EDITORIAL

Widya Artini Wiyogo

As we approach World Sight Day, observed annually on the second Thursday of October, the Indonesian Association of Ophthalmology always organizes various activities related to this day, particularly to raise awareness about visual impairment in the community. This focus is crucial because Indonesia has a significant blindness rate (3%), with cataracts remaining the main issue, however visual impairment due to cataracts can be restored through cataract surgery.[1] Glaucoma is also among the top five causes of blindness. It becomes a serious problem when someone's vision has deteriorated significantly, as vision cannot be restored even with glaucoma surgery due to severe damage to the retinal nerve fiber layers and optic disc pallor. Additionally, the number of glaucoma patients in Indonesia has increased substantially due to an aging population. Severe visual field loss might occur in people with advanced open-angle glaucoma and angle-closure glaucoma, which encroaches on central vision and eventually reduces visual acuity. Glaucoma patients often present with advanced disease in at least one eye, with severe visual field restriction usually reducing their quality of life and increasing the risk of falls and fractures. These patients are often associated with socioeconomic deprivation.[2] Guidelines from the National Institute for Health and Care Excellence (NICE) in the UK suggest that patients presenting with advanced glaucoma should be offered trabeculectomy as a primary intervention.[3] However, this suggestion does not yet have consensus in Indonesia. Even in the UK, this guidance is generally not followed due to concerns about potential sight-threatening surgical complications and a lack of evidence supporting primary surgery. It is believed that reducing intraocular pressure is the only proven effective treatment for halting the progression of glaucoma. Therefore, we reviewed the results of managing late-advanced stage primary glaucoma in Indonesian eyes after performing combined phacoemulsification and trabeculectomy to evaluate the efficacy and safety, mean intraocular pressure (IOP) reduction, and vision-threatening complications.

The medical records of Indonesian eyes with late-advanced stage primary glaucoma at JEC Eye Hospital & Clinics were retrospectively reviewed. Eyes with secondary glaucoma, pseudophakia, and retinal diseases were excluded. Data collection included IOP, visual acuity, visual field, optic disc ratio, retinal nerve fiber layer thickness, and IOP-lowering medication used preoperatively and up to 12 months postoperatively. Complications, if any, were also noted. Paired T-tests and Wilcoxon tests were utilized to analyze the results.

A total of 47 eyes from 40 subjects were analyzed in this study. The majority of the subjects were male (52.5%), with a mean age of 62.60 ± 9.95 years. Most eyes had primary open-angle glaucoma compared to primary angle-closure glaucoma (62.5% vs. 37.5%). The mean visual field deviation (dB) was -22.68 ± 6.90 at baseline and -23.31 ± 7.04 postoperatively ($p<0.35$). The mean IOP (mmHg) was 29.08 ± 11.39 at baseline and 15.11 ± 6.40 ($p<0.0001$) after 12 months of follow-up. IOP reductions of ≥ 20% were achieved in 41/47 eyes (87.2%), with a mean IOP reduction of 43%. The mean medication use decreased from 3.91 ± 1.25 medications per eye at baseline to 1.38 ± 1.21 at the last follow-up ($p<0.0001$), with a mean IOP-lowering medication reduction of 60% after 12 months of follow-up. Sixteen out of 47 eyes (34%) were medication-free at the last follow-up. No vision-threatening or wipe-out complications were observed.

