmus, and anterior and posterior segment examination results. Data on the history of craniofacial surgery and strabismus surgery were also collected. The postoperative strabismus surgery results, including BCVA, ocular alignment, and extraocular movement, were recorded at 2 weeks, 1–2 months, and 6 months postoperatively. The patients who had not been ophthalmologic examination were excluded.

BCVA was measured using a method appropriate for the patient age, cooperation, and underlying diseases. Visual acuity was converted to logMAR and analyzed. According to the definition of visual impairment by the World Health Organization (WHO), visual impairment (VI) refers to vision in the better eye worse than 6/12. Mild VI is defined as visual acuity ≤ 6/18, moderate VI as ≤6/60, severe VI as ≤3/60, and blindness VI as ≤1/60. For preverbal children, visual impairment is defined as the inability to fixate and follow in the better eye.[8]

Refraction was measured for each eye. The refractions of each eye were calculated to the spherical equivalent. Myopia was defined as ≥ -0.5 diopters, while hyperopia was defined as ≥ +2.0 diopters. Significant astigmatism was defined as ≥ -0.75 diopters.

Ocular alignment was measured by the alternate prism cover test at both distance and near, with BCVA in the primary position. The Krimsky test was employed to measure ocular alignment in non-cooperative patients. Ocular deviation was recorded in prism diopters (PD). The success of strabismus surgery was defined as a deviation of ≤10 PD.

Statistical analysis

In this study, descriptive statistics were utilized to summarize both the demographic data and clinical characteristics of the patients. For categorical data, we presented the data as frequencies and percentages. In cases where continuous data adhered to a normal distribution, we reported the mean and standard deviation (SD); alternatively, for non-normally distributed data, the median and interquartile range (IQR) were utilized. Visual acuity data were transformed into logarithm minimal angle of resolution (logMAR) units for the purpose of the statistical analysis.

Descriptive outcomes were expressed as numbers and percentages with the corresponding 95% confidence intervals (CIs). Ocular findings in different subgroup analyses were compared using either the chi-squared or Fisher exact test, depending on the number of findings in each group. The chi-squared test was used when sample sizes in all categories were adequate while Fisher's exact test was employed otherwise, when the expected frequencies in any cell of the contingency table fell below five. A p-value less than 0.05 was considered statistically significant in these comparisons. All analyses were conducted using STATA version 16 (StataCorp, Lakeway, TX, USA).

RESULTS

There were 123 craniosynostosis patients, and their medical records were reviewed. Of these, 65 (52.84%) cases were male and 58 (47.15%) cases were female. There were 70 cases (56.91%) diagnosed as non-syndromic craniosynostosis and 53 cases (43.08%) diagnosed as syndromic craniosynostosis. The syndromic craniosynostosis cases comprised Crouzon syndrome (15 cases), Apert syndrome (8 cases), Pfeiffer syndrome (2 cases), and other syndromes (28 cases). The mean age at first visit was 3.11 years old, with a median age of 1 year old (ranging from 3 days to 43 years old). Table 1 presents the data.

Visual acuity

The best-corrected visual acuity (BCVA) at first visit can be recorded in logMAR units for 51 eyes. Overall, the cases were classed as good fix and follow (145 eyes), fair fix and follow (3 eyes), fixation but not follow (4 eyes), not fix and follow (10 eyes), no light perception (1 eye), and missing data due to uncooperative patients or immature visual development (32eyes) (Fig 1). The average BCVA at first visit was 6/12–6/15 (logMAR 0.335). Of the 246 eyes total in the study, 145 eyes (72.36%) had a visual acuity of 6/12 or better and were classed as good fix and follow. Out of 107 patients with visual impairment at the first visit, 92 (85.98%) had no visual impairment at the last visit, while the other 15 (14.02%) still had visual impairment, with 8 out of these latter 15 patients having mild visual impairment (Fig 1).

The mean duration of follow-up was 5.16 years. The mean BCVA was 6/9.5–6/12 (logMAR 0.25) for 143 eyes, and good fix and follow was observed in 82 out of 93 eyes. Additionally, there were 8 eyes that did not fix and follow, 1 eye with hand motion, 1 eye with finger count, 1 eye with no light perception, and 10 eyes with missing out data due to uncooperative patients. The visual acuity recorded during the last visit examination included 236 eyes with visual acuity ≥ 6/12 and good fix

TABLE 1. Demographic data of the craniosynostosis patients (n = 123 patients).

Characteristics	Number (%)
Sex	
Male	65 (52.84%)
Female	58 (47.15%)
Category	
Non-syndromic craniosynostosis	70 (56.91%)
Syndromic craniosynostosis	53 (43.08%)
Crouzon syndrome	15 (12.20%)
Apert syndrome	8 (6.50%)
Pfeiffer syndrome	2 (1.63%)
Other syndromes	28 (22.76%)
Age at first presentation; year	
Mean (± SD)	3.11 (±6.01)
Median (Range)	1 (range 3 days – 43 years)
Age at last presentation; years	
Mean (± SD)	8.27 (±8.06)
Median (Range)	6 (range 11 days – 43 years)

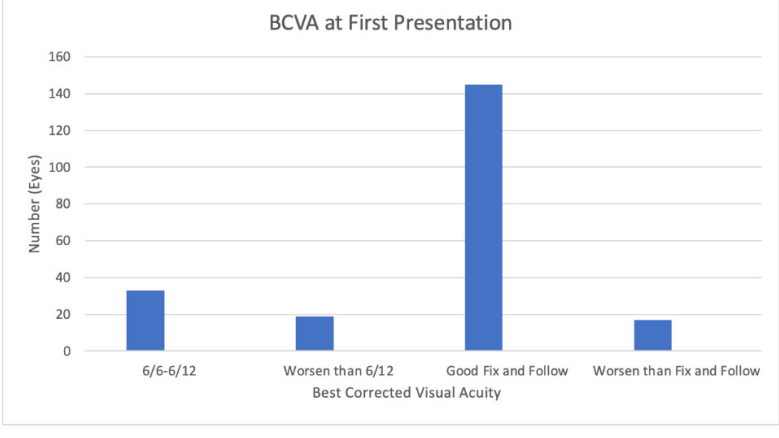

Fig 1. Visual acuity at first visit (N=214 eyes)
Abbreviation: BCVA = Best-corrected visual acuity.

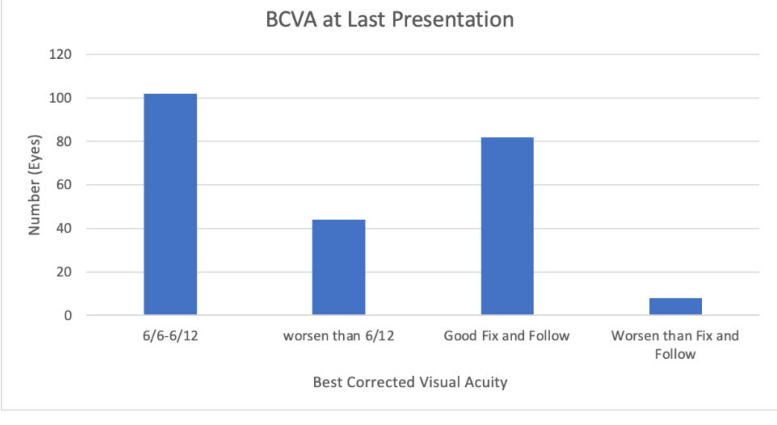

Fig 2. Visual acuity at last visit. (N=236 eyes)
Abbreviation: BCVA = Best-corrected visual acuity.

and follow in 184 eyes (75.80%) (Fig 2). Also,100 out of the 123 (81.30%) patients had no visual impairment at the last visit (Table 4).

Ocular findings

Refraction errors were recorded for 144 eyes, while 102 eyes were unable to be recorded due to uncooperative patients. Among the recorded data, hyperopia was found in 25 eyes (17.36%), myopia in 18 eyes (12.5%), and astigmatism in 74 eyes (51.39%) (Table 2).

Ocular findings in the craniosynostosis patients included strabismus at the primary position in 28 out of 123 cases (22.76%), lagophthalmos in 17 cases (13.82%), and exposure keratopathy in 15 cases (12.2%). Corneal ulcer was observed in 5 cases and perforated cornea in 1 case, both of which were attributed to lagophthalmos and exposure keratopathy. The other findings were ptosis in 11 out of 123 cases (8.94%), proptosis in 10 cases (8.13%), nasolacrimal duction obstruction (NLDO) in 10 cases (8.13%), epiblepharon in 6 cases (4.88%), nystagmus and entropion in 3 cases each (2.44%), glaucoma in 2 cases (1.63%), and optic disk atrophy, optic nerve hypoplasia, chronic dacryocystitis, euryblepharon, preceptal cellulitis, retinal dystrophy, entropion, and globe subluxation in 1 case each, as shown in Table 2.

TABLE 2. Ocular findings.

	Number (%)
Refractive error	
Hyperopia	25 (10.16%)
Myopia	18 (7.32%)
Astigmatism	74 (51.39%)
Strabismus	28 (22.76%)
Lagophthalmos	17 (13.82%)
Exposure keratopathy	15 (12.20%)
Corneal ulceration	5 (4.07%)
Perforation of cornea	1 (0.81%)
Ptosis	11 (8.94%)
Proptosis	10 (8.13%)
Nasolacrimal duct obstruction	10 (8.13%)
Epiblepharon	6 (4.88%)
Nystagmus	3 (2.44%)
Entropion	3 (2.44%)
Glaucoma	2 (1.63%)
Optic nerve atrophy	1 (0.81%)
Optic nerve hypoplasia	1 (0.81%)
Retinal dystrophy	1 (0.81%)
Chronic dacryocystitis	1 (0.81%)
Globe subluxation	1 (0.81%)
Euryblepharon	1 (0.81%)
Preseptal cellulitis	1 (0.81%)

Strabismus and strabismus surgery outcomes

Twenty-eight of the 87 strabismus (32.18%) cases had strabismus confirmed at the primary position. We were not able to examine the other 36 patients due to uncooperation and visual immaturity. The most common strabismus was exotropia (18 cases). Among the 18 exotropia patients, two were found to have V pattern exotropia, and four patients were esotropia. The other six patients had combined strabismus, involving both exotropia and vertical deviation. Eight (5 cases exotropia and 3 cases esotropia) out of the 28 patients underwent strabismus surgery. The strabismus surgery details of the 8 patients are shown in Table 3.

The average BCVA preoperatively assessed in 12 eyes (6 cases) (in logMAR) was 6/12–6/15 and one case displayed good central, steady, and maintained (CSM) visual activity in both eyes. Postoperative BCVA evaluated in 14 eyes showed an average of 6/12, with one patient achieving good CSM in both eyes.

The average ocular deviations preoperatively for exotropia and esotropia were 38.75 PD (range 25–45 PD) and 46.67 (range 45–50 PD), respectively. Postoperatively, the mean ocular deviation was 3.2 PD (range 0–25 PD) in exotropia patients and 6.67 PD (range 0–20 PD) in esotropia patients. The success rate of strabismus surgery was 50%.

Comparing syndromic vs. non-syndromic craniosynostosis

Visual acuity, refractive error and ocular diseases were analyzed to compare between syndromic and non-syndromic craniosynostosis. The number of cases with no visual impairment at first visit in non-syndromic craniosynostosis was better than for syndromic craniosynostosis, but this difference did not reach statistical significance. However, the visual impairment of the syndromic craniosynostosis group at the last visit was worse than for the non-syndromic group, with statistical significance (p-value = 0.007). The refractive errors did not differ between the two groups. To compare other ocular diseases, the incidences of strabismus, nasolacrimal duct obstruction, proptosis, lagophthalmos, and exposure keratopathy in the syndromic craniosynostosis group were higher than in the non-syndromic craniosynostosis group, with statistical significance, as shown in Table 4.

TABLE 3. Patients' data related to strabismus surgery.

Patient	Pre-operative BCVA	Pre-operative alignment, PD	Muscle surgery, mm	Post-operative BCVA	Post-operative alignment, PD
1	Could not evaluate	XT 25, IOOA OD	BLR rec 6 RIO myectomy 8	6/15 OU	Orthotropia
2	6/12 OU	IOOA OS	LIO rec 10	6/9 OU	ET 16, IOOA OU
3	6/9 OU	XT 40	BLR rec 8	6/12 OU	XT 12
4	6/24, 6/9	ET 45, IOOA OU	BMR rec 5 IOAT OU	6/12, 6/9	ET 20, IOOA OS
5	6/24, 6/60 6/15, 6/30	ET 45 XT 20	BMR rec 6 LLR rec 9	6/15, 6/9 6/15, 6/30	XT 8, DVD OU Orthotropia, DVD OD 14
6	6/9, 6/7.5 6/9, 6/9	XT 45 ET 30, LHT 14	BLR rec 8.5 Advancement LLR to original insertion LIO myectomy 10	6/6 OU 6/7.5, 6/9.5	Orthotropia E 5
7	Good CSM OU	ET 50	BMR rec 6	Good CSM OU	Orthotropia
8	6/12 OU 6/12, 6/9 6/15, 6/12	XT 45 XT 30, IOOA OU XT 25, RHT 12	BLR rec 8 BMR res 5.5 BIO rec RLR rec 4 RSR rec 5	6/9.5 OU 6/15, 6/12 6/9 OU	XT 30 XT 25, RHT 12, V pattern XT 25 IOOA OU, SOUA OU

Abbreviations: ET = esotropia, XT = exotropia, LHT = left hypertropia, RHT = right hypertropia OU = both eyes, OD = right eye, OS = left eye, E = esophoria, IOOA = inferior oblique overaction, SOUA = superior oblique overaction, BMR = bilateral medial rectus muscle, BLR = bilateral rectus muscle, LLR = left lateral rectus, BIO = bilateral inferior oblique, RIO = right inferior oblique, LIO = left inferior oblique, RSR = right superior rectus, IOAT = inferior oblique anteriorization, DVD = dissociated vertical deviation, rec = recession, BCVA = best-corrected visual acuity, CSM = central, steady, and maintained, PD = prism diopter, mm = millimeters.

DISCUSSION

Our study investigated both syndromic and non-syndromic craniosynostosis in Thailand over the past 20 years, examining a total of 123 cases in our medical records. The majority of the patients experienced good visual outcomes. When comparing the non-syndromic and syndromic craniosynostosis groups, the non-syndromic group exhibited good visual outcomes during the last visit and a lower incidence of other ocular diseases compared to the syndromic group.

Hind AM et al. evaluated 165 cases and reported that 76.7% achieved a final best-corrected visual acuity (BCVA) better than 6/12 in the better eye.[4] Khan SH et al. conducted a 21-year review involving 141 children with syndromic craniosynostosis (Crouzon, Pfeiffer, Apert, and Saethre–Chotzen syndromes), revealing that 61.2% achieved a visual acuity of 6/12 or better.[5]

Rafique Ali AA et al. conducted a retrospective study over 6 years of 37 craniosynostosis patients in Malaysia, finding a 32.1% prevalence of visual impairment.[6] Additionally, Tay T et al. explored the prevalence of visual impairment in syndromic craniosynostosis over 22 years, reporting a 35.5% prevalence for bilateral visual impairment and 9.1% for unilateral visual impairment.[7]

TABLE 4. Ocular findings in syndromic and non-syndromic craniosynostosis.

Characteristics	Non-syndromic craniosynostosis		Syndromic craniosynostosis		p-value	Percent Difference (95% CI)
	Total patients	Number of patients (%)	Total patients	Number of patients (%)		
Visual acuity at first visit						
No visual impairment	65	58 (89.23%)	42	34 (80.95%)		
Visual impairment	65	7 (10.77%)	42	8 (19.05%)	0.228	8.28 (-23.54, 5.09)
Visual acuity at last visit						
No visual impairment	67	62 (92.54%)	51	38 (74.51%)		
Visual impairment	67	5 (7.46%)	51	13 (25.49%)	*0.007	18.03 (-32.06, -4.72)
Refractive errors						
Hyperopia	40	9 (22.50%)	31	6 (19.35%)	0.747	3.15 (-16.60, 21.27)
Myopia	40	6 (15.0%)	31	6 (19.35%)	0.627	4.35 (-23.04, 13.01)
Astigmatism	40	22 (55.0%)	31	20 (64.52%)	0.418	9.52 (-30.41, 13.13)
Strabismus	56	13 (23.21%)	31	15 (48.39%)	*0.016	25.18 (-44.27, -4.51)
Lagophthalmos	70	5 (7.14%)	53	12 (22.64%)	*0.014	15.50 (-29.01, -2.98)
Exposure keratopathy	70	5 (7.14%)	53	10 (18.87%)	*0.049	11.73 (-24.86, 0.15)
Ptosis	70	4 (5.71%)	53	7 (13.21%)	0.149	7.50 (-19.64, 2.97)
Proptosis+	70	1 (1.43%)	53	9 (16.98%)	*0.002	15.55 (-27.85, -5.58)
Nasolacrimal duct obstruction+	70	1 (1.43%)	53	9 (16.98%)	*0.002	15.55 (-27.85, -5.58)
Epiblepharon	70	4 (5.71)	53	2 (3.77%)	0.621	1.94 (-7.69, 10.47)
Nystagmus+	70	1 (1.43%)	53	2 (3.77%)	0.404	2.34 (-11.40, 4.46)

* Statistically significant (p-value < 0.05)

+ Fisher's exact tests

Our study revealed that 85.98% of patients showed no visual impairment during their initial visit, while 14.02% exhibited visual impairment. With a mean follow-up duration of 5.16 years, the percentage of patients with a last recorded visual acuity of ≥6/12, with good fixation and follows was 75.80%. Notably, the incidence of visual impairment in our study was lower than in other comparable studies. The observed improvement in visual outcomes during the final visit may be attributed to the early treatment of amblyopia and refractive errors.

A number of previous studies have documented ocular findings in craniosynostosis. Hind AM et al. reported a prevalence of astigmatism of 67.2%.[4] Khan SH et al. identified astigmatism as the most common refractive error, at 40.3%.[5] Rafique Ali AA et al. reported the common refractive errors were astigmatism (45.6%), hyperopia (18.2%), and myopia (13.5%), respectively.[6] In our study, abnormal refractive errors included astigmatism at 30.08%, followed by hyperopia at 10.16% and myopia at 7.32%. Astigmatism was the most common refractive error, which correlated with previous studies.[4-6]

In Hind AM et al.'s research, nearly half of their patients exhibited exotropia with a V pattern.[4] The other ocular findings were optic disk swelling and/or pallor (18.2% of eyes), signs of corneal exposure (9.6%), and corneal scar (2.9%). Khan SH et al. reported a 70% prevalence of strabismus in syndromic craniosynostosis.[5] Rafique Ali AA et al. found that strabismus occurred

in 50.6% of craniosynostosis patients, often alongside other ocular manifestations, such as proptosis in 78.6% of cases, lagophthalmos in 53.3%, exposure keratopathy in 30.6%, and optic disc atrophy in 13.7%.[6]

In our study, strabismus was found in 23% of cases, with exotropia being the most common type. Eight patients underwent strabismic operations. Although the mean postoperative ocular deviation in both exotropia and esotropia groups was within 10 PD, three patients required more than one surgery. One patient showed the absence of the right superior oblique in our study. Strabismus surgery is performed after craniofacial surgery. Furthermore, strabismic surgeries are complicated due to abnormal orbits and anomalies of extraocular muscles.[9] Surgical success in craniosynostosis patients was 50%, compared to 60.2% in normal subjects.[10] The lower surgical success in craniosynostosis patients was attributed to the thinner and weaker extraocular muscles and abnormal orbital structure.[9-11]

Craniosynostosis patients are at risk of developing lagophthalmos and exposure keratopathy. Our study identified 5 patients with corneal ulcers, and 1 patient with corneal perforation due to a corneal ulcer. Ophthalmologists need to be aware of these serious findings and prescribe lubricating medications to prevent exposure keratopathy. In our study, one patient required permanent tarsorrhaphy due to severe exposure keratopathy.

Rostamzad P et al. conducted a systematic review on the prevalence of ocular anomalies in craniosynostosis. They reported proptosis in 86% of cases, optic atrophy in 8%–29%, entropion in 2%–50%, and nasolacrimal duct obstruction (NLDO) in 60%[12]); while our study found lower prevalence rates for proptosis, optic atrophy, entropion, and NLDO compared to Rostamzad's research.

We conducted a comparison of visual acuity, refractive errors, and ocular diseases associated with craniosynostosis between non-syndromic and syndromic groups. The visual outcomes in the syndromic group were worse than those in the non-syndromic group. Additionally, syndromic craniosynostosis patients exhibited significantly higher rates of strabismus, proptosis, NLDO, exposure keratopathy, and lagophthalmos compared to the non-syndromic craniosynostosis patients. The increased prevalence of ocular diseases in syndromic craniosynostosis patients can be attributed to the presence of multiple sutures abnormalities, mid-face abnormalities, and developmental issues, which are more pronounced than in non-syndromic craniosynostosis patients.[13]

This study offers insights into visual prognosis in craniosynostosis, which is valuable for counseling purposes. It lists the high incidence of ophthalmologic findings, providing a guideline for other ophthalmologists to consider when dealing with craniosynostosis. Early detection and treatment of manageable ophthalmologic conditions can prevent additional diseases and complications, including amblyopia from strabismus and refractive errors, as well as corneal complications from lagophthalmos and exposure keratopathy.

However, it is essential to note the limitations of this study, as it involved a retrospective review of medical records. Many data points were missing due to the challenges associated with conducting complete ocular examinations in craniosynostosis patients which most were infant of children. Ocular manifestations like visual acuity, strabismus, and amblyopia are believed to result from various mechanical processes. For example, the underlying neurodevelopmental disorders prevented a comprehensive ophthalmologic examination from being conducted in a single session. The visual acuity test in uncooperative children provides qualitative data only, making it challenging to compare directly with the visual acuity of adults or cooperative children. Interestingly, the number of patients with recorded visual acuity measurements at both the initial and final visits was inconsistent. Therefore, we assumed that younger children have a different normal range of visual acuity compared to older children, which gradually becomes similar to that of adults with normal vision. Older children typically cooperate well during visual acuity tests and eye examinations. However, allowing the visual acuity measured at the last visit to affect results might lead to unclear outcomes. Moreover, childhood eye exams and the results of strabismus surgery varied depending on the individual ophthalmologist. Our study examined medical records and surgical outcomes from multiple ophthalmologists, introducing some degree of bias. Future studies could provide more comprehensive data on eye exams and the accuracy of strabismus surgery results when conducted by a single ophthalmologist and surgeon.

To overcome these limitations, future studies should aim to include larger sample sizes to enhance the statistical power and improve the generalizability. Nevertheless, we believe that our study presents real-life statistics and highlights the fact that with proper methodology it is possible to significantly improve the reliability and validity of research findings.

In summary, our findings indicate a higher prevalence of visual impairment among patients with craniosynostotic syndromes. Notably, the majority of these visual impairments are amenable to treatment with timely intervention, particularly through strabismic therapy. Although

the prevalence of abnormal ophthalmologic findings is relatively low, their impact on visual impairment remains significant. Therefore, regular ophthalmologic evaluations are essential for patients diagnosed with craniosynostosis to facilitate early detection of abnormalities and prompt management. Further research, including genetic evaluations, is warranted to enhance the diagnostic accuracy and overall understanding of craniosynostotic syndromes.

CONCLUSION

The visual outcomes in the craniosynostosis patients were good. The majority of the patients did not have visual impairment. Common ophthalmologic manifestations were refractive error, strabismus, lagophthalmos, and exposure keratopathy. Syndromic craniosynostosis patients had poor visual outcomes and ocular findings more often than the non-syndromic patients. The success rate for strabismus surgery in craniosynostosis patients was about half. A multidisciplinary team is necessary to treat craniosynostosis patients. Early ocular examination should be provided to craniosynostosis patients to prevent serious ocular complications.

Conflict of Interest

The authors declare that they have no conflicts of interest related to the publication of this research.

Author Contributions

SS: general research process, framework of the study, supervision, conceptualization, methodology, writing-original draft preparation, review and editing; TS: general research process, framework of the study, supervision, review and editing WS: methodology, data analysis, review and editing. All authors have read and agreed to the final version of the manuscript.

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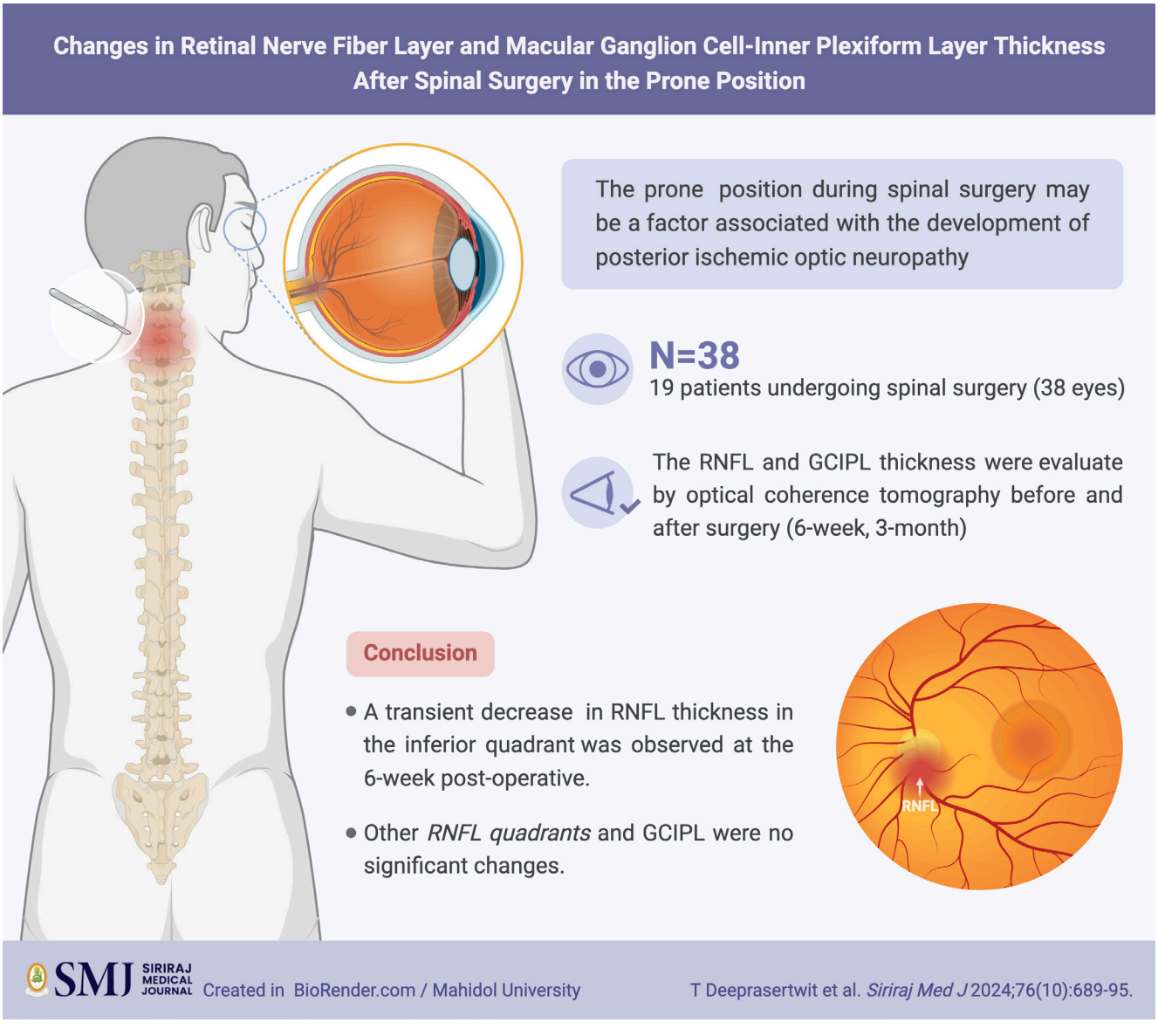
Changes in Retinal Nerve Fiber Layer and Macular Ganglion Cell-Inner Plexiform Layer Thickness after Spinal Surgery in the Prone Position

Thoranis Deeprasertwit, M.D.[1], Piya-Orn Bunyaprateepra, M.D.[1], Niphon Chirapapaisan, M.D.[1], Sirichai Wilartratsami, M.D.[2], Pratuangsri Chonphimai, BS[1]., Nuchanat Ritthison, BNS[1], Yanee Mukdar, BS[1]., Akarawit Eiamsamarng, M.D.[1,*]

[1]*Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand,* [2]*Department of Orthopedics Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*



*Corresponding author: Akarawit Eiamsamarng
E-mail: akarawit.eia@mahidol.ac.th
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ORCID ID:http://orcid.org/0009-0002-6073-8106
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ABSTRACT

Objective: Postoperative visual loss resulting from posterior ischemic optic neuropathy (PION) after spinal surgery is rare but devastating. A potential risk factor is prolonged spinal surgery in the prone position. We hypothesized that if this risk factor is linked to PION, the retinal nerve fiber layer (RNFL) and macular ganglion cell-inner plexiform layer (GCIPL) should decrease post-surgery.

Materials and Methods: The prospective cohort study was conducted in patients undergoing spinal surgery in the prone position. The RNFL and GCIPL thickness by optical coherence tomography before and after spinal surgery (6-week, 3-month post-operative) were analyzed.

Results: Nineteen patients (38 eyes) completed the study with three follow-up timepoints. The mean age was 53.78+/-12.71 years. No significant changes were observed in the RNFL thickness and macular ganglion cell-inner plexiform layer changes at the 6 weeks and 3 months follow-ups, except for the RNFL at the inferior quadrant at 6 weeks follow-up. There were also no patients who experienced visual loss.

Conclusion: A transient decrease in RNFL thickness in the inferior quadrant was observed at the 6-week post-operative follow-up after spinal surgery. The prone position during surgery may be an intraoperative factor associated with the development of perioperative PION in patients undergoing spinal procedures.

Keywords: Retinal nerve fiber layer; macular ganglion cell-inner plexiform layer; spinal surgery; prone position; posterior ischemic optic neuropathy (Siriraj Med J 2024; 76: 689-695)

INTRODUCTION

Postoperative visual loss following non-ocular surgeries has been documented since 1982.[1-3] This complication has been reported in various procedures, including coronary artery bypass graft[4], open heart surgery[5], radical neck dissection6, liver transplantation[7], and spinal surgery.[2,8] A decade-long (1996-2005) retrospective analysis of data from the Nationwide Inpatient Sample in the US identified spinal fusion, cardiac, and non-spinal orthopedic surgeries as having the highest incidences of postoperative visual loss,[2] with a prevalence of 8.64 cases per 10,000 in cardiac surgery and 3.09 cases per 10,000 in spinal fusion.[2] The most commonly associated conditions with postoperative visual loss include posterior ischemic optic neuropathies (PION), cortical blindness, and retinal vascular occlusion.[2] Although postoperative visual loss after non-ocular surgeries is rare, it can lead to devastating complications.

The etiology of perioperative PION remains elusive. Previous reports have identified several potential contributing factors, including prolonged surgeries in the prone position, decreased ocular perfusion pressure, hemodilution or anemia, blood loss, intraoperative hypotension, and the administration of large volumes of intravenous fluids.[2,11]

Previous research has shown a decrease in the thickness of the retinal nerve fiber layer (RNFL) six weeks after incidents of postoperative ION.[12] To investigate the possible relationship between these risk factors and perioperative PION, our study hypothesizes that even patients who do not experience significant postoperative visual loss may still exhibit a reduction in RNFL and macular ganglion cell-inner plexiform layer (GCIPL) thickness post-surgery. The measurement of RNFL and GCIPL thickness can be done accurately using Optical Coherence Tomography (OCT), a widely used non-invasive tool to diagnose various optic nerve diseases.[12]

To explore these factors, including the role of prolonged surgeries in the prone position, we chose spinal surgery as our context. This surgery is increasingly common, leading to a surge in research aimed at enhancing patient safety. One notable area of research involves using AI to predict preoperative and postoperative venous thromboembolism in patients undergoing surgery for spinal metastasis.[13] Additionally, there are studies focused on survival analysis and identifying prognostic factors for metastatic epidural spinal cord compression, comparing cases with preoperatively known and unknown primary tumors.[14] However, there remains a scarcity of clinical studies on perioperative Posterior Ischemic Optic Neuropathy (PION), and most of our knowledge is derived from isolated case reports or retrospective reviews. We designed this study as a prospective investigation to provide a more comprehensive understanding of PION following surgery. We also collected intraoperative data to identify potential factors associated with perioperative PION. This study focuses on analyzing RNFL and GCIPL thickness using OCT in patients both before and after spinal surgery.

MATERIALS AND METHODS

Patients and data collection

This study was structured as a prospective cohort investigation. We enrolled patients diagnosed with spinal conditions who were scheduled for spinal surgery at Siriraj Hospital from November 2013 to June 2015 following prior approval from the Siriraj Institutional Review Board. All patients provided written informed consent, and the study adhered to principles of the Declaration of Helsinki. The inclusion criteria specified that patients be 18 or older, with no pre-existing ocular diseases or conditions impacting the optic nerve. We also ensured that candidates did not have ocular or systemic conditions known to affect RNFL thickness, such as diabetes mellitus, glaucoma, age-related macular degeneration, optic neuropathy, or a history of ocular surgery or trauma. We excluded patients with other optic nerve disorders, including ischemic optic neuropathy, glaucoma, neuroretinitis, perineuritis, and optic neuropathy related to central nervous system infections, toxicity, or malignancy. Patients with macular diseases or those with pathologic myopia (spherical equivalent refractive error >6.0 diopters) were also excluded. Participants who had disabilities precluding examination or were at risk of loss to follow-up were excluded as well.

After obtaining informed consent, we gathered patient data, including age, spinal disease diagnosis, planned surgery type, medical history, and current medication regimen. A comprehensive ophthalmic examination was conducted for each patient, which included Best Corrected Visual Acuity (BCVA), non-contact tonometry, slit lamp examination, fundoscopy, color vision assessment, and evaluation for relative afferent pupillary defects. Retinal nerve fiber layer (RNFL) and macular ganglion cell-inner plexiform layer (GCIPL) thickness measurements were obtained using the Cirrus SD-OCT from the Cirrus HD-OCT 5000 system (Software Version: 6.0.0.599, Carl Zeiss Meditec). We applied the optic disc cube (200x200) and macular cube (512x128) scan protocols. These ophthalmic evaluations were performed on both eyes of each participant the day before surgery and were repeated during two post-operative follow-up visits scheduled for 6 weeks and 3 months. The follow-up appointments were synchronized with the orthopedic clinic's schedule for postoperative care. The RNFL and GCIPL thickness were measured in microns and segmented into average, superior, temporal, nasal, and inferior quadrants of the optic disc for each eye. Additionally, we meticulously recorded intraoperative data, which included the patient's position, episodes of hypotension, blood loss, and duration of operative procedure.

Data analysis

Statistical analysis was performed using means and standard deviations (SD) for continuous variables, and medians (min, max) for categorical data. RNFL and GCIPL thickness measurements, taken before and after surgery for each eye, were analyzed using linear mixed models. Furthermore, multivariate analysis of these models was employed to assess the relationship between intraoperative factors and changes in thickness.

RESULTS

Our study, designed as a pilot investigation studying the effects of spinal surgery, initially recruited a total of 60 patients. However, due to the high attrition rate during the data collection phase, two-thirds of the patients failed to follow-up. Ultimately, 19 patients (equal to 38 eyes) completed all three rounds of follow-up assessments. The participant pool was fairly gender-balanced, with ten males and nine females. The average age of the study population was 53.78+/-12.71 years. Most patients (63.2%) had no prior medical or ocular comorbidities (Table 1).

The mean preoperative BCVA, measured in logmar, was 0.1061 (SD: 0.10407). At the three-month post operative mark, the mean BCVA logmar was 0.1178 (SD: 0.09081). There was no statistically significant difference observed between preoperative and postoperative BCVA logmar values.

The most common spinal conditions among participants in this study were cervical pondylomyelopathy, affecting 6 out of 19 patients, (31.6%), and ossification of the posterior longitudinal ligament, seen in 5 out of 19 patients (26.3%). All 19 patients underwent surgery in the prone position, with thirteen experiencing intraoperative hypotension. The mean operative time was 215.88 minutes, with a median time of 180 minutes (range: 95 to 385 minutes). The average intraoperative blood loss was 997.78 milliliters, with a median loss of 250 milliliters, (range: 20 to 4200 milliliters (Table 2).

OCT analysis yielded results that showed no statistically significant changes in RNFL thickness, both in the overall average measurement and across all quadrants, at the 6-week and 3-month post-operative follow-up points. However, a notable decrease was observed in the inferior quadrant of the RNFL at the 6-week follow-up, when compared to pre-surgical RNFL measurements. Nevertheless, at the 3-month follow-up, RNFL thickness in the inferior quadrant showed no significant thinning compared to the preoperative baseline (Table 3). Similarly, GCIPL thickness measurements, both the average measurement and quadrant-specific data, also revealed no statistically significant changes at the 6-week and 3-month follow-up

TABLE 1. Demographic data of patients.

Demographic data of patients	
Age (mean±SD)	53.78±12.71
Gender: n (%)	
Male	10 (52.6%)
Female	9 (47.4%)
Medical history: n (%)	
None	12 (63.2%)
Hypertension and dyslipidemia	4 (21.1%)
Diabetes mellitus	3 (15.8%)

Abbreviation: SD: standard deviation

TABLE 2. Demographic data of operations.

Demographic data of operations	
Spinal disease: n (%)	
Cervical spondylosis myelopathy	6 (31.6%)
Ossification of the posterior longitudinal ligament	5 (26.3%)
Spinal stenosis	3 (15.8%)
Herniated nucleus pulposus	3 (15.8%)
Spondylolisthesis	2 (10.5%)
Operative Time (minute)	
Mean ± SD	215.88 ± 85.041
Median (min-max)	180 (95-385)
Hypotension: n (%)	
No	6 (31.6%)
Yes	13 (68.4%)
Blood loss (ml.)	
Mean ± SD	997.78 ± 1365.924
Median (min-max)	250 (20-4200)

Abbreviation: SD: standard deviation.

TABLE 3. Thickness of retinal nerve fiber layer and macular ganglion cell-inner plexiform layer in each quadrant, preoperative and postoperative, at 6 weeks and 3 months.

	Time			p-value	
	Preoperative	6 weeks Post-operative	3 months Post-operative	Pre and post 6 weeks	Pre and post 3 months
RNFL, Mean (SD)					
Average	96.11 (8.71)	94.59 (8.79)	94.83 (9.28)	0.247	0.092
Superior	119.74 (13.65)	120.65 (13.22)	118.36 (13.10)	0.065	0.362
Nasal	73.26 (8.44)	72.38 (10.04)	72.22 (10.07)	0.674	0.518
Inferior	123.74 (15.40)	119.62 (16.18)	122.44 (16.31)	0.030	0.681
Temporal	67.63 (11.79)	67.21 (12.09)	67.47 (12.20)	0.994	0.547
GCIPL, Mean (SD)					
Average	79.42 (11.17)	78.35 (11.32)	79.36 (10.35)	0.524	0.460
Superior	80.19 (12.43)	79.35 (12.00)	80.39 (9.88)	0.864	0.887
Inferior	76.69 (14.20)	75.41 (14.09)	76.64 (14.88)	0.449	0.379
Supero-nasal	81.39 (13.91)	81.03 (12.48)	82.36 (9.82)	0.787	0.451
Infero-nasal	79.31 (13.23)	78.68 (12.89)	79.11 (13.37)	0.867	0.282
Infero-temporal	80.31 (8.25)	79.24 (7.16)	79.00 (11.18)	0.771	0.109
Supero-temporal	78.78 (9.01)	78.09 (7.96)	79.06 (9.70)	0.909	0.905

Abbreviations: SD: standard deviation, Significant differences are shown in bold ($p<0.05$).
RNFL: retinal nerve fiber layer, GCIPL: macular ganglion cell-inner plexiform layer.

assessments. At the end of the follow-up period, none of the study patients experienced any form of visual loss or developed new ocular conditions.

DISCUSSION

Perioperative PION is an exceptionally rare condition characterized by an elusive etiology. It is characterized by the sudden, and painless onset of severe visual impairment, with an initially normal optic disc appearance, following non-ocular surgical procedures.[15] It typically presents as bilateral visual loss, though unilateral cases have also been documented.[15,16] The most severe cases may result in visual acuity reduced to mere finger counting or even a complete loss of light perception.[17,18] This condition predominantly affects middle-aged and otherwise healthy individuals.

The causation of perioperative PION is likely multifactorial, with potential risk factors including hemodilution, anemia, hypotension resulting from significant blood loss, and extended surgical durations.[15] Spinal surgeries conducted with the patient in the prone position have a particular association with perioperative PION. The hypothesis is that venous engorgement during surgery could increase pressure within the optic nerve, and thus contribute to its occurrence. This theory is supported by the observation of increased intraocular pressure when individuals, whether awake or anesthetized state, are placed in the prone position.[19] Additionally, the posterior optic nerve's blood supply, particularly in its watershed area, is thought to be especially vulnerable to elevated venous pressure due to its reliance on small end vessels.[15,20,21]

None of the participants in this study experienced postoperative visual loss throughout the entire follow-up period. Furthermore, no statistically significant changes were detected in RNFL thickness, both overall and across all quadrants, at the 6-week and 3-month post-operative time points. However, a specific reduction in RNFL thickness was noted in the inferior quadrant at the 6-week follow-up mark compared to the preoperative RNFL measurements. Remarkably, this reduction in the inferior quadrant was not present at the 3-month follow-up, indicating a return to baseline levels (refer to Table 3). Similarly, GCIPL thickness measurements, both

overall average and by quadrants, showed no statistically significant changes at the 6-week and 3-month post-operative assessments.

It is essential to note that a recent prospective study reported significant RNFL thinning in the nasal and inferior regions just one day after spinal surgery in patients who underwent surgery in the prone position.[19] This discrepancy may be explained by the temporary nature of the thinning observed in the inferior quadrant at 6 weeks in this study, possibly due to a mild degree of ischemia that subsequently resolved. It is important to recognize that the sample size of this study might be too small to conclusively determine this effect. Furthermore, while postoperative ION can occur due to various factors, including severe and prolonged hypotension, anemia, and hemodilution, these conditions may not have been severe enough in this study to significantly impact the RNFL and GCIPL.

In this study, no direct link was found between episodes of hypotension and changes in RNFL and GCIPL thickness. The factors contributing to the onset of perioperative PION, specifically hypotension and anemia, remain unclear, as PION can develop in patients even without these risk factors. Furthermore, it is challenging to establish a direct relationship between surgery duration, volume of blood loss, and the incidence of perioperative PION.

A limitation of this study is the relatively small sample size, which constrains the precision of the results. Future research should aim to recruit a larger pool of participants, control for variables such as examiner bias, and ensure consistent follow-up timing to achieve more accurate and significant results, particularly assessment of RNFL thickness in the inferior quadrant.

CONCLUSION

The data indicates a trend toward reduced RFNL thickness in the inferior region of the optic disc relative to preoperative measurements. This suggests the prone position during surgery may be an intraoperative factor linked to the development of perioperative PION.

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Conflict of interest

There are no conflicts of interest to declare.

Author contribution statement

Conceptualization, TD; methodology, PB and NC; software, DS; validation, SW, AE, TD and DS; formal analysis, NC and YM; investigation, PB; resources, SW; data curation, AE and YM; writing—original draft, TD; writing—review and editing, NP; visualization, DS; supervision, NC and SW; project administration, TD and, AE; Selection of patients, SW. All authors read and agreed to the published version of the manuscript.

Data availability statement

The datasets generated and analyzed during the study are available from the corresponding author upon reasonable request.

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An Evaluation of the Precision of Ocular Trauma Score and Factors for Poor Visual Outcomes in Open Globe Injury: A Retrospective Analysis of Resource-limited Hospital Settings

Takarn Oughtkaew, M.D.[1], Siwatus Puangrab, M.D.[2,*]

[1]Department of Ophthalmology, Bueng Kan Hospital, Bueng Kan, Thailand, [2]School of Medicine, Walailak University, Nakhon Si Thammarat, Thailand.

ABSTRACT

Objective: To evaluate the accuracy and validity of ocular trauma scores (OTS) among patients with open globe injury (OGI) in rural hospital settings and to identify the determinants predicting poor visual outcomes.

Materials and Methods: A single-center retrospective cohort study was conducted through a chart review of OGI patients between July 2018 and June 2023 at Bueng Kan Hospital. Demographic and preoperative factors affecting the final visual outcome were evaluated. OTS score for each patient was calculated and categorized. Final visual acuity (VA) after 6 months was compared to the predicted VA from OTS study. Poor visual outcome was defined as legal blindness after 6 months of treatment.

Results: Thirty-nine eyes from patients with a mean age of 44.05 years were evaluated. Most subjects were male (94.87%), and workplace injuries were the most common (78.38%). Compared to the OTS study, patients in OTS category 2 achieved a significantly higher percentage of better final VA, while categories 3 and 4 showed similar outcomes. OTS category 1 patients had a lower proportion of no light perception (NLP) outcomes, though the difference was not significant. Poor visual outcomes were predicted by initial VA (OR=4.64), wound extension ≥10 mm (OR=20.66), and lens injury (OR=7.44).

Conclusion: OTS is beneficial for predicting final vision in patients with OGI, particularly with less severe trauma. Severe cases can sometimes result in better-than-expected visual outcomes, emphasizing the need for cautious management and counseling by ophthalmologists. Factors that estimate poor visual outcomes involve poor initial VA, wound extension ≥10 mm, and lens damage.

Keywords: Eye injury; prognosis; ocular trauma score; rural area; resource-limited setting (Siriraj Med J 2024; 76: 696-704)

INTRODUCTION

Open globe injury (OGI) is a serious but preventable eye condition and remains a national public health concern. OGI can lead to permanent visual loss, resulting in limitation of daily life activities as well as psychiatric issues.[1] Previous studies have shown more incidences in young adults and high etiology in occupational-related injuries.[2-6] Based on recent reports, a global incidence of OGI ranging between 3.40 and 12 per 100,000 population was noted.[4,7-9]

Not only are treatment and visual rehabilitation crucial processes to achieve favorable outcomes, but the management of a patient's vision expectation is also a challenging topic. To date, a significant amount of

**Corresponding author: Siwatus Puangrab*
E-mail: si_watus@hotmail.com
Received 27 July 2024 Revised 18 August 2024 Accepted 26 August 2024
ORCID ID:http://orcid.org/0000-0002-4564-2993
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research has been conducted to find the determinants of visual outcomes after OGI.[2-6,8,10-12] Ocular trauma score (OTS) is a simplified categorical system commonly used to assess visual acuity after treatment by using simple six parameters from an initial eye examination.[13,14] Validation of OTS in OGI is also widely studied, mostly at tertiary eye centers, and the results tend to be useful for counseling impacted patients and their families.[5,10,12] Although OTS is reliable and reproducible to estimate the best corrected visual acuity (BCVA) after treatment,[15-17] some studies found patients with OGI have the actual BCVA better than BCVA predicted by OTS especially in more severe injuries (categories 1 and 2).[12,18] Recent publications about the validation of OTS found that the effectiveness of OTS to estimate BCVA for overall categories is still inconclusive. Further research is necessary to develop an optimized ocular trauma prognosticating system.[19]

In resource-limited settings, cost-effectiveness is frequently concerned, and treatment options are often restricted so these can influent final visual outcome. Moreover, there is limited literature on the validation of OTS at hospitals with limited resources, especially those available only to general ophthalmologists.

This study aims to evaluate the accuracy and validity of OTS in patients with OGI in resource-limited hospital settings and to identify the factors predicting poor visual outcomes.