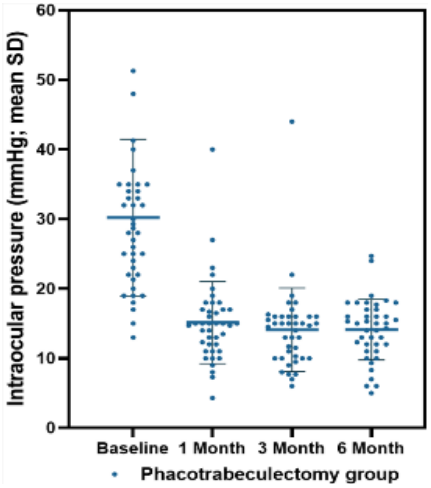

Fig 1. IOP at baseline and follow-up

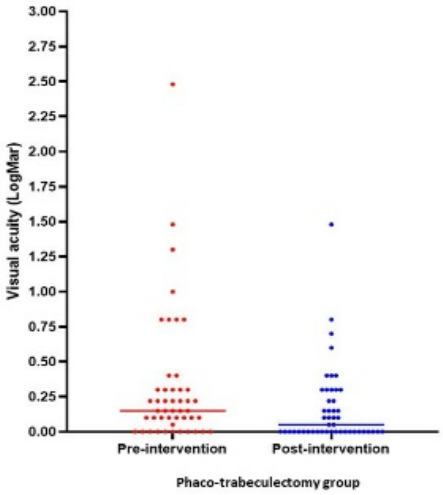

Fig 2. BCVA (in logMAR units) at baseline and follow-up

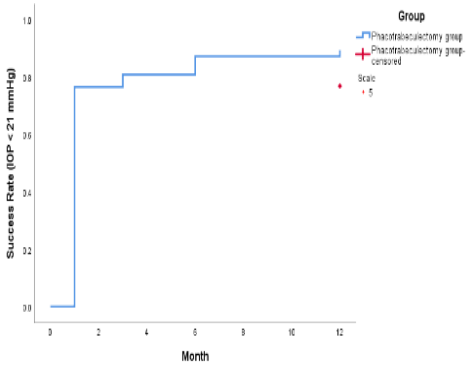

Fig 3. Kaplan-Meier survival curve of surgical outcome

Our findings indicate significant IOP reduction and increased visual acuity after combined phacoemulsification and trabeculectomy in late-advanced primary glaucoma patients, observed over 12 months of follow-up. However, after 12 months, four eyes developed reduced vision due to glaucoma progression, and one eye developed age-related macular degeneration. No unexplained loss of vision occurred immediately after surgeries, indicating no occurrence of wipe-out was found in this study. Further follow-up on retinal nerve fiber

layer damage sensitivity is crucial. During continued observation of these patients, they required at least two types of glaucoma eye drops. Another study showed no evidence of any differences between pre-post trabeculectomy compared to medication only, using a questionnaire for EQ-5D-5L, HUI-3, and GUI at 24 months in advanced glaucoma eyes. That study also reported greater IOP reduction to 12.4 (SD 5.7) mm Hg at four months, remaining around 12 mmHg in the trabeculectomy group. At 24 months, the modest deterioration in visual acuity was potentially due to the development of early cataracts in the trabeculectomy group.[3]

A sustained reduction in intraocular pressure is recognized as the most effective method of preventing further visual field loss in glaucoma eyes. For patients, maintaining their quality of life and independence is the most important outcome of their glaucoma management. Combining cataract surgery with glaucoma surgery is indeed recommended. However, other studies have shown that combined surgery can cause an inflammatory reaction leading to the failure of glaucoma surgery, so it is recommended to perform surgeries in stages.[4-7] It should be emphasized that the condition of glaucoma patients in Indonesia is usually severe. Patients often forget to use their glaucoma medication due to advanced age, difficulty in administering medication, and the high cost of glaucoma eye drops. Therefore, combined surgical management needs to be considered as it can reduce eye pressure and improve visual acuity in one procedure. If performed carefully and correctly, it is quite safe. Hopefully, our small study will provide more information on managing late-advanced primary glaucoma and can be considered by ophthalmologists.