MATERIALS AND METHODS

This study was conducted with consideration for the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) guideline and received approval from the research ethics committee at Bueng Kan Hospital (research number: BKHEC2023-47). The medical records of patients who were diagnosed with OGI between July 2018 and June 2023 at Bueng Kan Hospital were reviewed retrospectively. The definition of OGI strictly followed based on the Birmingham Eye Trauma Terminology (BETT)[20], including penetrating ocular injury, perforating ocular injury, ruptured globe, and intraocular foreign body (IOFB). Patients under the age of 15 years old who could not be evaluated for visual acuity or had concurrent ocular diseases or loss to at least 6-months follow-up were excluded. The collected data included age, gender, mechanism of injury, causative objects, and time to hospital, as well as initial eye examination, associated injury, and visual status at the most recent visit. The location of injury was defined by the most posterior point of the wound into 3 zones, comprising zone 1 for an injury limited to the cornea and limbus, zone 2 for an injury involving anterior 5 mm of sclera from the limbus, and zone 3 for an injury involving beyond posterior 5 mm from the limbus.[21] The raw score of OTS was calculated from the initial eye examination and classified into 5 categories. Final visual outcome was evaluated by BCVA at least 6 months after trauma and used for evaluating the accuracy of OTS. Poor visual outcome was defined as legal blindness by evaluate the BCVA ≤ 3/60 (Snellen equivalent of 20/400) or 1.3 LogMAR after 6 months of treatment.

Statistical analysis

For descriptive statistics, continuous data including age, time to hospital, and visual acuity were analyzed using mean and standard deviation (SD) or median and interquartile range (IQR). Categorical data including gender, activity, and mechanism of injury, as well as causative objects, zone of injury, and other factors affecting OGI, were analyzed by percentage.

The patients were grouped into poor visual outcome group (legal blindness) and good visual outcome group (non-legal blindness). The association between final visual outcome and predictive determinants, including demographic data, initial VA, mechanism of injury, wound location, lens injury, relative afferent pupillary defect (RAPD), retinal detachment, vitreous hemorrhage, IOFB, endophthalmitis and eyelid injury were analyzed using univariate and multivariate logistic regression.

Based on the OTS scoring system, the actual and predicted final VA in each category were assessed by testing for equality of proportion. Statistical analysis was calculated using the STATA program, and a P-value less than 0.05 was considered significant.

RESULTS

Forty-five patients were diagnosed with OGI, all with unilateral involvement. Six patients were excluded with two subjects lost to follow-up, two were pediatric patients, and two others had missing data. Remaining 39 patients were analyzed with a mean age (SD) of 44.05 (16.57) years old. Most subjects were male (n=37, 94.87%), and workplace (n=29, 78.38%) was the most common setting for eye injury. In this study, occupational-related activities including mowing (n=11, 28.21%) and agriculture (n=9, 23.08%) were found to be frequent activities. For causative objects, high-velocity objects (n=11, 28.21%) were more common than others, followed by wood branches from agricultural activities. The median (IQR) time to hospital was 3 (2,15) hours. The demographic data and circumstances causing OGI comparing between poor and good final visual outcome are shown in Table 1.

TABLE 1. Comparison of patients' demographic data and circumstance causing Open Globe Injury (OGI) between poor and good final visual outcome group.

Patient's Characteristics	Final Visual Outcome Group		P-value
	Poor (n=18)	Good (n=21)	
Age in years (SD)	39.86 (17.56)	47.63 (15.16)	p = 0.927[a]
Sex n,%			
Male	17 (94.44)	20 (95.24)	p = 0.911[b]
Female	1 (5.56)	1 (4.46)	
Setting n,%			
Workplace	14 (77.78)	15 (71.43)	p=0.031[c]
Home	4 (22.22)	0 (0.00)	
Traffic	0 (0.00)	1 (4.76)	
Outdoor	0 (0.00)	3 (14.29)	
Recreation	0 (0.00)	1 (4.76)	
Assault	0 (0.00)	1 (4.76)	
Activity n,%			
Mowing	6 (33.33)	5 (23.81)	p=0.567[c]
Gardening	3 (16.67)	6 (28.57)	
Repair	4 (22.22)	2 (9.52)	
Sport	1 (5.56)	0 (0.00)	
Blunt	3 (16.67)	3 (14.29)	
Sharp	1 (5.56)	3 (14.29)	
Firework	0 (0.00)	2 (9.52)	
Causative object n,%			
High-velocity metal	1 (5.56)	5 (23.81)	p=0.108[c]
High-velocity object	8 (44.44)	3 (14.29)	
Metallic	2 (11.11)	2 (9.52)	
Wood	1 (5.56)	6 (28.57)	
Glass	2 (11.11)	1 (4.76)	
Elastic	3 (16.67)	1 (4.76)	
Stone	1 (5.56)	2 (9.52)	
Explosive	0 (0.00)	1 (4.76)	
Time to hospital (hour), Median (IQR)	3 (2,15)	4 (2,9)	p = 0.7950[d]

Note: NA, not applicable. Statistical test notations: 'a' represents the independent t-test; 'b' denotes the Pearson chi-square; 'c' denotes Fischer's exact test; 'd' denotes the Mann-Whitney U test.

Most patients (n=24, 61.54%) initially presented with VA of light perception (LP) and hand movement (HM) followed by 1/200-19/200 (n=5, 12.82%), 20/200-20/50 (n=5, 12.82%). Four patients (n=4, 10.26%) presented with NPL, and one patient (2.56%) had VA better than 20/40. At the 6 months follow-up, most eyes showed improvement in visual acuity. Fig 1 shows the distribution of initial VA and final VA at 6 months follow-up in each OTS category. Patients presenting with VA of NLP or LP/HM were often classified into OTS categories 1 and 2, indicating more severe injuries. No patients in OTS category 1 attained a final VA better than PL/HM. Conversely, patients in OTS category 2 exhibited a wider range of final VA outcomes compared to other groups.

For assessing the accuracy of OTS, half of them (n= 20, 51.28%) were initially grouped in category 2 at the first visit, while 10 eyes (25.64%) were in category 1, 8 eyes (20.51%) were in category 3, and one eye (2.56%) was grouped in category 4. However, no eye in this study was classified as category 5. The final VA of patients in

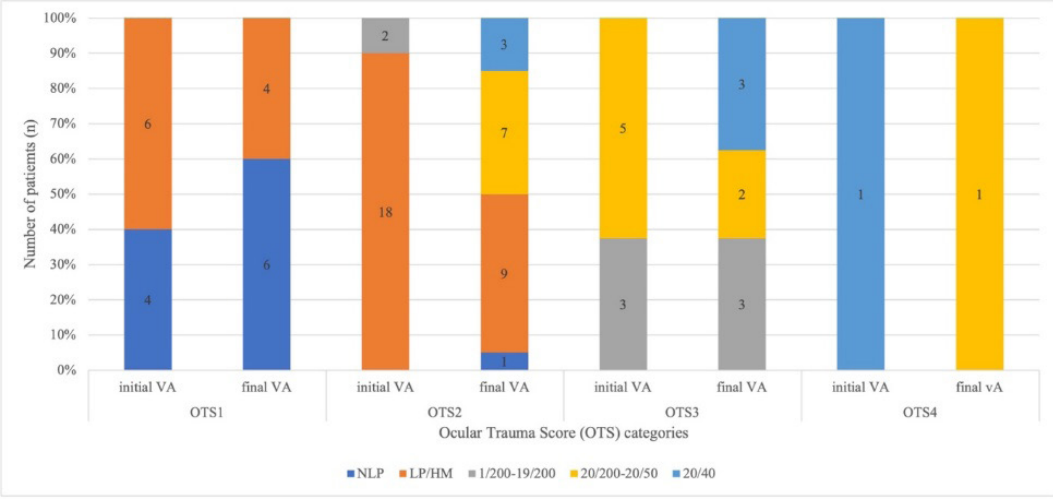

Fig 1. Distribution of Initial VA and final VA classified into each OTS category.
Note: OTS1, OTS category 1. OTS2, OTS category 2. OTS3, OTS category 3. OTS4, OTS category 4. No patients in OTS category 5. Initial VA, initial visual acuity. Final VA, visual acuity at 6 months follow-up.

each category were grouped into five final VA groups, as shown in Table 2. There was no significant difference in patients with OTS categories 3 and 4 between this study and the OTS study. However, patients with OTS category 2 had the significantly lower percentage of NLP group than the OTS study. There were increase in the proportion of LP/HM group and achieved significantly higher percentage of 20/200 to 20/50 group than the OTS study. In patients with OTS category 1, the majority of final VA was still in NLP group like the OTS study even though the insignificantly lower proportion of patients with final VA of NLP than the OTS study was observed. The percentage comparison of final visual acuity between the OTS study and this study classified into each category is shown in Table 2.

In this study, the average initial VA for overall patients was 2.3 LogMAR (Snellen equivalent of 20/3990). Rupture globe was found to be the major mechanism of injury (n=20, 51.28%) followed by penetrating ocular injury (n=16, 41.03%). Zone 1 injury was the most common wound location (n=18, 46.15%). At the first ophthalmic evaluation, 22 eyes (56.41%) were found to have lens injury, while 18 eyes (46.51%) had a relative afferent pupillary defect (RAPD). Retinal detachment and vitreous hemorrhage were also found in 6 (15.38%) and 8 (20.51%) eyes, respectively. Two eyes (5.13%) showed evidence of endophthalmitis, and 2 other eyes (5.13%) had concurrent eyelid laceration. For univariate regression analysis, many factors predict poor visual outcomes, including initial VA (p<0.001), penetrating ocular injury (p=0.033), wound zone 3 (p=0.025), wound extension greater than or equal to 10 mm (p<0.001), lens injury (p<0.001) and RAPD (p<0.001). Comparisons and differences between final visual outcome groups are shown in Table 3.

For multivariate analysis, factors predicting poor final visual acuity include initial VA (OR=4.64, 95%CI=1.33-16.22), wound extension greater than or equal to 10 mm (OR=20.66, 95%CI=2.07-206.18) and lens injury (OR=7.44, 95%CI=1.20-45.95). Other factors that did not show significant differences are detailed in Table 4.

Eight patients (20.51%) were referred to a tertiary eye center due to IOFB, retinal detachment, and endophthalmitis, while the remaining 31 eyes (79.49%) could be treated at rural hospitals. Consequently, twenty-two eyes were found to have traumatic cataracts. The median (IQR) initial VA of patients with traumatic cataracts was 2.5 (2.3-2.7) LogMAR. Nine of them underwent cataract surgery with or without intraocular lens implantation. The median final VA of patients who underwent cataract surgery was 1.51 LogMAR. As the baseline initial VA of patients with lens injuries differed significantly between those who underwent cataract surgery and those who did not (p = 0.02), linear regression was employed to adjust for baseline differences in presenting VA. The results indicate that patients with lens injuries who received cataract surgery exhibited a significantly better final VA compared to those who did not undergo surgery, with a difference of 0.78 LogMAR (p = 0.016).

DISCUSSION

Among ocular injuries overall, OGI ranks as a high-risk problem in terms of visually-threatening conditions. Worldwide incidence varies and runs to 12 per 100,000

TABLE 2. Distribution of Final Visual Outcome for Patients at Final Follow-up Compared Between Ocular Trauma Score Study and This Study

OTS Category	Data Set (N)	Final Visual Acuity Group									
		NLP		LP/HM		1/200 to 19/200		20/200 to 20/50		20/40 and better	
		% (95%CI)	P value	% (95%CI)	P value	% (95%CI)	P value	% (95%CI)	P value	% (95%CI)	P value
1	OTS (215)	73		17		7		2		1	
	This study (10)	60.0 (29.3-90.4)	0.3545	40.0 (9.6-70.4)	0.0528	0.0 (0.0-0.0)	0.3856	0.0 (0.0-0.0)	0.6514	0.0 (0.0-0.0)	0.7506
2	OTS (374)	28		26		18		13		15	
	This study (20)	5.0 (4.6-14.6)	**0.0220**	45 (23.2-66.8)	0.0527	5 (4.6-14.6)	0.1302	35 (14.1-55.9)	**0.0034**	10 (3.1-23.1)	0.5312
3	OTS (808)	2		11		15		28		44	
	This study (8)	0.0 (0.0-0.0)	0.6862	0.0 (0.0-0.0)	0.3200	37.5 (4.0-71.0)	0.0747	25 (5.0-55.0)	0.8501	37.5 (4.0-71.0)	0.7111
4	OTS (378)	1		2		2		21		74	
	This study (1)	0.0 (0.0-0.0)	0.9199	0.0 (0.0-0.0)	0.8864	0.0 (0.0-0.0)	0.8864	100	0.0524	0.0 (0.0-0.0)	0.0916
5	OTS (376)	0	N/A	1	N/A	2	N/A	5	N/A	92	N/A
	This study (0)	N/A		N/A		N/A		N/A		N/A	

Note: NA, not applicable. The p-value was calculated by comparing independent proportions.

TABLE 3. Characteristics of eyes sustaining open globe injury by final vision status.

Eye Characteristics	Number of eyes, %	Final Visual Outcome Group		P-value
		Good (n=18)	Poor (n=21)	
Presenting VA, (LogMAR) Median (IQR)	2.3 (1.9,2.7)	2.1 (1,2.3)	2.7 (2.3,2.7)	p<0.001[a]
Mechanism of injury				
1 rupture	20 (51.28)	7 (38.89)	13 (91.90)	Reference
2 penetrate	16 (41.03)	11 (61.11)	5 (23.81)	p=0.033
3 perforate	0 (0.00)	0 (0.00)	0 (0.00)	N/A
4 IOFB	3 (7.69)	0 (0.00)	3 (14.29)	p=0.230
Wound Zone				
Zone 1	18 (46.15)	9 (50.00)	9 (42.86)	Reference
Zone 2	15 (38.46)	9 (50.00)	6 (28.57)	p=0.546
Zone 3	6 (15.38)	0 (0.00)	6 (28.57)	p=0.025
Wound extension				
Extent <10 mm	26 (66.67)	17 (94.44)	9 (42.86)	Reference
Extent ≥10 mm	13 (33.33)	1 (5.56)	12 (57.14)	p<0.001
Lens injury	22 (56.41)	5 (27.78)	17 (80.95)	p<0.001
RAPD	18 (46.51)	1 (5.56)	17 (80.95)	p=0.001
Retinal detachment	6 (15.38)	1 (5.56)	5 (23.81)	p=0.113
Vitreous hemorrhage	8 (20.51)	3 (16.67)	5 (23.81)	p=0.590
Endophthalmitis	2 (5.13)	0 (00.00)	2 (5.13)	p=0.180
Eyelid laceration	2 (5.13)	1 (5.56)	1 (4.76)	p=0.913

Note: NA, not applicable. Statistical test notation: 'a' denotes the Wilcoxon Test.

TABLE 4. Multivariable exploratory analysis for factors associated with poor vision following open globe injury.

Eye Characteristics	Odds Ratio	95% CI	P-value
Age	1.03	0.98 - 1.08	0.274
Female	1.04	0.043 - 25.14	0.982
Presenting VA, (LogMAR)	4.64	1.33 - 16.22	0.016
Mechanism of injury			
1 rupture	Reference		
2 penetrate	0.24	0.06 - 1.00	0.049
3 perforate	N/A		
4 IOFB	N/A		
Wound Zone			
Zone 1	Reference		
Zone 2	0.45	0.08 - 2.57	0.371
Zone 3	N/A		
Wound extension			
Extent <10 mm	Reference		
Extent ≥10 mm	20.66	2.07 - 206.18	0.010
Lens injury	7.44	1.20 - 45.95	0.031
RAPD	4.05	0.23 - 72.17	0.341
Retinal detachment	1.18	0.03 - 49.69	0.930
Vitreous hemorrhage	1.56	0.32 – 7.70	0.550
Endophthalmitis	N/A		
Eyelid laceration	0.25	0.009 - 6.93	0.412

Note: NA, not applicable

people per year based on the latest report in the US.[9] In this study, young male adults with occupational-related situations face a high risk of OGI. This finding was correlated with agricultural activity in this area and similar to prior reports at several tertiary centers that showed most patients were young men with either work-related or domestic injuries.[15,18,22] The revelation that workplace-related incidents are the leading cause of OGIs in this study advocates for stringent safety protocols and the adoption of protective eyewear to mitigate risk. The role of high-velocity objects and natural elements like wood branches as prevalent causative agents further underscores the need for targeted preventive strategies in specific occupational and recreational settings.

Half of the patients in this study were classified by OTS as category 2, followed by categories 1, 3, and 4, respectively. Patients with high raw OTS scores represented less severe OGI, which was graded in the higher category. On the other hand, patients with lower raw OTS scores had more severe injuries, which were graded in a lower category. In less severe patients, there was no significant difference between the percentage of predicted final visual outcomes in the OTS group and this study group. In OTS category 2, the significantly lower proportion of final VA in NLP group was noted. Furthermore, the proportion of patients in the LP/HM group increased, and they achieved a significantly higher percentage in the final VA of 20/200 to 20/50 compared to the OTS study. For patients classified as OTS category 1, most had final visual acuity (VA) in the NLP group, similar to the OTS study, although there was a slightly lower proportion of patients with final VA in the NLP group compared to the OTS study, but this difference was not statistically significant. These results may show a more favorable final visual outcome in patients with more severe OGI when predicting final VA by OTS. Similar to other research in various tertiary centers, such as in China, OTS prediction was not significantly different when compared with actual visual outcomes postoperatively in OTS categories 3, 4, and 5 ($P > 0.05$), while the prognosis of patients with OTS categories 1 and 2 was better than OTS study (P=0.001, 0.007), respectively.[23] In Korea, final visual acuities assessed using OTS categories were similar to those of OTS study in OTS categories 3, 4, and 5, and more favorable in OTS categories 1 and 2.[12] Northern Thailand reported a lower proportion of poor visual outcomes for eyes in OTS categories 1 and 2, while a concordance in proportions was observed in eyes in OTS categories 3 and 4.[2] From this study, there is agreement to be cautious in management, especially in the case of severe OGI. The authors' observation of better-than-anticipated visual outcomes in lower OTS categories challenges the score's predictive accuracy in the unique settings of this study. This discrepancy invites a critical evaluation of the applicability of OTS beyond the original scoring system, suggesting that local environmental, clinical, and possibly occupational factors could influence injury outcomes. This finding aligns with studies questioning the universal applicability of OTS, advocating for context-specific adaptations to enhance its prognostic relevance.

For the predictive determinants of visual outcomes, many other centers report that presenting VA is one of the strong predictive factors affecting visual prognoses.[9,15,17,22,24-29] Furthermore, other factors include RAPD, posterior involvement, length of wound, rupture mechanism, retinal detachment, and endophthalmitis. Other studies found the presence of adnexal injuries is another influential factor affecting visual outcomes.[26] and a significant increase risk of secondary enucleation.[30] Moreover, traumatized eyes with no light perception require vitreoretinal surgery. It was also found that ciliary body damage, severe vitreous hemorrhage, and closed funnel RD increase the risk of no light perception after treatment. Analysis in this study indicated that the factors predicting poor final visual outcomes include poor initial VA (OR=4.64, 95%CI=1.33-16.22), wound extension more than 10 mm (OR=20.66, 95%CI=2.07-206.18), and lens injury (OR=7.44, 95%CI=1.20-45.95). Penetrating ocular injury may contribute to achieving more favorable vision than other mechanisms of injury (OR=0.24, 95%CI=0.06-1.00). The identification of initial VA, wound extension, and lens injury as predictors of poor visual outcomes is consistent with existing literature, emphasizing their universal prognostic significance. These factors underscore the complexity of OGI management, where a multifaceted approach considering both clinical findings and the mechanism of injury is pivotal. The variation of influential factors between publications may be attributed to the mode of injury, population, surgical instrument technology, experience of surgeon, and cataract surgery following primary surgical repair. Further study in a larger population and subgroup analysis are needed to clarify the associated predictive determinants.

Literature reports exist about the effect of time on surgery and final visual outcomes. The time lag between the injury and surgery was found to adversely affect the final visual outcomes.[31] Another study by Blanch RJ et al. found that time to primary repair is essential by a reduction in predicted visual acuity of 0.37 LogMAR for every 24 hours of delay (95% CI 0.14 to 0.6).[32] In contrast, a report from Makhoul KG et al. found that the time

to repair OGI within 24 hours did not influence the final VA.[33] Patients in rural areas also had significantly worse final VA than city dwellers and had higher rates of endophthalmitis and enucleation.[34] Rural patients had a longer time elapsed from injury to presentation (P = 0.023, average 12.04 hours vs 7.53 hours).[35] Due to the long distance from a nearby tertiary care center, the median time (IQR) to the hospital in this study was 3 (2,15) hours, and no significant difference was found between the final visual outcome group (p=0.8). However, the absence of a significant association between time to hospital presentation and visual outcomes in this study contrasts with existing evidence. This divergence could reflect the unique aspects of the study settings, such as variability in injury severity, access to care, or the small number of patients for evaluation, thus warranting further investigation.

The current study, while offering valuable insights, is not without limitations. The retrospective design and sample size may limit the generalizability of the findings of this study. Additionally, the unique socioeconomic and healthcare context of the settings in this study may influence the applicability of the results of this study to other regions. Future research should aim to validate and refine prognostic tools like the OTS in diverse settings, incorporating larger, multicentric cohorts to capture the broad spectrum of factors influencing OGI outcomes. Investigating the impact of timely intervention, advanced surgical techniques, and rehabilitation services in resource-limited settings will further elucidate pathways to optimizing care for OGI patients.

CONCLUSION

In resource-limited settings, OTS is suitable for predicting final vision in patients with OGI, especially in less severe trauma. A more favorable final visual outcome can be found in severely injured cases, highlighting the need for ophthalmologists to be cautious in management and counseling. The factors predicting poor visual outcomes include poor initial VA, wound extension of more than 10 mm, and lens injury.

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Author Contributions

T.O. conceived the idea, designed the protocol, prepared the abstract, wrote and edited the manuscript. S.P. refined the methodology, analyzed the data, and reviewed the final manuscript.

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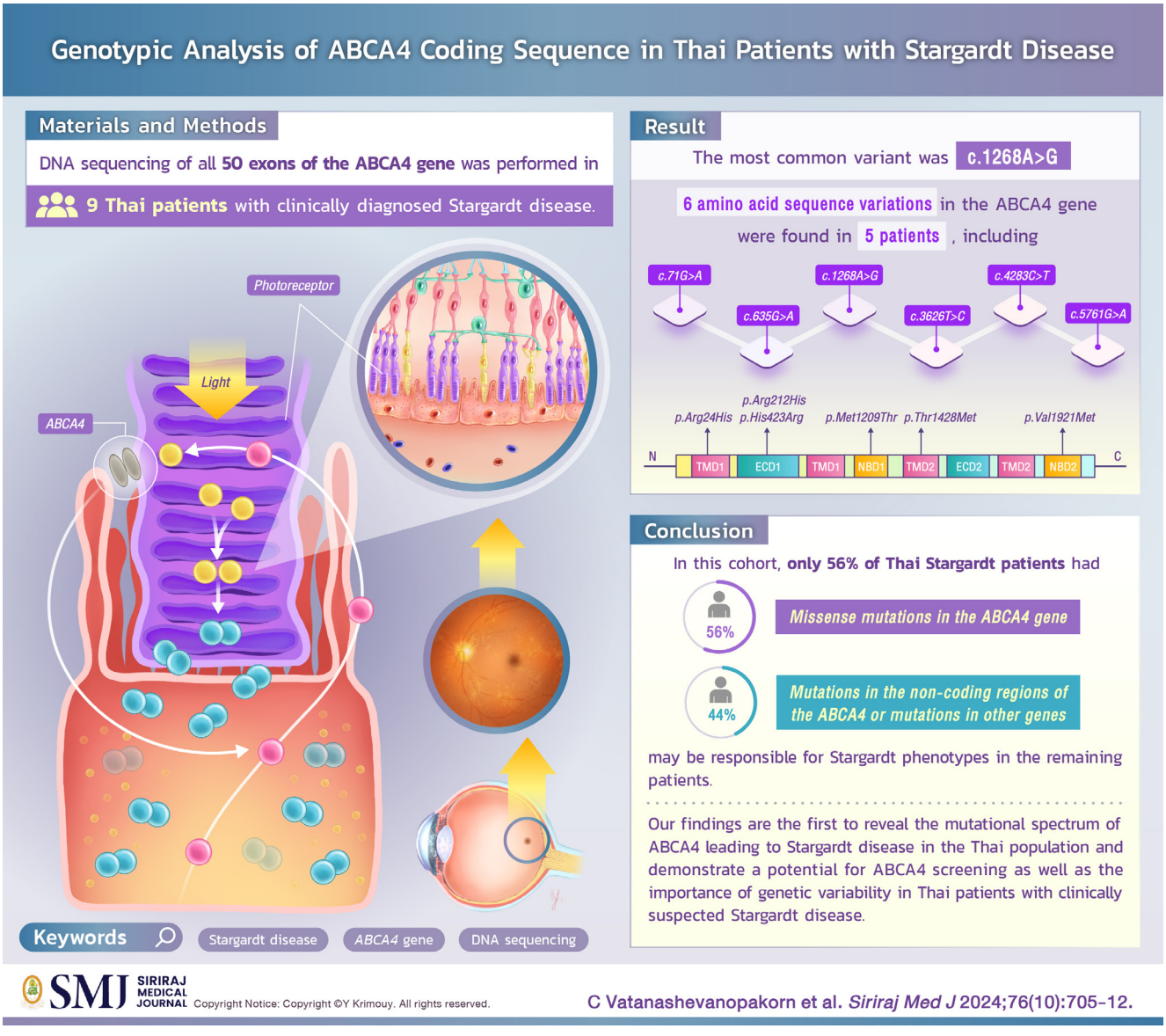
Genotypic Analysis of *ABCA4* Coding Sequence in Thai Patients with Stargardt Disease

Chinnavuth Vatanashevanopakorn, M.D., Ph.D.[1,2], Rungtip Soi-ampornkul, Ph.D.[1,2], Natapat Chaisidhivej, M.D.[1], Asavarak Sompohnmanas, M.D.[1], Dhanach Dhirachaikulpanich, M.D., Ph.D. [3], Nutnicha Tantarungsee, M.Sc.[1,2], Saranporn Piampradad, M.D.[4], Supalert Prakhunhungsit, M.D.[4], Nopasak Phasukkijwatana, Ph.D., M.D.[4,*]

[1]Department of Biochemistry, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Siriraj Center for Regenerative Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3]Research Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [4]Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.



*Corresponding author: Nopasak Phasukkijwatana
E-mail: nopasak.sioph@gmail.com
Received 25 April 2024 Revised 12 July 2024 Accepted 1 August 2024
ORCID ID:http://orcid.org/0000-0002-2317-771X
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ABSTRACT

Objective: To study the mutational spectrum of the *ABCA4* gene in Thai patients with Stargardt disease.

Materials and Methods: DNA sequencing of all 50 exons of the *ABCA4* gene was performed in nine Thai patients with clinically diagnosed Stargardt disease.

Results: Amino acid sequence variations in the *ABCA4* gene were found in five patients. Six missense mutations, c.71G>A, c.635G>A, c.1268A>G, c.3626T>C, c.4283C>T, and c.5761G>A, previously associated with Stargardt disease, were identified in our cohort. The variant c.1268A>G was the most prevalent in our study.

Conclusion: In this cohort, only 56% of Thai Stargardt patients had missense mutations in the *ABCA4* gene. Mutations in the non-coding regions of the *ABCA4* or mutations in other genes may be responsible for Stargardt phenotypes in the remaining patients. Our findings are the first to reveal the mutational spectrum of *ABCA4* leading to Stargardt disease in the Thai population and demonstrate a potential for *ABCA4* screening as well as the importance of genetic variability in Thai patients with clinically suspected Stargardt disease.

Keywords: Stargardt disease; *ABCA4* gene; DNA sequencing (Siriraj Med J 2024; 76: 705-712)

INTRODUCTION

Stargardt disease, also known as fundus flavimaculatus, is a prevalent form of familial macular degeneration. The disease is associated with mutations in the *ABCA4* (STGD1, MIM 248200), *ELOVL4* (STGD3, MIM 600110) and *PROM1* (STGD4, MIM 603786).[1-3] STGD1, the most prevalent subtype of Stargardt disease, has a prevalence between 1:8,000 and 1:10,000, and exhibits an autosomal recessive inheritance pattern with high genotypic and phenotypic heterogeneity.[1,2] Patients with STGD1 generally carry homozygous or compound heterozygous mutations in the *ABCA4* gene.[1,6] *ABCA4* encodes a 2,273-amino acid ATP binding cassette (ABC) transporter, primarily located in the outer segment discs of rod and cone photoreceptor cells. Its primary function is to transport N-retinylidene-phosphatidylethanolamine (N-Ret-PE) across the disc membranes from the lumen to the cytoplasm. This process is vital for preventing the accumulation of toxic bis-retinoid compounds that can lead to photoreceptor degeneration.[3] Consequently, mutations in the *ABCA4* can lead to the accumulation of these harmful compounds, resulting in visual impairment in STGD1 patients.

Over 1,200 *ABCA4*-variants are associated with STGD1.[1,4] Interestingly, data from several studies reveal a broad spectrum of *ABCA4* mutations across different ethnicities.[5-8] In this study, DNA sequencing of all 50 *ABCA4* exons was performed using genomic DNA of nine Thai patients with Stargardt disease. To our knowledge, this is the first study reporting *ABCA4* variants in the Thai population with Stargardt disease.

MATERIALS AND METHODS

Participants

This study was approved by the Siriraj Institutional Review Board (SIRB), with protocol no 798/2560 (EC2), COA no Si 112/2018. Informed consent was obtained from all participants prior to their involvement in the study. Nine Thai patients with clinically confirmed Stargardt disease were recruited from the Ophthalmology Clinic at Siriraj Hospital, Bangkok, Thailand. The diagnosis was based on clinical characteristics and ocular electrophysiologic findings reported by *Fishman et al.*[9] including pisciform flecks or pigmentary changes in the fundi of the patients. The disease was classified into four clinical stages for analysis. We recorded ophthalmic findings such as best corrected visual acuity (BCVA, logMAR), outcomes of fundoscopic examinations, Humphrey visual field (HVF), optical coherence tomography (OCT), fundus autofluorescence (FAF) and ocular electroretinography (ERG). Additionally, six milliliters of blood was drawn from each participant for mutational analysis.

Isolation of genomic DNA

Genomic DNA was extracted from blood samples using genomic DNA mini kit (Geneaid) according to the manufacturer's instruction. Genomic DNA samples were kept at -20°C.

Polymerase chain reaction (PCR) of *ABCA4* gene

The coding regions and adjacent intronic sequences of the *ABCA4* gene were amplified by PCR using primers (Supplementary Table 1) from a previously published

study.[10] The PCR reaction consisted of 100 ng of genomic DNA template, 0.2 µM primer mix and 12.5 µl Taq 2X PCR master mix (New England BioLabs), bringing the total reaction volume to 25 µl. The PCR protocol initiated with a denaturation step at 95°C for 5 minutes, followed by 35 cycles of 95°C for 30 seconds, annealing at 55°C for 30 seconds, and a final extension at 72°C for 30 seconds. It concluded with an elongated extension at 72°C for 10 minutes. After PCR-amplification, the products were purified using the GenepHlow™ PCR cleanup kit (Geneaid) in accordance with manufacturer's protocol.

DNA sequencing and data analyses

Sanger sequencing of the PCR products was performed with 5 µM primers using 3730xl DNA analyzer (Applied Biosystems) at the ISO9001:2015 and ISO13485:2016-certified service sequencing lab (Bionics, Korea). Sequencing data was analyzed by aligning it with *ABCA4* reference sequence (NG_009073.1 and NM_00350) using ApE v2.0.61 (M. Wayne Davis). Missense variants identified through this process were then evaluated for potential deleterious effects using in silico prediction algorithms, specifically PolyPhen-2[11] and SIFT.[12] PolyPhen-2 is a web-based tool that predicts structural and functional consequences of amino acid substitution within human proteins. The tool briefly works by selecting a set of homologous sequences with a clustering algorithm then constructing and refining its multiple alignments. Sequence-based features and structural-based features of the substitution site are extracted and fed to a probabilistic classifier. The functional significance of an allele replacement is predicted from its individual features by a naïve Bayes classifier trained using supervised machine-learning. Sequences are predicted to be benign (Poly-Phen score ≤0.446), possibly damaging (Poly-Phen score >0.446 and ≤0.908) or probably damaging (Poly-Phen score >0.908). SIFT is a sequence homology-based tool that distinguishes tolerant from intolerant amino acid substitutions and predicts phenotypic effects from amino acid substitutions. The tool utilizes PSI-BLAST to search for similar sequences, then the closely related sequences that may have similar function to the query sequence are identified by PSI-BLAST and MOTIF. Alignment of the selected sequences is performed by PSI-BLAST and calculation of normalized probabilities for all possible substitutions from the alignment is done using Dirichlet mixture model. Positions with normalized probabilities less than 0.05 are predicted to be deleterious while those with normalized probabilities at least 0.05 are predicted to be tolerated. Classification of the identified variants was done according to the joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[13]

RESULTS

ABCA4 mutational spectrum

Nine patients (3 males and 6 females) clinically diagnosed with Stargardt disease were recruited. The age of onset ranged from 5-58 years old (median 35 years old). Sequencing the 50 exons of the *ABCA4* gene revealed 11 point mutations, of which 6 were missense and 5 were synonymous (Fig 1 and Table 1).

There were 5 patients with at least one missense mutation (P1, P4, P5, P6 and P8). We could not identify missense mutations of the *ABCA4* exons in the other 4 patients and they carried only silent mutations (P2, P3, P7 and P9). Interestingly, all 6 missense mutations identified in our cohort were in heterozygous state. There were 3 patients being compound heterozygous for 2 missense mutations (P4, P6 and P8) and 1 patient for 3 missense mutations (P5). Whether there could be interactions between different heterozygous mutations in these patients needs further studies.

There were 3 patients carrying at least one probably damaging mutation predicted by PolyPhen and SIFT scores (P4, P6 and P8). However, they did not show different clinical phenotypes in terms of age of onset and visual acuity compared to the rest of the subjects.

Of note was that patients P2 and P3 were siblings and showed early onset of the disease compared to the others. However, there were no missense mutations found in their *ABCA4* exons, suggesting that mutations in other genes may be responsible for their phenotypes.

The details of each patient were described below.

Case series

Sanger sequencing of genomic DNA from patient P1, a 54-year-old female patient presenting with decreased visual acuity and recent logMAR BCVA of 0.94 OD and 0.92 OS, uncovered a heterozygous missense mutation in exon 10 (1268A>G). This mutation has been previously associated with STGD1.[14] Additional three polymorphisms (141A>G, 4530G>A and 6069T>C, Table 2) were also identified. No family history of eye disease were found in this patient.

Patient P2, diagnosed with Stargardt disease, exhibited recent BCVA of 2 OD and 1.72 OS. Additionally, he displayed delayed development, attributed to juvenile type neuronal ceroid lipofuscinosis. Sanger sequencing of the *ABCA4* exons for this patient identified heterozygosity for three silent mutations, 141A>G, 5814A>G and 5844A>G.

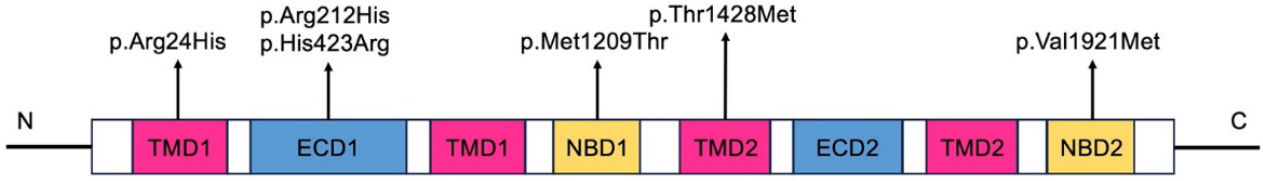

Fig 1. Distribution of *ABCA4* non-synonymous mutations found in this study. ECD1 - exocytoplasmic domain 1; ECD2 - exocytoplasmic domain 2; NBD1 - nucleotide binding domain 1; NBD2 - nucleotide binding domain 2; TMD1 - transmembrane domain 1; TMD2 - transmembrane domain 2.

TABLE 1. *ABCA4* variants in this study.

***ABCA4* mutations**				**Pathogenicity prediction**		**Allele frequency in patients**	**ACMG Variant interpretation**	**Reference**
Reference SNP	Exon	Nucleotide change	Amino acid change	PolyPhen*	SIFT**			
rs4847281	2	c.141A>G	-	-	-	14/18	benign	(28)
rs62645958	2	c.71G>A	Arg24His	0.98	0.01	1/18	likely pathogenic	(29, 30)
rs6657239	6	c.635G>A	Arg212His	0.977	0.04	2/18	benign	(15, 16, 17, 18)
rs3112831	10	c.1268A>G	His423Arg	0	0.63	5/18	benign	(14, 20, 21, 22, 23, 31, 32)
rs76258939	25	c.3626T>C	Met1209Thr	0	1	1/18	benign	(27, 33)
rs1800549	29	c.4283C>T	Thr1428Met	0.01	0.09	2/18	benign	(4, 24, 25, 34)
-	30	c.4530G>A	-	-	-	1/18	benign	This study
rs61753032	41	c.5761G>A	Val1921Met	0.979	0	1/18	likely pathogenic	(25, 35)
rs4147857	41	c.5814A>G	-	-	-	2/18	benign	(28, 32)
rs2275029	42	c.5844A>G	-	-	-	2/18	benign	(28)
rs1762114	44	c.6069T>C	-	-	-	15/18	benign	(28)

*PolyPhen score: >0.908 probably damaging, ≤0.908 and >0.446 possibly damaging, ≤0.446 benign

**SIFT score: <0.05 deleterious, ≥0.05 tolerated

Abbreviations: ACMG, American College of Medical Genetics and Genomics; SNP, single nucleotide polymorphism

Furthermore, he was found to be a homozygote for the 6069T>C silent mutation. His sibling, patient P3, also diagnosed with Stargardt disease (recent BCVA of 2 OD and 0.02 OS) displayed normal development but carried the same mutations.

Patient P4, a 42-year-old female, had been experiencing progressive blurred vision for six years and had a recent BCVA of 1.5 OD and 1.42 OS. Mutational analysis revealed compound heterozygous missense mutations in exon 6 (635G>A) and exon 10 (1268A>G). Additionally, the patient was found to be homozygous for two single nucleotide polymorphisms (SNPs, 141A>G and 6069T>C) (Table 2).

Sequence analysis of the complete *ABCA4* exons from the genomic DNA of a male patient (patient P5) diagnosed with Stargardt disease and with a recent BCVA of 1.52 in both eyes revealed three compound heterozygous missense mutations in exon 10 (1268A>G), exon 25 (3626T>C) and exon 29 (4283C>T). Additionally, two synonymous mutations were identified in exon 2 (141A>G) and exon 44 (6069T>C).

TABLE 2. Participants' characteristics and type of *ABCA4* mutation found.

Patient	Gender	Age of onset (years)	logMAR BCVA		Clinical stages	*ABCA4* mutations		
			OD	OS		Reference SNP	Nucleotide change	Amino acid change
P1	Female	36	0.94	0.92	3	rs3112831	c.1268A>G	His423Arg
						rs4847281	c.141A>G	-
						-	c.4530G>A	-
						rs1762114	c.6069T>C	-
P2	Male	5	2	1.72	1	rs4847281	c.141A>G	-
						rs4147857	c.5814A>G	-
						rs2275029	c.5844A>G	-
						rs1762114	c.6069T>C	-
P3	Male	5	0	0.02	1	rs4847281	c.141A>G	-
						rs4147857	c.5814A>G	-
						rs2275029	c.5844A>G	-
						rs1762114	c.6069T>C	-
P4	Female	35	1.5	1.42	1	rs6657239	c.635G>A	Arg212His
						rs3112831	c.1268A>G	His423Arg
						rs4847281	c.141A>G	-
						rs1762114	c.6069T>C	-
P5	Male	23	1.52	1.52	3	rs3112831	c.1268A>G	His423Arg
						rs76258939	c.3626T>C	Met1209Thr
						rs1800549	c.4283C>T	Thr1428Met
						rs4847281	c.141A>G	-
						rs1762114	c.6069T>C	-
P6	Female	50	0.46	0.44	2	rs62645958	c.71G>A	Arg24His
						rs3112831	c.1268A>G	His423Arg
						rs4847281	c.141A>G	-
						rs1762114	c.6069T>C	-
P7	Female	35	1.02	1.04	4	rs4847281	c.141A>G	-
						rs1762114	c.6069T>C	-
P8	Female	21	1.02	0.98	1	rs6657239	c.635G>A	Arg212His
						rs61753032	c.5761G>A	Val1921Met
						rs4847281	c.141A>G	-
P9	Female	58	1.14	2	4	rs4847281	c.141A>G	-
						rs1762114	c.6069T>C	-

Abbreviations: logMAR, logarithm of the minimum angle of resolution; BCVA, best corrected visual acuity; OD, right eye; OS, left eye

Patient P6, a female diagnosed with Stargardt disease, had a current BCVA of 0.46 OD and 0.44 OS. Sanger sequencing of her *ABCA4* genes revealed two heterozygous non-synonymous mutations: 71G>A and 1268A>G. These mutations result in an amino acid change from arginine to histidine (Arg24His) and from histidine to arginine (His423Arg), respectively (Table 2). Additionally, this patient was found to be homozygous for the synonymous mutations 141A>G and 6069T>C.

In patient P7, a 55-year-old female diagnosed with Stargardt disease, two benign variants, 141A>G and 6069T>C, were found in a homozygous state within *ABCA4* coding sequence. The onset of her disease was at age 45, and her recent BCVA was 1.02 OD and 1.04 OS. Sanger sequencing of all *ABCA4* exons in this patient did not reveal any pathogenic variants.

In patient P8, a 33-year-old female diagnosed with Stargardt disease, sequencing revealed two pathogenic heterozygous variants and one polymorphism. At the time of sequencing, her BCVA was 1.02 OD and 0.98 OS. The 635G>A mutation, resulting in an amino acid change from arginine to histidine (Arg212His), is associated with STGD1.[15-18] Similarly, the pathogenic 5761 G>A variant, which causes a change of valine to methionine, was found in this patient. Additionally, she was homozygote for the 141A>G polymorphism.

Patient P9, a 63-year-old female, presented with a BCVA of 1.14 OD and 2 OS. Her clinical features were consistent with Stargardt disease. Genetic testing found her to be homozygous for two *ABCA4* polymorphisms, 141A>G and 6069T>C.

DISCUSSION

This is the first study to investigate *ABCA4* variants in Thai patients with Stargardt disease. In our cohort, four patients (P4, P5, P6 and P8) carried compound heterozygous missense mutations in the *ABCA4* gene, one patient (P1) was heterozygous for a single ABCA4 variant leading to amino acid change, while four patients (P2, P3, P7 and P9) presented with SNPs but no *ABCA4* mutant alleles. Out of the six missense mutations in our cohort, three (c.71G>A, c.635G>A and c.5761G>A) were classified as pathogenic or likely pathogenic, and the remaining three (c.1268A>G, c.3626T>C and c.4283C>T) were deemed benign or likely benign.[13] Mutant variants were evenly distributed across the six functional domains of the *ABCA4* protein (Fig 1). Specifically, two mutations (c.635G>A and c.1268A>G) were found in the exocytoplasmic domain 1 (ECD1) of the protein. Within the transmembrane domain (TMD 1 and 2, two mutant variants were found (c.71G>A for TMD1 and c.4283C>T for TMD2). Two additional missense mutations were also detected in nucleotide binding domain (NBD) 1 and 2 (c.3626T>C for NBD1 and c.5761G>A for NBD2). Thus, no *ABCA4* variant hot spots were found in our cohort, which is consistent with previous reports in other ethnicities.[5,19]

The most prevalent disease-associated variant in our study was c.1268A>G (44.44%). Pathogenicity prediction tools, PolyPhen and SIFT, have classified this variant as benign or tolerated (Table 1). Despite an occurrence in the normal German population, it is the most frequently observed variant in Stargardt disease patients in the United States, where it is associated with abnormal electroretinogram findings.[20,21] A study involving a Sicilian family indicated that the c.1268A>G variant could potentially delay the onset of Stargardt disease.[22] Similarly, another study proposed its implication in late-onset forms of Stargardt disease.[23] Interestingly, in our study, the average age of onset of patients with this variant was higher, but not significantly, compared to patients without it (36 vs 29 years old, unpaired t-test, p=0.6388). Furthermore, when comparing patients of similar ages (P4 vs P7 and P6 vs P9), the fundoscopic findings for those carrying the c.1268A>G (P4 and P6) appeared to be more preserved than in those without the variant (P7 and P9) (Fig 2). This suggests that the c.1268A> G variant may influence the clinical phenotype, which aligns with findings from previous studies.

In this study, 55.55% of Stargardt disease patients were found to have identifiable *ABCA4* mutations, which is comparable to previous reports.[8,17,24,25] The investigation was limited to the coding regions of *ABCA4*, meaning that patients without detected mutations might have unidentified *ABCA4* mutations in non-coding regions or mutations other genes associated with Stargardt disease. A more comprehensive whole genome sequencing approach might be required to identify disease-associated mutations in these patients. In addition, another limitation of this study is a low number of patients. Other studies investigating *ABCA4* variants in Stargardt disease and/or retinitis pigmentosa involved more patients (ranges from 40 to 345).[5,17,19,26,27] Thus, it this likely that the *ABCA4* variants reported in this study, which solely comprises patients from the Ophthalmology Clinic at Siriraj Hospital who consented to genetic testing, may not fully represent the genetic diversity of Thai patients with Stargardt disease. Further research is warranted to explore genetic heterogeneity of Stargardt disease in the Thai population.

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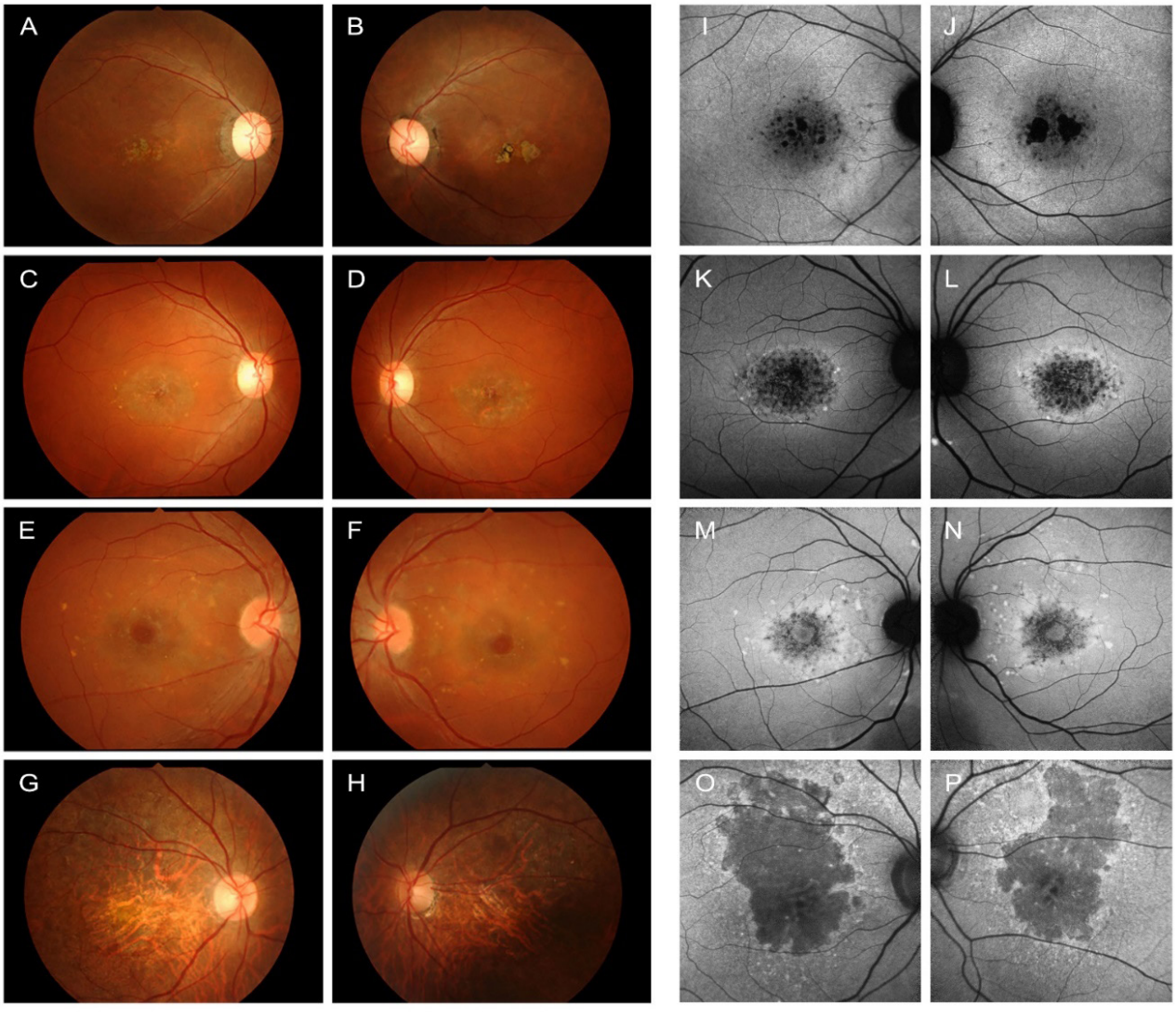

Fig 2. Fundus photographs (A-H) and corresponding fundus autofluorescence images (I-P) comparing Stargardt patients with and without the c.1268A>G variant at similar ages (patients P4, 37 years old vs P7,35 years old and patients P6, 51 years old vs P9, 59 years old). Patient P4 (A, B, I and J) exhibited foveal retinal pigment epithelial (RPE) atrophy in both eyes, as well as hyperpigmented clumps of RPE in the left eye. The c.1268A>G variant was present in this patient. In contrast, patient P7 (C, D, K, and L) did not possess the variant and exhibited more severe RPE atrophy in both eyes. Patient P6 (E, F, M and N), who carried the variant, displayed fishtail-shaped flecks in the macular region with multiple small RPE atrophic foci better seen in by autofluorescence in both eyes. On the contrary, patient P9 (G, H, O and P) did not harbor the variant and demonstrated more extensive RPE atrophy with absorbed flecks in both eyes.