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ORIGINAL ARTICLE

COMPARISON OF VISUAL ACUITY RESULTS AFTER FEMTOSECOND LASER-ASSISTED IN SITU KERATOMILEUSIS (FS-LASIK) AND SMALL INCISION LENTICULE EXTRACTION (SMILE)

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ABSTRACT

Introduction: *Two of the most popular refractive surgery methods currently used are Femtosecond Laser-Assisted In Situ Keratomileusis (FS-LASIK) which creates a flap using femtosecond laser and stromal ablation using excimer laser, and Small Incision Lenticule Extraction (SMILE), a flapless procedure in which a lenticule is extracted through a small incision. The aim of this study is to compare the visual acuity results of FS-LASIK and SMILE.*
Methods: *This is a descriptive cross-sectional study. Data were collected from the medical record of patients who underwent FS-LASIK or SMILE procedure at Cicendo Eye Hospital, the national eye centre, in 2022. Patients were followed up at 1 day, 1 week, and 1 month postoperatively and visual acuity outcomes between the two procedures were compared.*
Results: *A slightly higher percentage of eyes in FS-LASIK (46.6%) achieved a UCVA of 1.0 at 1 day postoperatively compared to SMILE (45.5%). At 1 week and 1 month, SMILE showed superior results with 83% and 94.6% of eyes achieving a UCVA of 1.0, meanwhile FS-LASIK had 72.2% and 86.2%. Residual refractive error at 1 month had a median of -0.6146 and -0.3125 in the FS-LASIK and SMILE groups.*
Conclusion: *This study found better UCVA results in the FS-LASIK group compared to the SMILE group at 1 day postoperatively. Meanwhile, UCVA at 1 week and 1 month postoperatively, showed superior results in the SMILE group. Residual refractive error at 1 month postoperatively also showed better results in SMILE than FS-LASIK.*
Keywords: *visual acuity, FS LASIK, SMILE*

INTRODUCTION

Refractive surgery is a procedure used to correct refractive errors, alleviating the need for glasses or contact lenses. Techniques and methods in this field are constantly evolving along with technology. Two of the most popular procedure currently used are Femtosecond Laser-Assisted In Situ Keratomileusis (FS-LASIK) and Small Incision Lenticule Extraction (SMILE). LASIK is a procedure that creates a corneal flap, followed by stromal ablation to alter the shape of the cornea. The use of femtosecond laser in FS-LASIK creates higher accuracy and precision in corneal flap creation compared to a microkeratome blade, used in LASIK, resulting in lower risk of complications. Refractive lenticule extraction is a more recently developed method which uses femtosecond laser to create an intrastromal lenticule to then be extracted.

Specifically in SMILE, the lenticule is extracted through a small incision, created by the same femtosecond laser. This flapless procedure results in a more biomechanically stable cornea, less anterior corneal innervation disruption causing less dry eye symptoms, as well as absence of flap-related complications.[1–3]

Both FS-LASIK and SMILE have been found to have excellent outcomes in terms of safety, efficacy, and predictability.[4–6] Although both procedures have similar outcomes, results regarding which procedure were superior to the other in terms of uncorrected visual acuity (UCVA) vary between certain postoperative timestamps. In a study conducted by T. Liu et al., FS-LASIK was shown to have better UCVA results at the very early stage of recovery, specifically at 2 hours and 4 hours postoperatively, although both results were similar and satisfactory at 24 hours. Results have varied the most between studies regarding the 24 hour timestamp, in which SMILE was shown to have better results in a study done by Ganesh et al., whereas according to M. Liu et al., FS-LASIK were superior. In the same study done by M. Liu et al., results at 1 week, 1, 3, and 6 months postoperatively had no statistically significant difference. Ganesh et al., also found UCVA results between the two procedures to be similar at 3 months postoperatively, although SMILE was still superior with less postoperative symptoms.[5–7]

Since the aim of refractive surgery is to improve a patient's refractive status, visual acuity becomes an extremely important parameter to asses as it is highly associated with patient satisfaction.[8] Minimal studies comparing the results of FS-LASIK and SMILE have been done in Indonesia. This study was conducted in Cicendo Eye Hospital as the National Eye Center of Indonesia, to compare the visual acuity results after FS-LASIK and SMILE.