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Author Contributions

CV provided conceptual input, designed experiments, analyzed sequencing and clinical data and wrote the manuscript. RS, NC and NT designed and performed experiments. AS and DD performed experiments and analyzed sequencing data. SPi collected and analyzed clinical data. SPr and NP provided conceptual input, collected and analyzed clinical data and co-wrote the manuscript. All authors approved the manuscript.

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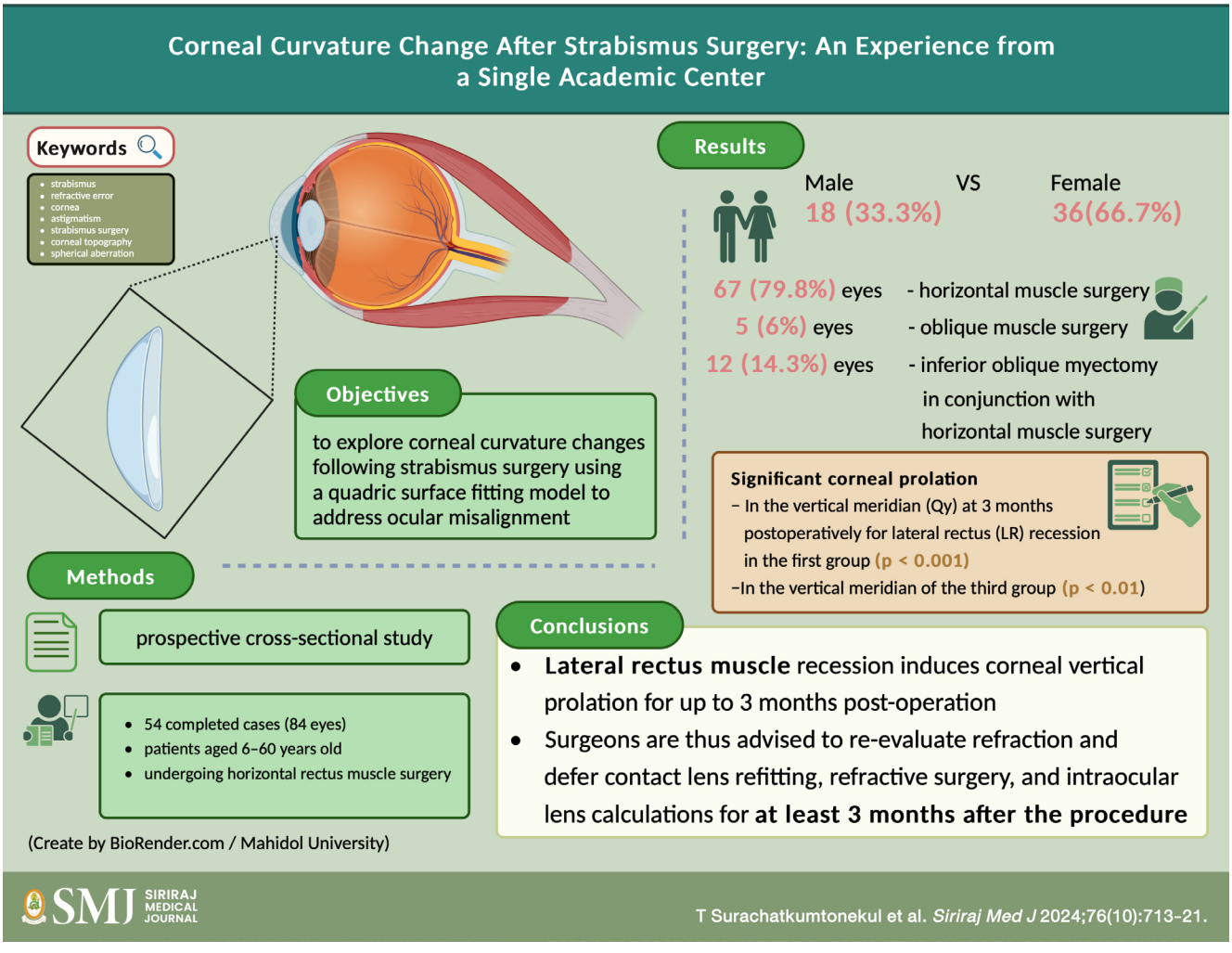
Corneal Curvature Change After Strabismus Surgery: An Experience from a Single Academic Center

Thammanoon Surachatkumtonekul, M.D.[1], Sasima Tongsai, Ph.D.[2], Kanchalika Sathianvichitr, M.D.[1], Prapasson Sangsre, M.Sc.[1], Manatsawin Saiman, B.Sc.[1], Wasawat Sermsripong, M.D.[1], Piyaphat Jaruniphakul, M.D.[1]

[1]Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Office for Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.



*Corresponding author: Thammanoon Surachatkumtonekul
E-mail: si95thim@gmail.com
Received 25 April 2024 Revised 22 August 2024 Accepted 23 August 2024
ORCID ID:http://orcid.org/0000-0002-0037-6863
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ABSTRACT

Objective: This study aimed to explore corneal curvature changes following strabismus surgery using a quadric surface fitting model to address ocular misalignment.

Material and Methods: In this prospective cross-sectional study, 54 completed cases (84 eyes) of patients aged 6–60 years old (mean 10 years old) undergoing horizontal rectus muscle surgery were examined using placido-based keratometry with the Oculus Keratograph 5M system. Data on corneal curvature were collected one week preoperatively, and again one week, one month, and three months post-operation. Asphericity in the vertical meridian (Qy) and horizontal meridian (Qx), and surgically induced astigmatism (SIA) were calculated.

Results: The 84 eyes included were categorized into three groups: horizontal muscle surgeries, oblique muscle surgery, and combined horizontal and oblique muscle surgeries. Significant corneal prolation (steep central, flat peripheral) was revealed in the vertical meridian (Qy) at 3 months postoperatively for lateral rectus (LR) recession in the first group ($p < 0.001$), and the mean SIA was 0.45 D (95% CI: 0.35–0.56 D). A similar effect was seen in the vertical meridian of the third group ($p < 0.01$), with a mean SIA at 3 months of 0.27 D (95% CI: 0.23–0.32 D).

Conclusion: Lateral rectus muscle recession induces corneal vertical prolation for up to 3 months post-operation. Surgeons are thus advised to re-evaluate refraction and defer contact lens refitting, refractive surgery, and intraocular lens calculations for at least 3 months after the procedure.

Keywords: Strabismus; refractive error; cornea; astigmatism; strabismus surgery; corneal topography; spherical aberration (Siriraj Med J 2024; 76: 713-721)

INTRODUCTION

The cornea is a structure that has elastic properties according to the well-formed biomechanics supporting its strength. Obviously, ophthalmic procedures that involve cornea or refractive surgeries can change its shape, thickness, and curvature.[1] However, procedures performed near the cornea can affect it as well, including trabeculectomy, scleral buckling, and upper lid surgery, which were shown to have pressure effects on the cornea.[2-5] The corneal curvature is crucial in the refractive property of the eye. Besides providing two-thirds of the refractive power of the eye, it is the main factor to consider in intraocular lens calculation[6-8] for ensuring accurate contact lens fitting and a main consideration in refractive surgeries.

Although many studies have shown that the corneal curvature and refractive property are changed after strabismus surgery, the results are still varied and unpredictable.[9-15] Assessing corneal change post a procedure depends on the area of the cornea that is chosen for analysis and how the procedures are categorized.

The aim of the present study was to determine the alteration pattern of corneal curvature after strabismus surgery, including horizontal and oblique muscle surgeries. The curvatures of the horizontal and vertical meridian were analyzed separately.

MATERIALS AND METHODS

Patients and Methods

The study adhered to the principles of the Declaration of Helsinki, and the experimental protocol received approval from the Institutional Review Board at the Faculty of Medicine Siriraj Hospital (SIRB) in January 2018 (COA no. Si 021/2018). We prospectively enrolled patients aged 6 and older who underwent strabismus surgery (medial rectus, lateral rectus, and/or inferior oblique muscle surgery) between February 2018 and October 2018 at Siriraj Hospital, Bangkok, Thailand. Patients with severe corneal diseases and/or corneal scars causing irregular astigmatism were excluded from the study. We provided detailed explanations of the study protocols to participants before their study participation and obtained their informed consent before collecting data.

Ophthalmological examination

The enrolled patients underwent a comprehensive eye examination to assess their eye function, refraction, and any diseases through three methods: 1. Test of best-corrected visual acuity (BCVA); 2. Auto-refraction and keratometry using the ARK-530A system (NIDEK CO., LTD, Japan); 3. Placido-based keratometry using the Oculus Keratograph 5M system (Oculus, Inc., USA). Two trained

ophthalmic technicians were assigned for the keratometry measurements. The patients' head positions were carefully checked, and they were required to maintain focus on the target during the keratometry measurements. To assess the reliability of their measurements, the ophthalmic technicians randomly did keratometry measurements of 30 eyes two times each.

We also conducted slit lamp examinations to evaluate the anterior segment of patients' eyes, searching for corneal pathologies that could affect the corneal curvature, such as corneal scars and corneal dystrophy. Pediatric and strabismus ophthalmologists examined the patients for their strabismic deviation angle and pattern.

These eye examinations were performed within 1 week before strabismus surgery and then again postoperatively at 1 week, 1 month, and 3 months. Pediatric ophthalmology staff or pediatric ophthalmology fellows, under the supervision of experienced staff, performed the strabismus surgeries. The amount of horizontal rectus muscle surgery was determined according to Marshall–Parks' surgical table.[16]

We used a conic model fitting approach to analyze corneal height data obtained with the Oculus Keratograph 5M, transforming them into Cartesian and polar coordinates. We employed a conic equation using an algorithm from Yury Petrov's ellipsoid fit method[17]:

$Ax^2 + By^2 + Cz^2 + 2Dxy + 2Exz + 2Fyz + 2Gx + 2Hy + 2Iz + J = 0$,

This equation was consistent with the one used in the study by Yue Di et al.[15] and offers certain advantages in terms of reducing localization errors and minimizing susceptibility to eye rotation during measurement.

The corneal eccentricity (e) was calculated for two axes using the following equations:

$$ex = \sqrt{1 - \frac{Rz^2}{Rx^2}}, \quad ey = \sqrt{1 - \frac{Rz^2}{Ry^2}},$$

where ex and ey represent eccentricities in the x- and y-directions, respectively, while Rx, Ry, and Rz represent the radii derived from the conic fitting model. Another term related to eccentricity is corneal asphericity (Q), which can be defined as $Q = -1e^2$.

Surgically induced astigmatism (SIA) is characterized by the differential between preoperative and postoperative refraction measurements. Villegas et al.[18] have posited that the correction of astigmatism exceeding 0.30 D is associated with a significant improvement in visual acuity. Consequently, the findings of our study underscore the clinical relevance of this value.

Statistical analysis

We calculated the required sample size to investigate the reliability of the two ophthalmic technicians for the placido-based keratometry measurements and to examine the relationship between strabismus surgery and changes in corneal refractive power after the strabismus surgery. The keratometry measurements taken by two ophthalmic technicians showed high reliability, with an ICC of 0.90. Thus, for participants whose measurements were conducted by both technicians, the average values were used to calculate changes in corneal curvature.

Therefore, using the Nquery Advisor for confidence interval [CI] method with a confidence level of 0.95, number of measurements of 2, and correlation distance limit of 0.09, we determined that a minimum sample size of 19 was needed.

To study the relationship between strabismus surgery and changes in corneal asphericity after strabismus surgery, we assumed a medium effect size of 0.15 (following Cohen's guidelines for multiple linear regression), an R^2 of 0.13, three independent variables, a significance level of 0.05, and a power of 0.80. Using Nquery Advisor, we calculated that a minimum sample size of 77 was required.

In this study, we designated corneal asphericity in the horizontal meridian as Qx and in the vertical meridian as Qy. To account for an occasional incomplete ring in the corneal topography caused by upper lid coverage, we used a central corneal diameter of 7 mm.

We utilized descriptive statistics to present the quantitative data, using the mean (SD) for normally distributed data and the median (range) for non-normally distributed data. For qualitative data, we reported numbers and percentages. To evaluate changes in corneal asphericity (Qx and Qy) before and after strabismus surgery, paired t-tests were employed to compare baseline measurements with those obtained at each follow-up time point. This within-subjects design, where the same individuals were assessed repeatedly, allows for a more sensitive analysis of changes over time by controlling for individual variability. While paired t-tests are generally not recommended for comparing multiple time points directly due to the increased risk of a Type I error, our study focused solely on comparing baseline values to follow-up measurements. This approach effectively mitigates the risk of inflated Type I error, as it avoids the multiple comparisons that can arise when comparing all possible pairs of time points.

The intra- and inter-rater reliability of the two trained ophthalmic technicians were assessed using the intraclass correlation coefficient (ICC) in a two-way mixed effects and two-way random effects model, respectively. To examine the relationship between age or

the amount of recession and the ratio of Qy at 3 months postoperatively to preoperative Qy (Qy3mo/Qypre), we employed Spearman's rho correlation coefficient and scatter plots. Multiple linear regression analysis was conducted to investigate the relationship between the surgical procedures and changes in corneal spherical aberration after strabismus surgery.

Data were prepared and analyzed using MATLAB 2018a (Math Works Inc., Natick, MA, USA) and PASW Statistics for Windows, Version 18.0 (Chicago: SPSS Inc., USA). A significance level of $P < 0.05$ was considered statistically significant.[19]

RESULTS

Sixty-eight patients were initially included in the study; however, 14 patients were subsequently excluded due to loss to follow-up (n = 13) or a change in their operation plan (n = 1). Consequently, 54 patients (representing 84 eyes) were enrolled in the study. Among these participants, 36 (66.7%) cases were female, with a median age of 10 years old (ranging from 6 to 60 years old). Of the 84 eyes from the 54 included patients, 67 (79.8%) eyes underwent horizontal muscle surgery, 5 (6%) eyes underwent oblique muscle surgery, and 12 (14.3%) eyes underwent inferior oblique myectomy in conjunction with horizontal muscle surgery. The types of surgeries were categorized as shown in Table 1. The inter-rater reliability of the two ophthalmic technicians in performing keratometry measurements for both the horizontal and vertical meridians was excellent (ICC = 0.983, 95% CI: 0.965–0.991 and ICC = 0.987, 95% CI: 0.975–0.993, respectively). The intra-rater reliability of each ophthalmic technician in performing keratometry measurements for both the horizontal and vertical meridians was also excellent, with ICC values ranging from 0.989 to 0.997, as shown in Table 2.

We categorized the procedures into three groups. The first group consisted of patients who underwent horizontal muscle surgery, and their data were analyzed separately for each extraocular muscle. The second group included patients who underwent inferior oblique myectomy (IO myectomy or IO anteriorization). The third group comprised patients who underwent inferior oblique myectomy in conjunction with horizontal muscle surgery, with most of them (9 out of 12) undergoing recession.

In the first group (horizontal muscle surgery), the horizontal meridian (Qx) tended to decrease, indicating a more prolate shape (steeper center and flatter periphery) in every procedure, but this effect was transient. Similarly, the vertical meridian (Qy) of medial rectus (MR) and lateral rectus (LR) recession procedures demonstrated prolation. However, we analyzed this in each extraocular muscle surgery and found that only LR recession showed a significant change in corneal astigmatism that persisted until 3 months postoperatively. This change demonstrated statistical significance ($P < 0.01$ at 1 week, and $P < 0.001$ at 1 month and 3 months) and was correlated with the "with-the-rule" pattern of the surgically induced astigmatism (SIA) change (mean 0.45D, 95% CI: 0.35–0.56D), as shown in Fig 1.

In the subgroup analysis, for the LR recession group, there was a moderate positive relationship between the ratio of Qy at 3 months postoperatively and preoperative Qy (Qy3mo/Qypre) and age ($rs = 0.531$, $n = 20$, $P = 0.016$) in the children and adolescents (aged 6–18 years old), while the correlation between Qy3mo/Qypre and the amount of recession showed a low negative relationship ($rs = -0.334$, $n = 22$, $P = 0.149$), as shown in Fig 2.

There were no significant changes in the vertical meridian in the resection medial rectus, recession medial rectus, resection lateral rectus, or recession and resection subgroups.

In the second group, horizontal meridian (Qx) decreased significantly before returning to near the preoperative value, with no specific pattern of alteration in the vertical meridian (Table 3). Although the Qx of the third group exhibited a similar pattern to the second group, the vertical meridian (Qy) showed a statistically significant decrease at 1 and 3 months after the surgeries (p-value = 0.027 and p-value = 0.007, respectively) (Table 4); however, the amount of change was not clinically significant (mean SIA was 0.27 D, 95% CI: 0.23–0.32D).

In the vertical meridian, multiple linear regression analyses showed that only the recession procedure had a significant relationship with a change in corneal asphericity after strabismus surgery at 1 month and 3 months,

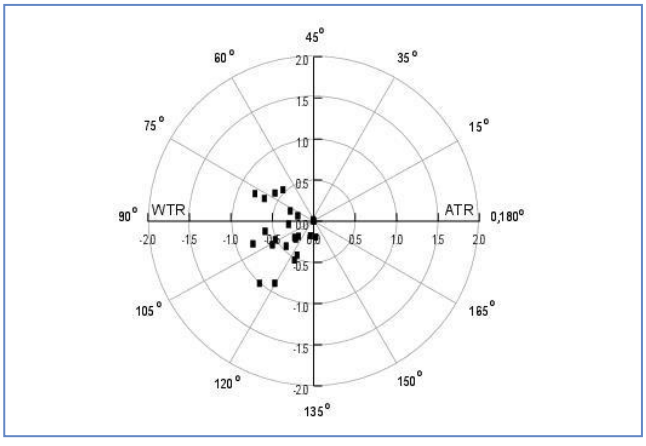

Fig 1. In the lateral rectus recession group, surgically induced astigmatism at 3 months postoperative demonstrated by double-angle vector analysis.

TABLE 1. Surgery classification and number of eyes for each operation

Procedure	Number (eyes) n = 84	Amount of muscle surgery; mm Mean (SD)
Horizontal muscle surgery (group 1)		
MR recession	19 (22.6%)	5.21 (0.56)
LR recession	22 (26.2%)	7.61 (0.67)
MR resection	8 (9.5%)	6.50 (0.50)
LR resection	9 (10.7%)	5.36 (0.48)
Resection & Recession	9 (10.7%)	
Inferior oblique (IO) myectomy (group 2)		
Inferior oblique myectomy 10 mm	5 (5.9%)	
Inferior oblique (IO) myectomy with horizontal muscle surgery (group 3)	12 (14.1%)	
With horizontal recession	9	
With horizontal resection	2	
With horizontal resection & recession	1	

Abbreviations: MR= medial rectus, LR= lateral rectus.

TABLE 2. Inter-rater and intra-rater reliability of the two ophthalmic technicians in performing the keratometry measurements

Ophthalmic technician	Asphericity					
	Horizontal meridian (Qx)			Vertical meridian (Qy)		
	ICC	95%CI	*p*-value	ICC	95%CI	*p*-value
Technician A (n=30)	0.995*	0.980, 0.999	<0.001	0.997*	0.987, 0.999	<0.001
Technician B (n=30)	0.992*	0.968, 0.998	<0.001	0.989*	0.955, 0.997	<0.001
Technician A&B (n=38)	0.983**	0.965, 0.991	<0.001	0.987**	0.975,0.993	<0.001

* Intra-rater reliability using two-way mixed effects model, ** Inter-rater reliability using two-way random effects model.

compared with the recession procedures (P = 0.003 and P = 0.014, respectively). Meanwhile, in group 3, in the horizontal meridian, the results from the multiple linear regression analysis showed that recession, inferior oblique (IO) myectomy, and IO myectomy with horizontal muscle surgery procedures had a significant relationship with changes in corneal asphericity after strabismus surgery, compared with recession procedures only at 1 week postoperatively (P = 0.030, P = 0.033, and P = 0.014, respectively).

DISCUSSION

This study showed a significant change in corneal curvature persisted until three months after the strabismus surgery in only lateral rectus (LR) recession procedures (0.45 diopter, D) and inferior oblique myectomy with horizontal muscle surgery procedures (0.27 D), specifically in the vertical meridian (Qy) which is perpendicular to the surgical axis. The force exerted by extraocular muscles during strabismus surgery can similarly influence the cornea, leading to what is known as a coupling

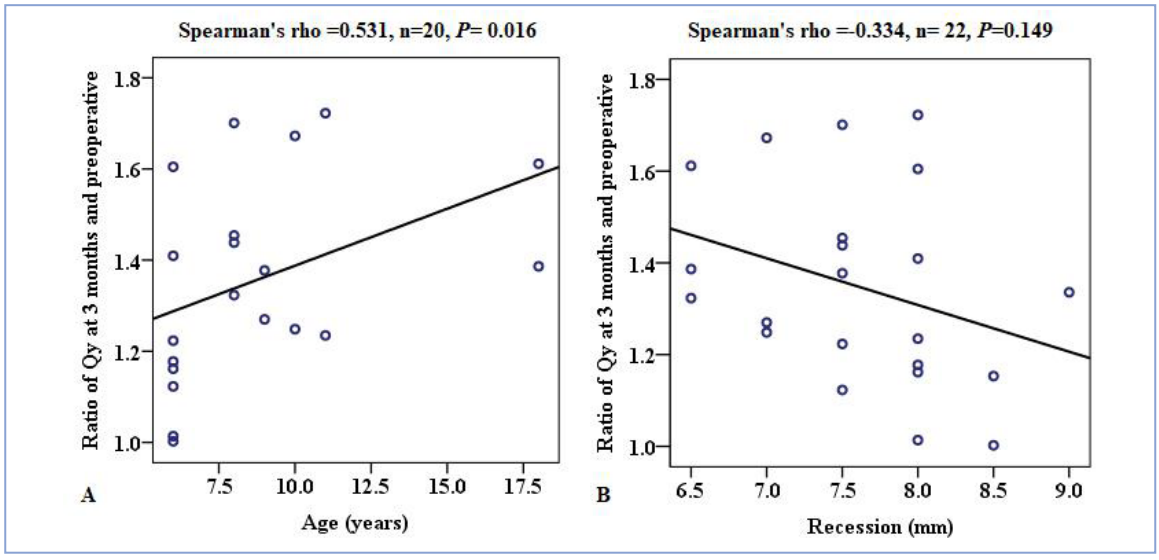

Fig 2. Spearman's rho correlation between the ratios of Qy at 3 months postoperative to preoperative (Qy_{3mo}/Qy_{pre}). A moderate positive relationship can be observed between age and Qy_{3mo}/Qy_{pre} (A) and a low negative relationship between the amount of recession and Qy_{3mo}/Qy_{pre} (B).

TABLE 3. Comparison between preoperative and 1 week, 1 month, and 3 months postoperative asphericity in the horizontal meridian (Qx)

Procedure	Asphericity in the horizontal meridian (Qx)			
	Pre-op mean (SD)	1 week post-op mean (SD)	1 month post-op mean (SD)	3 months post-op mean (SD)
Group 1 (n=68)				
MR recession (n=19)	-0.191 (0.112)	-0.245 (0.127)	-0.196 (0.119)	-0.171 (0.078)
		***P* = 0.008**	*P* = 0.608	*P* = 0.370
LR recession (n=22)	-0.296 (0.083)	-0.318 (0.111)	-0.308 (0.100)	-0.302 (0.121)
		P = 0.132	*P* = 0.266	*P* = 0.661
MR resection (n=8)	-0.268 (0.161)	-0.297 (0.169)	-0.302 (0.176)	-0.267 (0.178)
		P = 0.547	*P* = 0.195	*P* = 1.000
LR resection (n=9)	-0.263 (0.168)	-0.279 (0.153)	-0.241 (0.132)	-0.241 (0.143)
		P = 0.133	*P* = 0.193	*P* = 0.251
R&R (n=9)	-0.250 (0.110)	-0.291 (0.110)	-0.277 (0.137)	-0.266 (0.126)
		P = 0.098	*P* = 0.250	*P* = 0.734
Group 2 (n=5)	-0.283 (0.09)	-0.363 (0.116)	-0.333 (0.090)	-0.323 (0.094)
		P = 0.063	*P* = 0.125	*P* = 0.188
Group 3 (n=12)	-0.255 (0.123)	-0.319 (0.119)	-0.289 (0.102)	-0.264 (0.108)
		***P* = 0.028**	***P* = 0.008**	*P* = 0.561

Group 1 = horizontal muscle surgery;
Group 2 = inferior oblique myectomy;
Group 3 = inferior oblique myectomy with horizontal muscle surgery
Abbreviations: R&R = resection and recession, MR = medial rectus, LR = lateral rectus.

TABLE 4. Comparison between preoperative and 1 week, 1 month, and 3 months postoperative asphericity in the vertical meridian (Qy)

Procedure	Asphericity in vertical meridian (Qy)			
	Pre-op mean (SD)	1 week post-op mean (SD)	1 month post-op mean (SD)	3 months post-op mean (SD)
Group 1 (n=68)				
MR recession (n=19)	-0.033 (0.016)	-0.040 (0.025)	-0.042 (0.019)	-0.038 (0.014)
		P = 0.282	***P* = 0.023**	*P* = 0.164
LR recession (n=22)	-0.032 (0.022)	-0.036 (0.021)	-0.040 (0.021)	-0.041 (0.023)
		***P* = 0.005**	***P* < 0.001**	***P* < 0.001**
MR resection (n=8)	-0.043 (0.031)	-0.042 (0.026)	-0.041 (0.028)	-0.039 (0.029)
		P = 0.312	*P* = 0.383	*P* = 0.039
LR resection (n=9)	-0.039 (0.021)	-0.039 (0.025)	-0.042 (0.023)	-0.043 (0.022)
		P = 0.913	*P* = 0.225	*P* = 0.102
R&R (n=9)	-0.028 (0.029)	-0.026 (0.031)	-0.027 (0.030)	-0.025 (0.029)
		P = 0.820	*P* = 1.000	*P* = 1.000
Group 2 (n=5)	-0.031 (0.018)	-0.025 (0.016)	-0.031 (0.020)	-0.027 (0.016)
		***P* = 0.011**	*P* = 0.751	*P* = 0.054
Group 3 (n=12)	-0.027 (0.020)	-0.031 (0.022)	-0.032 (0.024)	-0.034 (0.024)
		P = 0.065	***P* = 0.027**	***P* = 0.007**

Group 1 = horizontal muscle surgery;
Group 2 = inferior oblique myectomy;
Group 3 = inferior oblique myectomy with horizontal muscle surgery
Abbreviations: R&R = resection and recession, MR = medial rectus, LR = lateral rectus; R&R.

effect. In our study, the reduced force on the horizontal meridian of the cornea, due to the recession of the LR muscle, was accompanied by an increased force on the vertical meridian, primarily from the superior rectus (SR) and inferior rectus (IR) muscles. This resulted in a change in corneal curvature, with less force acting on the horizontal meridian and more on the vertical meridian. This phenomenon of corneal curvature change in the perpendicular meridian to the surgical axis can be explained by Gauss's law of elastic domes.[20,21]

Similar to many previous studies that showed a with-the-rule corneal astigmatism change following lateral rectus muscle recession procedures[9–15,22–24], our study also showed that this astigmatism change persisted until 3 months post-operation.

The change in corneal curvature in the vertical meridian in the combined horizontal muscle surgery in the IO myectomy group (0.27 D) was less pronounced than in the LR recession procedure group (0.45 D), which may have been due to a weakening effect on the vertical meridian caused by the IO myectomy.

In the IO myectomy with horizontal muscle surgery procedures group, the majority of cases involved combined horizontal muscle recession. This likely explains why the Qy value progressively became prolate, similar to what was observed in LR and MR recession. Eum SJ

et al.'s study[25] showed that combined inferior oblique anterior transposition and horizontal muscle surgery resulted in transient incyclotorsion that persisted for 1 week post-operation, which differed from our study, in which it persisted for 3 months, with the difference likely because of the different operations and corneal astigmatism measurement method used.

Conversely, in the resection and recession (R&R) group, the forces from strengthening were offset by a weakening effect. In another study involving an R&R group, Schworm et al.[9] reported an increase in keratometry (K) values for the cornea adjacent to the resection and a decrease in K values for areas adjacent to the recession. Consequently, there was no significant change in asphericity in both the vertical and horizontal meridians in the R&R group. While there is less research on resection compared to recession, the available data suggest there is no significant change in corneal curvature or overall refraction.[9,14]

El Gendy HA et al.[26] found that recession had more powerful effects on corneal astigmatism compared to other operations, and that even one muscle recession had a greater effect on the cornea than multiple other muscle surgeries. These results were the same way as in our study. This corneal curvature change may explain why some poststrabismus surgery patients complained of blurred vision. In our study, the patients may have blurred vision at less than the 3 months period post-operation.

There are some limitations of our study to note, including the different number of cases in each group and the short follow-up period of only three months post-surgery. A longer period of follow-up may potentially show stronger evidence of corneal astigmatism; particularly as Al Tamini E et al.'s study[14] suggested that corneal curvature changes could continue for up to six months after surgery. Future research could consider extending the study period to a longer period post-surgery for further exploration of this phenomenon.

CONCLUSION

Only LR recession significantly affected the corneal curvature in the vertical meridian, resulting in a more prolate shape that persisted for at least three months post-surgery. Further, this was not only statistically significant but also clinically relevant, with a mean surgically induced astigmatism (SIA) of 0.45 D (95% CI: 0.35–0.56 D) in a with-the-rule pattern. As a result of these findings, we recommend giving preoperative advice about a possible refractive error change and a cautious approach to postoperative management.

Conflict of Interest

The authors declare that they have no conflicts of interest related to the publication of this research.

Author Contributions

TS: general research process, framework of the study, supervision, writing-original draft preparation, review and editing; ST: methodology, data analysis, review and editing; KS: framework of the study, resources, methodology, data collection, data analysis; PS: access to crucial research components (equipment); MS: access to crucial research components (equipment); WS: data analysis; PJ: data analysis, review and editing. All authors read and approved the final manuscript.

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Efficacy and Safety of Pilocarpine Eye Drops Combinations for Treating Presbyopia in a Thai Population: A Randomized Crossover Trial

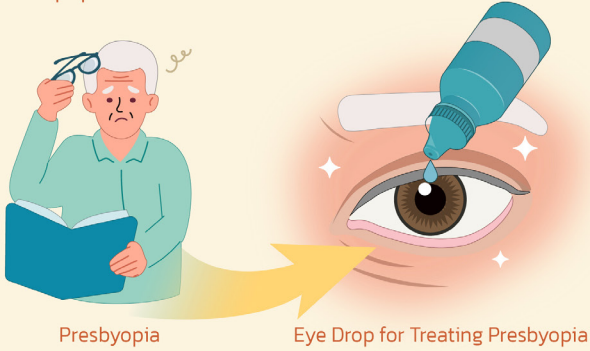
Thammanoon Surachatkumtonekul, M.D.[1,*], Pinpilai Jutasompakorn, M.D.[2], Anchalika Klinniyom, M. Pharm.[3], Wasawat Sermsripong, M.D.[1], Kiatthida Hokierti, M.D.[1], Prapasson Sangsre, M.Sc.[1], Ketchanya Rungsiri, BPH[1]

[1]Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, [2]Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, [3]Pharmacy Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Efficacy and Safety of Pilocarpine Eye Drops Combinations for Treating Presbyopia in a Thai Population: a randomized crossover trial

Objectives

This study aimed to assess the **effectiveness** and **side effects** of various concentrations of pilocarpine eye drops (1.5%, 1.25%, and 1%), with and without 0.1% brimonidine, in treating presbyopia in a Thai population.



Methods

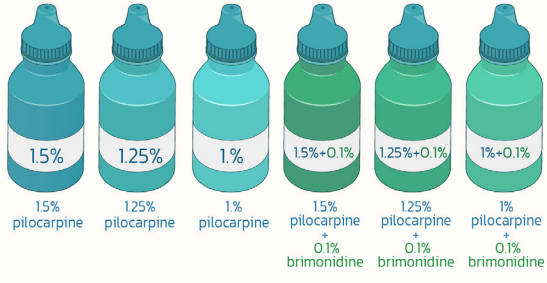
Prospective

Randomized

Double-blinded

Crossover

The participants ranged from 40 to 60 with presbyopia
Participants were randomly assigned to **6 groups** concentrations and type of eyedrops to receive :



Results

N=10 **30%** male, median age **46.5** years old with presbyopia, Refractive errors +/- 0.5D

1.25% pilocarpine | 1.25% pilocarpine + 0.1% brimonidine

showed significant **improvement in near visual acuity** at all time points (statistically significant with Bonferroni correction)

ADVERSE EFFECTS

More common with **1.5% pilocarpine + 0.1% brimonidine**, including **red eye**

Hours after application	Pre	2	4	6
1.25% pilocarpine	0.18 (0.18,0.3)	0.1 (0,0.18)*	0.1 (0,0.18)*	0.09 (0,0.18)*
1.25% pilocarpine + 0.1% brimonidine	0.18 (0.1,0.18)	0 (0,0.18)*	0 (0,0.18)*	0.05 (0,0.18)

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*Corresponding author: Thammanoon Surachatkumtonekul
E-mail: si95thim@gmail.com
Received 25 April 2024 Revised 8 July 2024 Accepted 8 July 2027
ORCID ID:http://orcid.org/0000-0002-0037-6863
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ABSTRACT

Objective: This study aimed to assess and compare the effectiveness and side effects of various concentrations of pilocarpine eye drops (1.5%, 1.25%, and 1%), with and without 0.1% brimonidine, in treating presbyopia, specifically in a Thai population.

Materials and Methods: A prospective, randomized, double-blinded, and crossover trial was conducted at Siriraj Hospital from August 2022 to April 2023. The study included emmetropic individuals aged 40 to 60 with presbyopia (near visual acuity not exceeding J1+) and refractive errors within +/- 0.5D. Ten subjects were randomly assigned to six groups for the different concentrations and type of eye drops using a computer-generated systematic randomization to receive 1.5%, 1.25%, and 1% pilocarpine with and without 0.1% brimonidine. And visual outcomes including visual acuity at distance and near were measured at 2, 4, and 6 hours post-application, with adverse effects monitored. Primary outcome was visual acuity at near after applied topical eye drops.

Results: Among the 10 participants (30% male, median age 46.5 years old), 1.25% pilocarpine and combined 1.25% pilocarpine + 0.1% brimonidine significantly improved near visual acuity at all time points (statistically significant with Bonferroni correction). Adverse effects, such as dry eye and irritation, were more common with 1.5% pilocarpine + 0.1% brimonidine.

Conclusion: In this preliminary study, 1.25% pilocarpine and 1.25% pilocarpine + 0.1% brimonidine showed promise in effectively treating presbyopia in the Thai study population, with acceptable side effect rates. Further research with larger sample sizes is needed to confirm these findings and provide more robust insights into presbyopia management in the Asian demographic.

Keywords: Presbyopia; pilocarpine; brimonidine; refractive errors (Siriraj Med J 2024; 76: 722-730)

INTRODUCTION

Presbyopia, a condition where the eye loses its ability to focus on near objects as people age, typically begins around the age of 40 years old, and is attributed to the crystalline lens becoming harder and losing its capacity to adjust power.[1-3] In 2015, an estimated 1.8 billion people worldwide experienced presbyopia, a number that may have potentially increased to 2.1 billion by 2020.[4,5] Notably, presbyopic individuals often report a lower quality of life, and uncorrected presbyopia is linked to productivity loss.[6-8]

Various treatment options exist for presbyopia, ranging from single reading glasses and bifocal or progressive glasses to monovision and multifocal contact lenses, refractive surgery, corneal inlays, and even 1.25% pilocarpine eye drops.[9,10]

Pilocarpine, which was discovered in 1874, has been employed in glaucoma treatment for well over a century now.[11,12] Its mechanism involves contracting the pupil and ciliary muscle, leading to pupil miosis and enhanced accommodation.[13,14] The resultant pupil miosis induces a pinhole effect, increasing the eye's depth of focus.[15] Brimonidine, an alpha-2 agonist affecting both the central and peripheral nervous systems, binds to the alpha-2 receptor and inhibits norepinephrine release. This action prevents pupil dilatation, resulting in a more miotic pupil in low light conditions.[16,17]

Despite various presbyopia treatments, the effectiveness of pilocarpine topical drugs in the darker iris pupil of the Asian population, potentially yielding distinct drug responses compared to Western populations should be kept in mind. Lyons JS et al. mentioned that pilocarpine has a potential to binds melanin in the iris and ciliary body, So we assumed that iris color may influence its desired response.[18]

Thus, this study aimed to evaluate the effectiveness and side effects of different concentrations of pilocarpine eye drops (1.5%, 1.25%, and 1%), both with and without 0.1% brimonidine, in treating a presbyopic Thai population.

MATERIALS AND METHODS

This study was performed according to the Consolidated Standards of Reporting Trials (CONSORT) guideline. The study protocol was reviewed and approved by the Siriraj Institutional Review Board. (SIRB), Siriraj Hospital, Mahidol University, Bangkok, Thailand. The IRB number was SI 611/2022. The registered number of the Thai clinical trials Registry was TCTR20220930004.

Prior to enrollment, all participants provided written informed consent. The sample size was determined using nQuery Advisor. Referring to a previous study[3], the mean near vision before treatment was J 8.6 with a standard deviation (SD) of 1.5, while at 2 hours post-treatment it was J 3.6 (SD=1), and the mean change was

5.9 (SD=0.8), with clinical significance set at 0.05 (type 1 error = 0.05, 2-sided) and power at 95%. Considering a 20% dropout rate, the total sample size for this study was established as 10 cases.

In defining the inclusion criteria, participants aged 40–60 years old with a distance visual acuity of 6/6 in both eyes were considered. All the participants demonstrated +/- 0.5 diopter (D) and astigmatism within 0.5 D as assessed by an autorefractor. To be classified as having presbyopia, participants were required to be unable to achieve J1+ with Rosenbaum near card visual acuity at 14 inches in each eye. The exclusion criteria were participants with myopia, hyperopia, or astigmatism exceeding 0.5 D. Individuals with other ophthalmic diseases impacting their vision, such as leukoma, cataract, glaucoma, and macular degeneration, were also excluded. Additionally, participants who had previously received drugs that could affect eye accommodation, such as psychotic drugs or anticholinergic drugs, were deemed ineligible for participation.

The withdrawal or termination criteria included participants experiencing serious side effects from the eye drops, such as severe conjunctivitis, keratitis, blurred vision, eye pain, or headache. Participants expressing an unwillingness to continue in the study were also subject to withdrawal.

Pilocarpine eye drops at concentrations of 1%, 1.25%, and 1.5% were prepared by diluting 2% pilocarpine eye drops with a balanced salt solution from the pharmacy unit at Siriraj Hospital. The 0.1% brimonidine eye drops used in the study were from AbbVie Inc. (USA). All the participants had a complete eye examination and their non-dominant eye was detected by the same ophthalmologist (TS). All the participants had tested visual acuity at distance and near which was performed by the same investigator, autorefraction, IOL Master 700 measure lens thickness and also pupil size, pre-instill the eye drop, and post-instill the eye drop at 2, 4 and 6 hours.

A crossover design was applied to our study because it provides an effective counterfactual comparison and helps eliminate baseline characteristic differences. This method is well-suited for research on presbyopia and the interventions using pilocarpine and brimonidine eye drops. Presbyopia, which is blurred near-sighted vision, is not curable with standard treatments. Both eyedrop medications have a rapid effect on accommodation. For these reasons, the crossover design was appropriate for this research.

Six different concentrations of the drug were utilized: 1% pilocarpine, 1.25% pilocarpine, 1.5% pilocarpine, 1% pilocarpine combined with 0.1% brimonidine, 1.25% pilocarpine combined with 0.1% brimonidine, and 1.5% pilocarpine combined with 0.1% brimonidine (separated bottle between pilocarpine and brimonidine). The initial concentration administered to each subject was randomized using the computer-generated systematic random sampling method, followed by the subsequent concentrations in the aforementioned order. Each bottle was administered 5 minutes apart. All participants would receive each eye drops (1%, 1.25%, 1.5% pilocarpine eye drops or combined with 0.1% brimonidine eye drop) in the same room and same luminance and had tested visual acuity at distance and near, autorefraction, pupil size, and lens thickness pre-instill the eye drop, and post-instill the eye drop at 2, 4 and 6 hours by each eye drops for 1 week apart.

The range of the duration of pilocarpine in USFDA was 3-12 hour and only one drop of each eye drops was then stopped to allow a 1-week wash-out period. After drug washout, randomly assigned to another group until the process was completed. Thus, the carryover effect was not established in this study.

Statistical analysis

Descriptive statistics were used to summarize the patients' demographic data and clinical characteristics, presented as frequencies and percentages for the categorical data. For the continuous data, the mean and standard deviation (SD) or median and interquartile range (IQR) were reported based on the data distribution. Visual acuity data were transformed into logarithm of the minimum angle of resolution (LogMAR) units when the participants could correctly read more than half of each line.

To compare the baseline characteristics with outcomes at 2, 4, and 6 hours after topical drug application within the same participant, statistical analyses was conducted. For non-normally distributed data, we applied the Wilcoxon signed-rank test; for normally distributed data, we used the paired t-test. The Bonferroni correction was incorporated to address multiple testing and adjust the p-value for statistical significance. All the analyses were performed using STATA version 16 (StataCorp, Lakeway, TX, USA).

RESULTS

In this study, we enrolled 10 emmetropic individuals, defined as having refractive errors within the range of +/- 0.5 D, with ages ranging from 41.8 to 50.5 years old (median 46.5), and all diagnosed with presbyopia (near visual acuity not reaching J1+). Comprehensive demographic data are provided in Table 1. Table 2

specifically outlines the participants' distance visual acuity, presented in LogMAR.

All ten subjects were randomly assigned to ten different sequences, as shown in Fig 1. Every subject completed the intended randomization protocol. All subjects were analyzed using intention-to-treat analysis, and no subject deviated from or dropped out of the protocol.

The comprehensive findings, covering visual acuity at near, pupil size, anterior chamber depth, lens thickness at pre-instillation and post-instillation points (2, 4, and 6 hours), and side effects were systematically documented, as shown in Tables 3-7.

Analyzing the data, we observed that visual acuity at distance (VAD) remained unchanged after instilling the eye drops across all groups involving the different treatments and combinations (Table 2). However, visual acuity at near (VAN) showed improvement in all groups after the instillation of eye drops, with clinical significance achieved at 2, 4, and 6 hours observed specifically in the 1.25% pilocarpine group and the 1.25% pilocarpine combined with 0.1% brimonidine group (Fig 2, Table 3). Notably, the VAN between the 1.25% pilocarpine and 1.25% pilocarpine combined with 0.1% brimonidine groups at all time points did not differ significantly.

Significant pupil constriction was found in all groups after the instillation of eye drops at all measured time points (Fig 3, Table 4). The anterior chamber depths were notably shallowed in all eye drops groups after instillation, with the exception of the 1% pilocarpine group (Fig 4, Table 5). Moreover, the lens thickness exhibited a significant increase in all combined groups (pilocarpine + brimonidine) (Fig 5, Table 6).

Adverse drug reactions, specifically eye discomfort, red eye, and blurred vision, were consistently observed in all eye drop groups, as evidenced in Table 7.

DISCUSSION

This investigation revealed that all concentrations of pilocarpine eye drops and the combination of pilocarpine and 0.1% brimonidine eye drops led to an improvement in near visual acuity. However, noteworthy clinical significance in the enhancement of near visual acuity at 2, 4, and 6 hours post-application was observed exclusively in the 1.25% pilocarpine eye drops and the combined 1.25% pilocarpine + 0.1% brimonidine eye drops groups.

Interestingly, the application of these eye drops did not disrupt the distance visual acuities in any of the groups. Pupil constriction was a consistent outcome in all groups, indicating a potential pinhole effect contributing to an increased depth of focus. While this pinhole effect can result in a clearer image by allowing only central light rays to reach the retina[19], it comes at the cost of reduced brightness, visual field, and optimal visual acuity.[20,21]

The shallowing of the anterior chamber depths was consistently observed in all eye drops groups, with the exception of the 1% pilocarpine eye drops group. This suggests that the iris-lens diaphragm moved forward more prominently with pilocarpine concentrations exceeding 1%, potentially inducing myopia. Pilocarpine's

TABLE 1. Patients' demographic data

Total n = 10 (%)	n (%)
Sex	
Male	3 (30%)
Female	7 (70%)
Underlying medical conditions	
HT	2 (20%)
DLP	2 (20%)
DM	2 (20%)
Ophthalmic diseases	
Dry eye disease	1 (10%)
Allergic conjunctivitis	1 (10%)
Age (median (IQR))	46.5 (41.8–50.5)
Non-dominant eye	
Right	5 (50%)
Left	5 (50%)

Abbreviations: HT = hypertension, DLP = dyslipidemia, DM = Diabetes mellitus, IQR = interquartile range

TABLE 2. VA at distance (LogMAR) after topical application: Median (Range)

Hours after application	Pre	2	4	6
1% pilocarpine	0 (0,04)	0 (0,0.44)	0 (0,0.2)	0 (0,0.06)
1.25% pilocarpine	0 (0,0.14)	0 (0,0.28)	0 (0,0.06)	0 (0,0.12)
1.5% pilocarpine	0 (0,0)	0 (0,0.24)	0 (0,0.34)	0 (0,0.34)
1% pilocarpine +	0 (0,0.18)	0 (0.12)	0 (0,0.42)	0 (0,0.22)
1.25% pilocarpine + 0.1% brimonidine	0 (0,0.22)	0 (0,0.74)	0 (0,0.36)	0 (0,0.42)
1.5% pilocarpine + 0.1% brimonidine	0 (0,0.06)	0 (0,0.76)	0 (0,0.84)	0 (0,0.48)

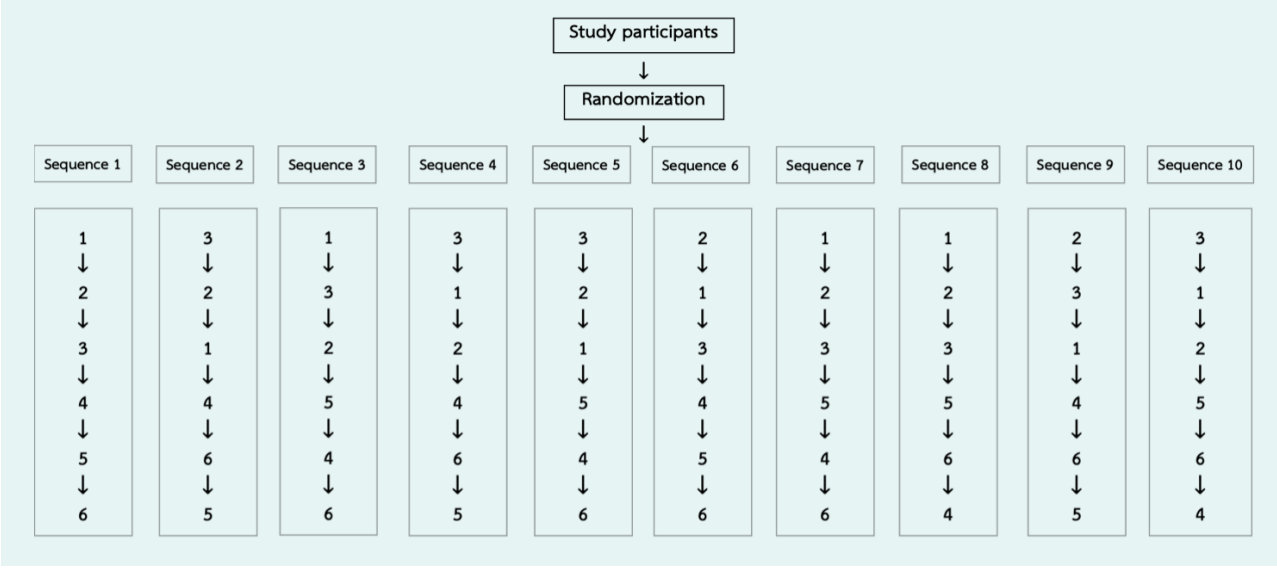

Fig 1. Flowchart, randomized controlled crossover design.
1 =1 % pilocarpine, 2 = 1.25% pilocarpine, 3 = 1.5% pilocarpine, 4 = 1% pilocarpine + 0.1% brimonidine, 5 = 1.25% pilocarpine + 0.1% brimonidine, 6 = 1.5% pilocarpine + 0.1% brimonidine

TABLE 3. VA at near (LogMAR) after topical application: Median (IQR)

Hours after application	Pre	2	4	6
1% pilocarpine	0.18 (0.1,0.18)	0.05 (0,0.18)	0.1 (0,0.18)	0 (0,0.18)
1.25% pilocarpine	0.18 (0.18,0.3)	0.1 (0,0.18)*	0.05 (0,0.18)*	0.09 (0,0.18)*
1.5% pilocarpine	0.14 (0.1,0.3)	0 (0,0.18)*	0.05 (0,0.3)	0.05 (0,0.18)
1% pilocarpine + 0.1% brimonidine	0.14 (0.1,0.18)	0.05 (0,0.18)	0.05 (0,0.18)	0.09 (0,0.18)
1.25% pilocarpine + 0.1% brimonidine	0.18 (0.1,0.18)	0 (0,0.18)*	0 (0,0.18)*	0.05 (0,0.18)*
1.5% pilocarpine + 0.1% brimonidine	0.1 (0,0.18)	0.05 (0,0.1)	0.05 (0,0.18)	0.05 (0,0.18)

Abbreviations: IQR = Interquartile range, * = statistically significant with the Wilcoxon signed-rank test and Bonferroni correction.

TABLE 4. Pupil size after topical application: Mean (SD)

Hours after application	Pre	2	4	6
1% pilocarpine	4.4 (0.93)	2.72 (0.67)*	2.96 (0.81)*	3.28 (0.87)*
1.25% pilocarpine	4.32 (0.71)	2.67 (0.73)*	2.98 (0.9)*	3.03 (0.74)*
1.5% pilocarpine	4.25 (0.77)	2.3 (0.49)*	2.47 (0.59)*	2.79 (0.53)*
1% pilocarpine + 0.1% brimonidine	4.37 (0.81)	2.21 (0.50)*	2.35 (0.61)*	2.52 (0.58)*
1.25% pilocarpine + 0.1% brimonidine	4.18 (0.88)	2.13 (0.55)*	2.28 (0.76)*	2.49 (0.71)*
1.5% pilocarpine + 0.1% brimonidine	4.24 (0.85)	2.07 (0.37)*	2.18 (0.40)*	2.34 (0.54)*

Abbreviations: SD = standard deviation, * = statistically significant with the Wilcoxon signed-rank test and Bonferroni correction

TABLE 5. Anterior chamber depth after topical application: Mean (SD)

Hours after application	Pre	2	4	6
1% pilocarpine	3.14 (0.29)	3.13 (0.27)	3.12 (0.28)	3.10 (0.31)
1.25% pilocarpine	3.14 (0.29)	3.11 (0.28)*	3.10 (0.28)*	3.11 (0.29)*
1.5% pilocarpine	3.14 (0.28)	3.11 (0.28)*	3.10 (0.27)*	3.10 (0.29)*
1% pilocarpine + 0.1% brimonidine	3.14 (0.28)	3.08 (0.27)*	3.08 (0.27)*	3.10 (0.27)*
1.25% pilocarpine + 0.1% brimonidine	3.14 (0.27)	3.07 (0.27)*	3.07 (0.26)*	3.10 (0.28)*
1.5% pilocarpine + 0.1% brimonidine	3.14 (0.28)	3.05 (0.26)*	3.05 (0.26)*	3.08 (0.25)*

Abbreviations: SD = standard deviation, * = statistically significant with the Wilcoxon signed-rank test and Bonferroni correction

TABLE 6. Lens thickness after topical application: Mean (SD)

Hours after application	Pre	2	4	6
1% pilocarpine	4.33 (0.34)	4.33 (0.34)	4.34 (0.34)	4.30 (0.34)
1.25% pilocarpine	4.34 (0.34)	4.34 (0.35)	4.34 (0.35)	4.34 (0.34)
1.5% pilocarpine	4.33 (0.34)	4.34 (0.34)	4.34 (0.34)	4.34 (0.35)*
1% pilocarpine + 0.1% brimonidine	4.33 (0.33)	4.36 (0.34)	4.36 (0.34)*	4.35 (0.34)
1.25% pilocarpine + 0.1% brimonidine	4.33 (0.34)	4.36 (0.34)*	4.36 (0.35)*	4.35 (0.35)
1.5% pilocarpine + 0.1% brimonidine	4.32 (0.34)	4.36 (0.35)*	4.37 (0.34)*	4.35 (0.34)*

Abbreviations: SD = standard deviation, * = statistically significant with the Wilcoxon signed-rank test and Bonferroni correction

TABLE 7. Side effects (Percentage)

Hours after application	2	4	6
1% pilocarpine	Eye discomfort (10%), Red eye (10%)	Eye discomfort (10%), Red eye (10%)	Eye discomfort (10%)
1.25% pilocarpine	Eye discomfort (20%)	Blurred (10%), Eye discomfort (20%)	Blurred (10%), Eye discomfort (20%)
1.5% pilocarpine	Blurred (20%), Eye discomfort (10%), Red eye (30%),	Blurred (20%), Eye discomfort (10%)	Blurred (20%), Eye discomfort (10%)
1% pilocarpine + 0.1% brimonidine	Blurred (20%)	Blurred (10%), Eye discomfort (20%)	Blurred (10%), Eye discomfort (30%)
1.25% pilocarpine + 0.1% brimonidine	Eye discomfort (30%), Blurred (20%)	Blurred (10%), Eye discomfort (30%),	Blurred (10%), Eye discomfort (10%)
1.5% pilocarpine + 0.1% brimonidine	Blurred (30%), Eye discomfort (30%)	Blurred (30%), Eye discomfort (20%)	Blurred (10%), Eye discomfort (50%)

physiological effects, including ciliary muscle contraction, pupil miosis, and lens forward movement, have been reported to contribute to this phenomenon.[22]

Apart from previously mentioned, Pilocarpine produces a variety of ocular and systemic adverse reactions. Ocular side effects include miosis, accommodative spasm, frontal headaches, twitching lids, conjunctival injection, cataractous changes, allergic reactions, increased permeability of the blood-aqueous barrier. Iritis and risk of retinal detachment also have been mentioned by USFDA[23] but very rare effects.

During the study, no severe adverse events were observed throughout the study The most frequently observed adverse events included discomfort, red eye, and blurred vision. These reactions were generally mild and of short duration.

Despite adverse drug reactions, such as eye discomfort, red eye, and blurred vision, being reported across all eye drops groups, these effects were not severe enough to pose a threat to vision or warrant the termination of the study or any participant's participation.

Although 1.25% pilocarpine eye drops have been approved by the US FDA for presbyopia treatment since 2021[24,25], they are currently unavailable in Thailand. This challenge fueled our team's curiosity, leading us to explore how to prepare and determine the most effective concentration of pilocarpine or combination of pilocarpine and 0.1% brimonidine eye drops for improving near vision in the Thai population. Our study demonstrated that both 1.25% pilocarpine eye drops and the combined 1.25% pilocarpine + 0.1% brimonidine eye drops significantly improved near visual acuity at 2, 4, and 6 hours post-application. Notably, these two concentrations did not exhibit a clinically significant difference in near vision at each time point. As a result, we recommend the preparation and use of 1.25% pilocarpine eye drops for presbyopia treatment

However, Evaluation of the efficacy of these agents is limited by heterogeneity in outcomes definition and the small number of comparative studies. Other limitations include the potential bias introduced by remembering the number on the Snellen chart in each sequence concentrations. We suggest a sample size that is larger will be better representative of the population and will hence provide more accurate results.

CONCLUSION

In summary, 1.25% pilocarpine eye drops and the combination of 1.25% pilocarpine + 0.1% brimonidine eye drops exhibited clinically significant improvements in near visual acuity at 2, 4, and 6 hours post-application without causing serious side effects. To deepen our comprehension, the process of diluting pilocarpine eye drops may require additional investigation regarding the stability and sterility of the dilution, particularly for their potential utilization in clinical practice.

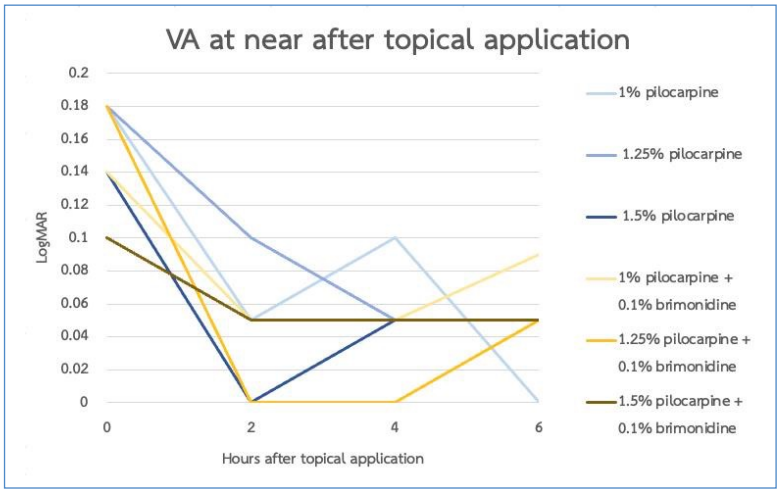

Fig 2. VA at near (LogMAR) after topical application.

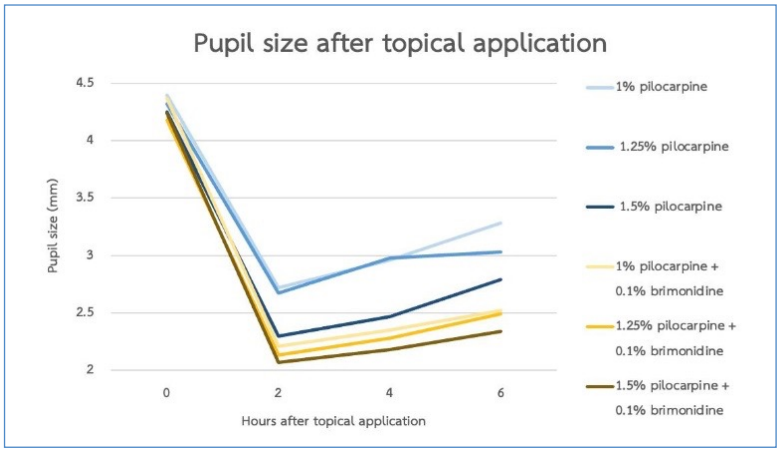

Fig 3. Pupil size after topical application.

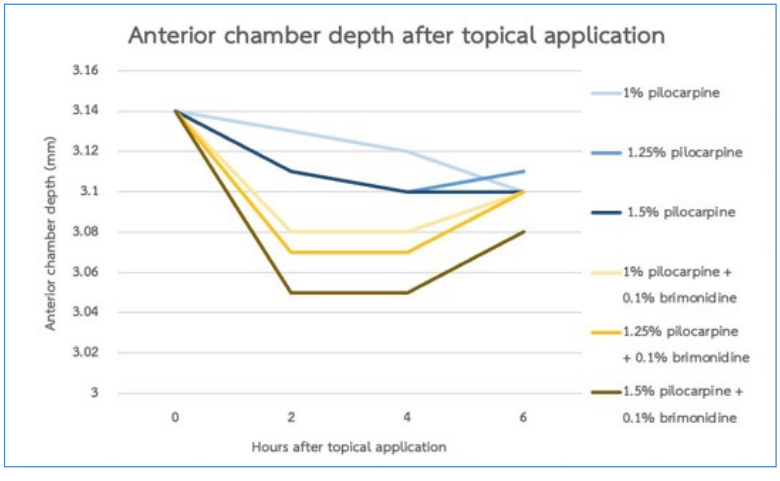

Fig 4. Anterior chamber depth after topical application.

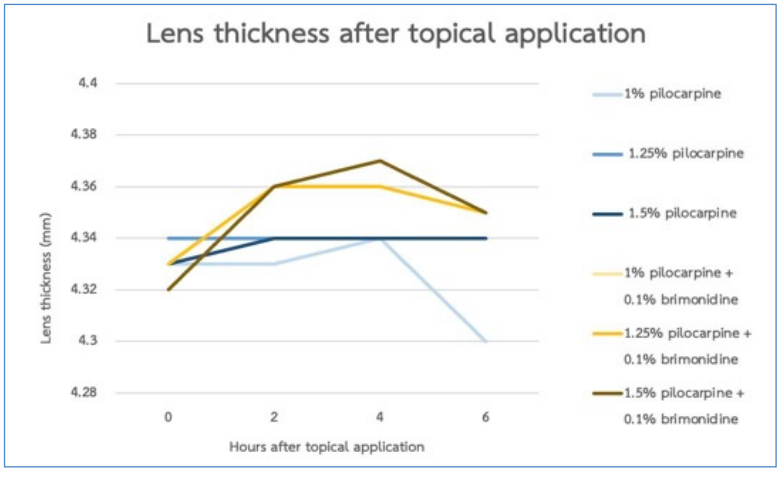

Fig 5. Lens thickness after topical application.

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Conflicts of Interest

The authors declare that they have no conflicts of interest related to the publication of this research.

Author Contributions

TS: general research process, framework of the study, supervision, procedure, data analysis, writing-original draft preparation, review and editing; WS: framework of the study, methodology, data analysis, review and editing; KH: framework of the study, validation, resources, methodology, data collection; PJ: provided access to crucial research components (equipment, drug), resources; AK: provided access to crucial research components (equipment, drug), resources; PS: data collection, investigation, project administration; KR: data collection, investigation, project administration. All authors read and approved the final manuscript.

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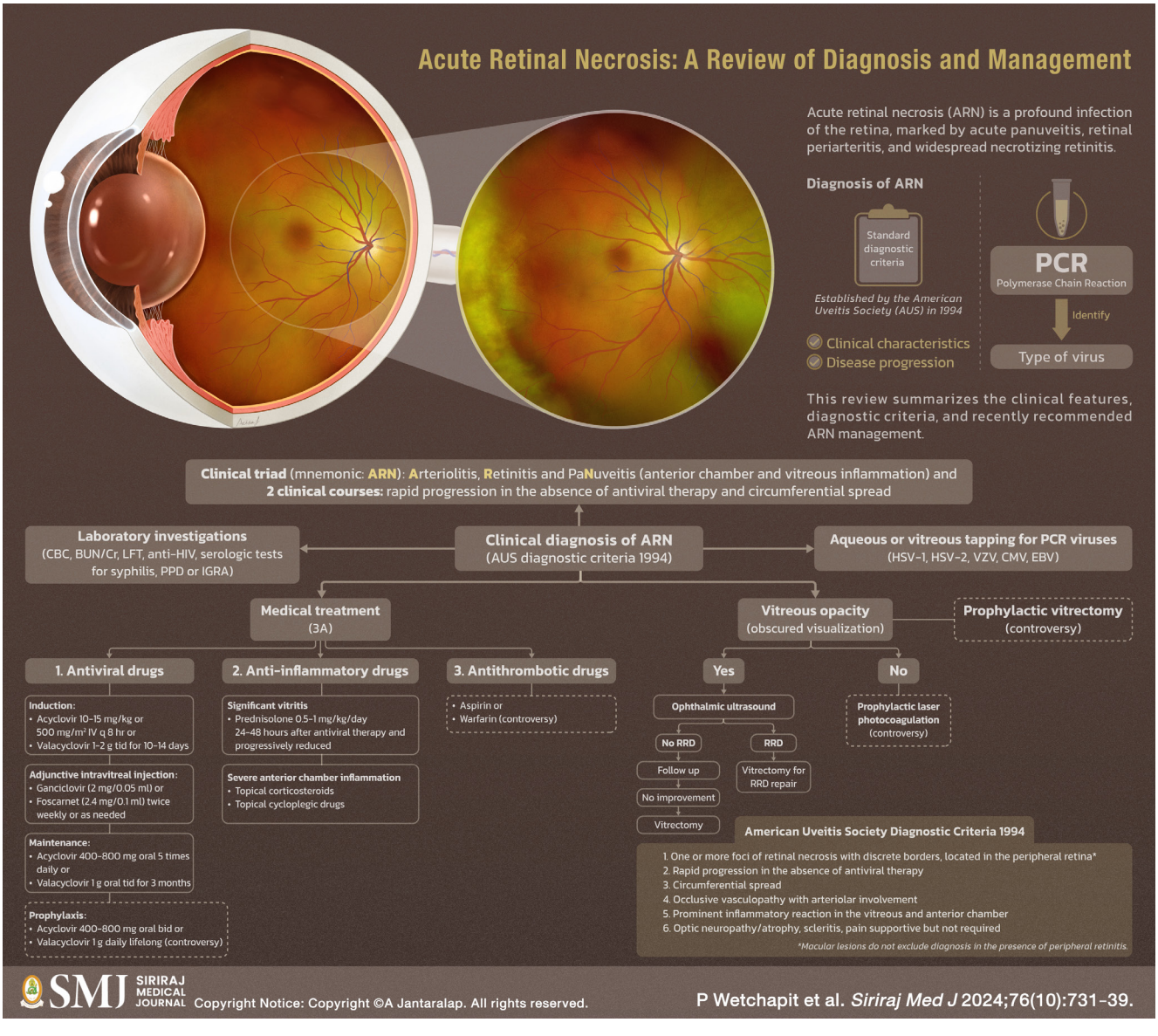
Acute Retinal Necrosis: A Review of Diagnosis and Management

Pattarat Wetchapit, M.D.[1], Usanee Tungsattayathitthan, M.D.[2], Sutasinee Boonsopon, M.D.[2], Nattaporn Tesavibul, M.D.[2], Pitipol Choopong, M.D., M.Sc.(epi)[2,*]

[1]Department of Ophthalmology, Suratthani Hospital, Suratthani, Thailand, [2]Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.



*Corresponding author: Pitipol Choopong
E-mail: pitipol.cho@mahidol.edu
Received 25 April 2024 Revised 1 May 2024 Accepted 9 May 2024
ORCID ID:http://orcid.org/0000-0001-8857-8488
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ABSTRACT

Acute retinal necrosis (ARN) is a profound infection of the retina, marked by acute panuveitis, retinal periarteritis, and widespread necrotizing retinitis. The etiology of ARN involves human herpesviruses, such as herpes simplex virus (HSV) and varicella-zoster virus (VZV), which can lead to severe visual impairment or even blindness. Diagnosis of ARN is based on clinical characteristics and disease progression according to the standard diagnostic criteria established by the American Uveitis Society (AUS) in 1994. The polymerase chain reaction (PCR) of aqueous specimens can enable identification of the type of virus. Early initiation of antiviral medication is essential for treatment efficacy to stop lesion progression, accelerate the healing process, and prevent contralateral eye involvement. Ocular complications of ARN include atrophic retina, multiple retinal breaks, rhegmatogenous retinal detachment (RRD), tractional retinal detachment (TRD), optic atrophy, macular edema, epiretinal membrane (ERM), and retinal and optic disc neovascularization. This review summarizes the clinical features, diagnostic criteria, and recently recommended ARN management.

Keywords: Acute retinal necrosis; necrotizing retinitis; panuveitis (Siriraj Med J 2024; 76: 731-739)

INTRODUCTION

Acute retinal necrosis (ARN) is an infrequent but severe retinal infection caused by human herpesviruses (HHV), which can result in significant visual impairment or even permanent blindness. In 1971, Urayama et al. provided the first account of ARN, reporting six patients with a clinical triad of unilateral acute panuveitis, retinal periarteritis, and diffuse necrotizing retinitis progressing to rhegmatogenous retinal detachment (RRD).[1] In 1977, Willerson et al. described two patients with bilateral acute retinal vaso-occlusive disease of an unknown etiology, in which the clinical courses were rapidly progressive necrotizing vasculitis and retinitis.[2] Young and Bird introduced the term "bilateral acute retinal necrosis (BARN)" in 1978 to describe a comparable condition identified in four patients.[3] In 1982, Culbertson et al. discovered herpesviral particles in the retina of an enucleated eye, and varicella-zoster virus (VZV) was confirmed in two enucleated eyes and in the vitreous culture of one eye in 1986.[4,5] Currently, the diagnosis of ARN is primarily based on clinical characteristics, with the presence of viruses in the intraocular fluid serving as confirmatory evidence.

This review summarizes the clinical features, diagnostic criteria, and recently recommended management of ARN based on current evidence so that ophthalmologists can confidently diagnose and provide timely treatment, which is essential for improving visual prognosis.

Epidemiology

The incidence of ARN worldwide is 0.50 to 0.63 cases per million population per year.[6-8] In Thailand, the prevalence of ARN has been documented to vary between 0.2% and 3.9%.[9-12] ARN can affect both immunocompetent or immunocompromised hosts without sex or race predilection.[13,14] Accounting for 70% of cases, VZV emerges as the leading cause of ARN, succeeded by herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2). Other rare causes of ARN are cytomegalovirus (CMV) and Epstein–Barr virus (EBV).[4,5] The bimodal age distribution at the onset of the disease demonstrates peaks at approximately 20 and 50 years of age.[15] VZV and HSV-1 ARN are more commonly found in patients older than 25 years old (mean age is 52 years old for VZV and 44 years old for HSV-1), whereas HSV-2 ARN is found predominantly in patients younger than 25 years old (mean age is 24 years old). This is due to the different ages of primary infection and reactivation of each herpes virus; specifically, HSV-2 is a reactivation of congenital infection, while VZV and HSV-1 are reactivations of the virus that were acquired during childhood or adulthood, but not perinatally.[16-18]

ARN can arise months to even years after primary infection or following cutaneous herpetic infection, such as chickenpox, shingle, herpes zoster ophthalmicus, or herpes genitalis. Concomitant herpetic keratitis and ARN can occur in approximately 20% of cases.[19] HSV-1 and HSV-2 ARN have a tendency to be associated with previous, concurrent, or subsequent herpetic encephalitis and meningitis, respectively.[16,17]

Clinical features

Most cases of ARN are unilateral diseases (65%–90%).[7,20] However, in bilateral disease or BARN, the disease may begin unilaterally and may become bilateral in up to 35% of cases with and 70% of cases without antiviral therapy. The second eye can be affected as early as 6 weeks or up to years after the attack of the first eye.[21,22]

ARN typically manifests as panuveitis, in which the symptoms include blurred vision, floaters, ocular pain, redness, and photophobia. The early course of the disease frequently exhibits anterior segment findings, including ciliary injection, keratic precipitates (small, stellate, large, or mutton fat KPs), anterior chamber cells and flares, posterior synechiae, and increased intraocular pressure. In the acute phase, posterior segment findings reveal vitritis, which represents an inflammatory response following cellular immunity to the virus. Multifocal patches of yellowish retinal infiltrates in the peripheral retina that progress circumferentially and posteriorly to confluent retinal necrosis are typical characteristics (Fig 1). Inflammation of the retinal vessels, predominantly arterioles or arteriolitis, is also a distinctive feature that can result in arteriolar occlusion and rapid retinal necrosis. Optic nerve involvement is typically characterized by disc hyperemia or swelling and a relative afferent pupillary defect. In addition, scleritis and episcleritis can occur.[8,23] Patients with VZV ARN are more likely to have severe presentations than those with HSV ARN.[6,8] In the late phase, fibrous membranes may develop on the retinal surface, causing the retina to contract, ultimately leading to retinal breaks at the junction of the normal and necrotic retina.[24-27]

Without treatment, retinitis tends to progress circumferentially by 360º in 5 to 10 days. Hence, dilated fundus examination is mandatory in every case before the diagnosis of anterior uveitis; otherwise, the diagnosis of ARN may be missed. Additionally, misleading treatment with systemic corticosteroids without antivirals can result in a severe rapid progression of retinitis and potentially devastating outcomes.

Diagnosis

Diagnosis of ARN relies on clinical features and disease progression, adhering to the standard diagnostic criteria established by the executive committee of the American Uveitis Society (AUS) in 1994.[28] In 2021, the Standardization of Uveitis Nomenclature working group established new classification criteria for research purposes.[29] Diagnostic criteria provide sensitivity while classification criteria provide specificity, which can support a low misclassification rate (Table 1). Table 2 presents the differential diagnoses of ARN.

Laboratory investigations

The key ancillary investigations for the diagnosis of ARN include the following.

1) Polymerase chain reaction (PCR) of aqueous or vitreous specimens. This method involves direct detection of the viral genome by DNA amplification. It has an 82% sensitivity, 91% specificity, 96% positive predictive value, and 87% negative predictive value.[30] The use of PCR enables identification of the viral species, reduces the chance of misdiagnosis, and supports a proper initiation of induction with antiviral therapy.[31] Aqueous tapping is easier to perform and safer with less complications than vitreous tapping. Aqueous sampling also offers a comparable yield for reporting positive PCR results with vitreous sampling.[32]

2) Goldmann–Witmer coefficient (GWC). This test involves detecting local antibody production. It has an 81% sensitivity, 98.7% specificity, 97% positive predictive value, and 91% negative predictive value.[33] Specifically, the GWC compares specific antibody production between intraocular fluid and serum, which can be calculated using the following equation:

$$GWC = \frac{\text{intraocular fluid specific Immunoglobulin (Ig) G titer} / \text{serum specific IgG titer}}{\text{intraocular fluid total Ig} / \text{serum total Ig}}$$

Result	interpretation
0.5–2	no specific intraocular antibody production
2–4	suggestive of specific intraocular antibody production
≥4	diagnostics of specific intraocular antibody production

3) IgG and IgM serology for herpes viruses. This test is not recommended for diagnosing ARN because it does not provide added value to the diagnostic process.

4) Endoretinal biopsy. This method is invasive and may be useful in cases in which the PCR result is negative but the clinical feature is highly suspicious or the cause of retinitis remains unknown.[34] The biopsy is performed at the demarcation line, especially in the acute phase of the disease, which increases the diagnostic yield.

5) Other methods include viral culture and immunocytochemistry from intraocular specimens, but these are generally limited by their poor sensitivity or specificity.[4,5]

Baseline blood and serology testing

Baseline blood testing includes complete blood count, blood urea nitrogen, creatinine, and liver function test performed before the initiation of antiviral medication to allow adjusting the dose and monitoring drug toxicity in patients with renal impairment based on an induction dose and a maintenance dose recommendation. Serology testing is often needed to rule out other infectious agents that can affect a the differential diagnosis of ARN (Table 2) and to assess the patient's immune status, including anti-HIV, syphilis, and tuberculosis testing.[31]

TABLE 1. Classification criteria for acute retinal necrosis.

Standardization of Uveitis Nomenclature (SUN) classification criteria 2021[29]
Criteria
1. Necrotizing retinitis involving the peripheral retina AND (either #2 OR #3)
2. Evidence of infection with either HSV or VZV
a. Positive PCR for either HSV or VZV from either an aqueous or vitreous specimen OR
3. Characteristic clinical picture
a. Circumferential or confluent retinitis AND
b. Retinal vascular sheathing and/or occlusion AND
c. More than minimal vitritis[a]
Exclusions
1. Positive serology for syphilis using a treponemal test
2. Intraocular specimen PCR-positive for cytomegalovirus or Toxoplasma gondii (unless there is immunocompromise, morphologic evidence for >1 infection, the characteristic clinical picture of acute retinal necrosis, and the intraocular fluid specimen has a positive PCR for either HSV or VZV)

Abbreviations: HSV = herpes simplex virus; PCR = polymerase chain reaction; VZV = varicella-zoster virus.
[a]Vitritis criterion not required in immunocompromised patients.

TABLE 2. Differential diagnoses of acute retinal necrosis.

Infectious causes	Immune-mediated causes	Masquerade syndromes
Cytomegalovirus retinitis	Behçet's disease	Vitreoretinal lymphoma
Progressive outer retinal necrosis	Ocular sarcoidosis	Leukemia
Atypical toxoplasma retinochoroiditis		
Syphilitic chorioretinitis		
Fungal or bacterial endophthalmitis		
Ocular toxocariasis		

Treatment

Antiviral medications

Early initiation of antiviral medication is crucial for treating patients with ARN effectively. The goal of treatment is to stop lesion progression, accelerate the healing process, and prevent contralateral eye involvement. It was found in one study that treatment with systemic acyclovir decreased the risk of contralateral eye involvement from 70% to 13%.[22] Table 3 summarizes the antiviral medications used in the treatment of acute retinal necrosis. The use of intravenous acyclovir for 10–14 days in the induction phase, followed by oral antiviral medication in the maintenance phase, is recommended as the standard initial treatment regimen. Regression of retinal lesions can be first seen 4–7 days after the initiation of treatment, and complete regression can be observed at 6–12 weeks.[23,35] The duration of treatment for the maintenance phase with oral medication is recommended up to 6 weeks to 3 months to decrease the incidence of contralateral eye involvement. Low-dose oral antiviral therapy may be prescribed for long-term use as a prophylactic regimen; however, there is no consensus on the duration of this regimen. Adjunctive therapy with a twice-weekly antiviral intravitreal injection to provide immediate therapeutic vitreous drug levels for the early treatment of ARN is recommended until retinitis is controlled (Fig 2). There is evidence supporting the effectiveness of intravitreal antiviral therapy combined with systemic acyclovir in lowering the risk of severe visual loss and incidence of RRD in ARN cases.[36]

Over the past several years, induction treatment with intravenous antiviral medications requiring hospitalization has shifted to the use of oral induction with newer antiviral medications that have been proven successful with greater bioavailability, including valacyclovir and famciclovir.[31,37] Valacyclovir, an oral prodrug, metabolizes rapidly to acyclovir during first-pass metabolism, displaying a greater bioavailability of 54%–60% compared to oral acyclovir's lower bioavailability of 15%–30%. A dose of 1 g 3 times/day has a plasma level comparable to intravenous acyclovir of 5 mg/kg every 8 hours, and a dose of 2 g 4 times/day has plasma levels comparable to intravenous acyclovir 10 mg/kg every 8 hours. Famciclovir is an oral prodrug of penciclovir that has higher bioavailability (77%) than oral acyclovir. Penciclovir has a similar potency and antiviral spectrum to acyclovir and a favorable safety profile. This should be considered in patients with acyclovir-resistant ARN.

Anti-inflammatory drugs

Systemic corticosteroids, like prednisolone 0.5–1 mg/kg/day with a tapering dose, may be initiated 24–48 hours after antiviral therapy to decrease the severe inflammatory response from vitritis, which can be significant and can limit visual acuity (VA). Topical corticosteroids are indicated in cases of anterior segment inflammation (>2+ cell grading or plasmoid aqueous formation) and posterior synechia formation.[38]

Antithrombotic drugs

Aspirin and warfarin were used in one study in an attempt to prevent thrombotic complications.[35] Aspirin 81–650 mg/day may be considered in the acute stage with corticosteroids to prevent optic nerve and retinal ischemia.[24] However, no clinical trials have proven the efficacy of aspirin.[39]

Prophylactic laser photocoagulation

The rationale for this is to prevent RRD. In this procedure, the laser is applied posterior to the demarcation line. Despite this, there is a lack of evidence suggesting

TABLE 3. Common antiviral medications used in the treatment of ARN[31, 34]

Treatment	Induction 14 days	Maintenance 3 months	Efficacy	Side effects
Systemic treatment				
Acyclovir	10–15 mg/kg or 500 mg/m^2 IV every 8 hours (1,500 mg/m^2/day)	VZV: 800 mg oral 5 times daily HSV: 400 mg oral 5 times daily	HSV-2 ~ HSV-1 > VZV >> CMV	Nephrotoxicity, neurotoxicity, malaise, diarrhea, nausea, vomiting
Valacyclovir	1–2 g 3 times daily	1 g 3 times daily	HSV-2 ~ HSV-1 > VZV >> CMV	Same as IV acyclovir
Famciclovir	500 mg 3 times daily	500 mg 3 times daily	HSV-1 > HSV-2 > VZV	Same as IV acyclovir
Intravenous Ganciclovir	5 mg/kg every 12 hours	5 mg/kg once daily	HSV-1 ~ CMV >> HSV-2, VZV	Thrombocytopenia, leukopenia, neutropenia, anemia, nephrotoxicity, diarrhea, nausea, vomiting, impairment of fertility, fetal toxicity and carcinogenesis based on animal data
Valganciclovir	900 mg twice daily	450 mg twice daily	HSV-1 ~ CMV >> HSV-2, VZV	Same as IV ganciclovir
Adjunctive intravitreal injection				
Ganciclovir	2 mg/0.05–0.1 ml twice weekly or as needed		HSV-1 ~ CMV >> HSV-2, VZV	Retinal detachment, vitreous hemorrhage, endophthalmitis
Foscarnet	2.4 mg/0.1 ml twice weekly or as needed		HSV-1 ~ HSV-2 ~ VZV > CMV	Same as IVT ganciclovir

CMV = cytomegalovirus; HSV-1 = herpes simplex virus type 1; HSV-2 = herpes simplex virus type 2; IV = intravenous; IVT = intravitreal; VZV = varicella-zoster virus.

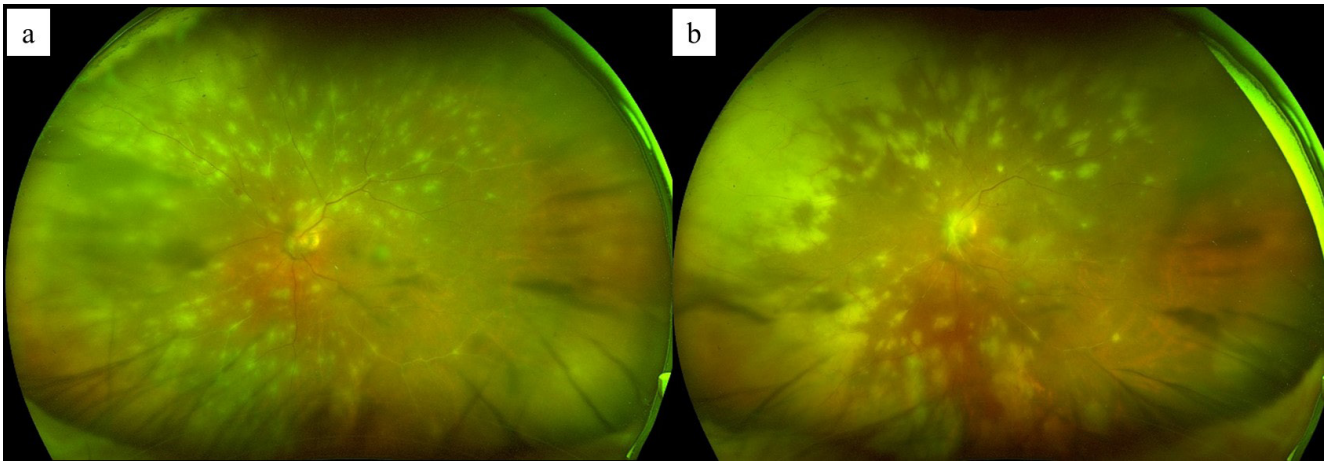

Fig. 1. Ultrawide-field fundus photograph of the left eye of an 80-year-old man with VZV ARN showing vitritis, occlusive arteriolitis, and multiple foci of retinal infiltrates with a discrete border at presentation (a). Two weeks later, the retinal infiltrates has become confluent and progressed circumferentially (b). ARN = Acute retinal necrosis; VZV = varicella–zoster virus

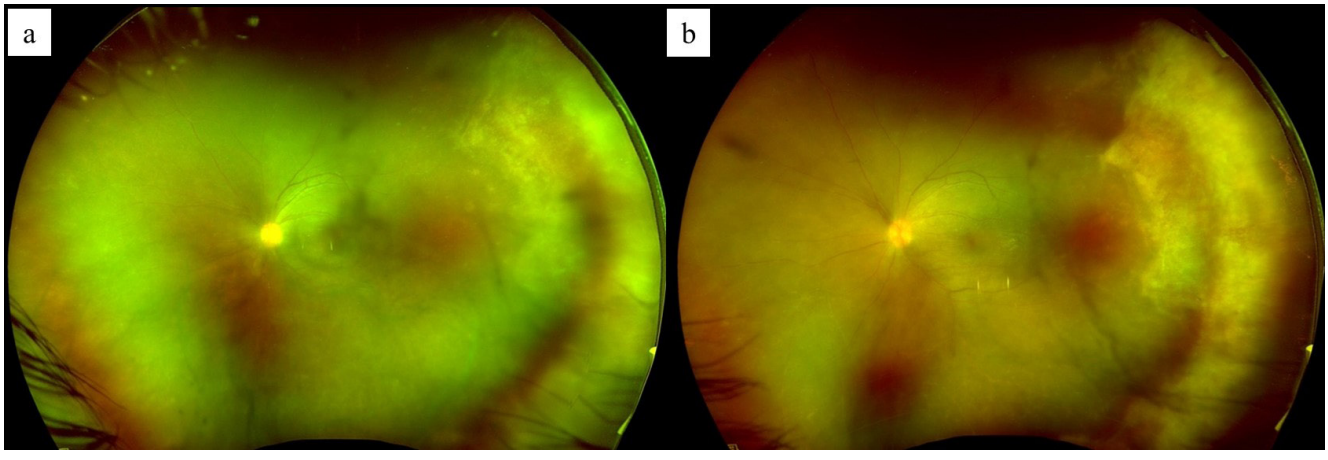

Fig. 2. Ultrawide-field fundus photograph of the left eye of a 13-year-old girl with HSV-2 ARN revealing vitritis, arteriolitis, and confluent retinitis in the temporal quadrant, with a partial response to acyclovir and IVT ganciclovir injections (a). Subsequent improvement in vitritis and retinitis was observed following adjunctive IVT foscarnet injections (b). ARN = Acute retinal necrosis; HSV-2 = herpes simplex virus type 2; IVT = Intravitreal.

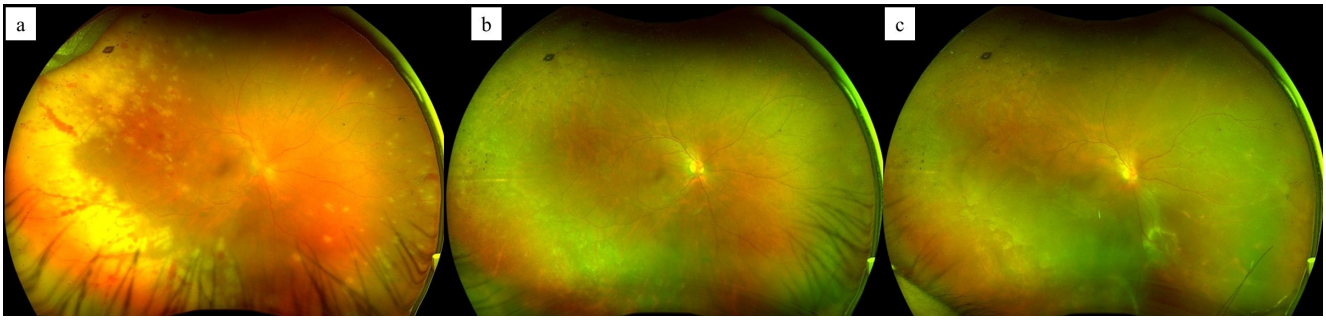

Fig. 3. Ultrawide-field fundus photograph of the right eye of a 48-year-old man with VZV ARN revealing occlusive vasculopathy and multiple foci of retinitis becoming confluent in the nasal quadrant (a). Resolution of ARN was observed after treatment with systemic acyclovir and IVT ganciclovir injections (b). Six months after the onset of ARN, RRD developed (c).

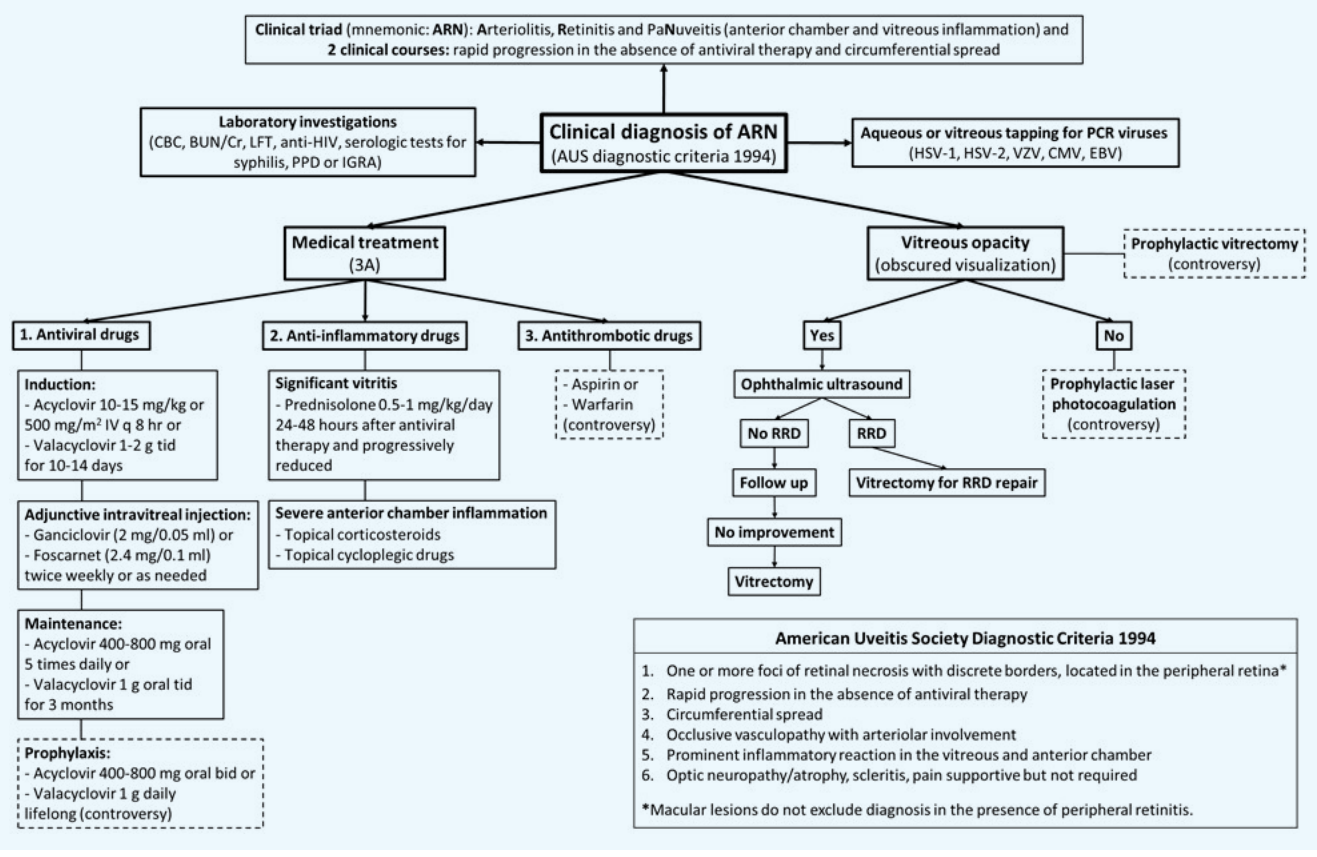

Fig. 4. Summarized diagnosis and management of acute retinal necrosis.
AUS = American uveitis society; BUN/Cr = blood urea nitrogen/creatinine; CBC = complete blood count; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; HSV-2 = herpes simplex virus type 2; IGRA = interferon-gamma release assay; IV = intravenous; LFT = liver function test; PPD = purified protein derivative; PCR = polymerase chain reaction; RRD = rhegmatogenous retinal detachment; VZV = varicella-zoster virus.

that prophylactic laser photocoagulation decreases the incidence of RRD due to limitations in the findings of various studies. Furthermore, laser photocoagulation can only be administered when there is adequate clarity of the ocular media to enable visualization during the procedure.[37]

Vitreoretinal surgery

Vitrectomy for the surgical repair of RRD

Pars plana vitrectomy with endolaser photocoagulation and silicone oil tamponade is the most frequently applied technique for retinal detachment repair. Despite this surgical repair technique allowing good anatomic results, the visual outcome may be poor from optic and retinal atrophy.[24]

Prophylactic vitrectomy

The rationale in this approach is the removal of inflammatory mediators and vitreous traction, applying laser demarcation of the necrotic retina, and placing a long-acting tamponade to prevent RRD. A retrospective case series showed that early prophylactic vitrectomy with or without silicone oil reduced the incidence of RRD but did not change the visual outcome. These results suggested that retinal ischemia and optic atrophy rather than secondary RRD were the main causes of poor final visual outcomes.[40]

Complications

In cases where patients do not receive treatment, inflammation naturally subsides within 2–3 months, resulting in a 360° peripherally atrophic retina and multiple retinal breaks. RRD is a frequent complication that can occur in 50%–75% of eyes within 1–3 months (Fig 3).[41] Tractional retinal detachment may occur as a consequence of vitreoretinal traction caused by severe vitritis. Development of optic atrophy is a frequent consequence in patients with initial optic disc edema. Macular edema is often caused by severe vitritis or is accompanied by an epiretinal membrane. Retinal and optic disc neovascularization may develop in patients with extensive retinal ischemia.

Prognosis

The visual prognosis of ARN is poor, particularly in patients who are not treated immediately. Poor visual outcomes are related to large areas of retinitis involving the posterior pole or macula, the presence of a relative afferent pupillary defect at the time of diagnosis, retinal detachment, increased age, relative immunosuppression, and a larger area of RRD.[42,43] Final VA is often limited by structural complications, including RRD, optic atrophy, macular edema, occlusive retinal vasculopathy, chronic vitritis, epiretinal membrane, macular hole, and macular ischemia. In one study, 48% of the involved eyes had a final VA < 6/60 at 6 months. Among ARN patients with retinal detachment, 60% of eyes ended up with VA < 6/60.[8] However, treatment with acyclovir and prednisolone was associated with a final VA > 6/60 with 32% of VZV ARN and 67% of HSV ARN eyes having a final VA >6/12.[6]

CONCLUSION

ARN, although rare, is a devastating disease that can lead to severe visual loss if not treated rapidly. When a patient presents with anterior segment inflammation, a dilated fundus examination should always be performed. Failure to do so may result in a misdiagnosis of ARN, and the administration of systemic corticosteroids alone can lead to severe and rapidly progressive ARN. We recommend that ophthalmologists should not wait until the fulfilling diagnostic criteria are met before starting treatment. If fundus examination reveals peripheral retinitis and/or a history of preceding cutaneous herpetic infection or HSV keratitis, ophthalmologists should immediately start induction treatment with antiviral medications with or without adjunctive intravitreal antiviral injection (Fig 4). Optimal treatment can effectively halt disease progression and prevent the involvement of the contralateral eye. PCR of an aqueous fluid specimen is useful for confirming the diagnosis of patients with suspected ARN; however, treatment should not be postponed while awaiting the PCR results owing to the nature of swift advancement of the disease in the absence of antiviral therapy. After induction treatment has been completed, oral maintenance should continue for approximately 3 months. Oral antiviral prophylaxis is still controversial and prophylactic laser photocoagulation or vitrectomy are currently inconclusive and require further study.

Conflicts of Interest

The authors confirm that we have no conflicts of interest to declare.

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