METHODS

This comparative study was approved by Padjadjaran University Research Ethics Committee and Cicendo Eye Hospital Research Ethics Committee. Data were collected from the medical record of patients who underwent FS-LASIK or SMILE from January 1st to December 31st of 2022 in Cicendo Eye Hospital, a tertiary referral hospital as well as the national eye center. Subjects were selected using total population sampling method. The inclusion criteria were patients with preoperative best corrected visual acuity (BCVA) equivalent to 1.0, ages 18 to 40 years old, and patients who came in for check-ups at 1 day, 1 week, and 1 month postoperatively unless UCVA results have reached 1.0. Subjects predicted to have residual refractive error during preoperative consultation, or those who underwent an enhancement procedure sooner than 1 month after the primary procedure were excluded.

Statistical analyses were performed with Microsoft® Excel 16.66.1 and IBM SPSS Statistics. Normality was tested using the Kolmogorov–Smirnov test and the Shapiro Wilk test. Mean ± standard deviation (SD) was used for quantitative variables that were normally distributed and median (minimum-maximum) was used for quantitative variables that were not normally distributed.

RESULTS

A total of 291 subjects (490 eyes) fit the criteria of this study, in which 226 subjects underwent FS-LASIK, 64 subjects underwent SMILE, and one subject underwent both procedures in different eyes. Therefore, 378 eyes underwent FS-LASIK and 112 eyes underwent SMILE. Preoperative data consisting of age, sex, and laterality are summarized in table 1. The median age for the FS-LASIK group was 19 and for the SMILE group was 20. In the FS-LASIK group, 153 patients were male (68%) and 73 were female (32%), while in the SMILE group, 27 patients were male (42%) and 37 were female (58%). Seventy-five patients in the FS-LASIK group only had 1 eye that fit the research criteria, while in 151 patients, both eyes fit the criteria. In the SMILE group, 17 patients had 1 eye that fit the criteria, and 47 patients had both eyes that fit the criteria.

Table 1. Preoperative Patient Data

Variable	FS-LASIK (n= 226)	SMILE (n= 64)	FS LASIK & SMILE (n= 1)
Age (years)			
Median (Min-max)	19 (18−38)	20 (18−39)	22
Sex			
Male (%)	153 (68%)	27 (42%)	0 (0%)
Female (%)	73 (32%)	37 (58%)	1 (100%)
Laterality			
1 eye (%)	75 (33%)	17 (27%)	0 (0%)
2 eyes (%)	151 (67%)	47 (73%)	1 (100%)

FS-LASIK = *femtosecond laser-assisted in situ keratomileusis*, SMILE = *small incision lenticule extraction*

Preoperative refractive status of all eyes are summarized in table 2. Preoperative UCVA values were categorized according to the World Health Organization (WHO) classification of vision impairment.[9] Most eyes in the FS-LASIK group had UCVA of <6/60-3/60, with 161 (42.6%) eyes, and UCVA of <6/18-6/60 with 99 (26.2%) eyes. Meanwhile, the vast majority of eyes in the SMILE group, 82 (73.2%) eyes, had had UCVA of <6/60-3/60. Eyes were also categorized based on preoperative spherical equivalent (SE) values (sum of the sphere power and half of the cylinder power) like those of a study conducted by Althomali.[10] Myopia was considered as a SE of less than 0, further categorized as low (≥ −0.50 diopters (D) and < −3.00 D) , moderate (≥ −3.00 D and < −6.00 D) and high (≥ −6.00 D). Hyperopia was considered as

a SE of higher than 0, further categorized as low to moderate (≥ +0.50 D and < +3.00 D) and high (≥ +3.00 D) hyperopia. The majority of the eyes in the FS-LASIK group, 205 (54.2%), were categorized as low myopia, while half of the eyes in the SMILE group were categorized as moderate myopia. The median spherical equivalent was -2.75 and -3.81 in the FS-LASIK and SMILE groups. The range in myopic spherical values were -0.25 up to -11.50 in the FS-LASIK group and -1.00 up to -8.00 in the SMILE group, hyperopic spherical values were +0.50 to +2.00 in the FS-LASIK group while SMILE had no hyperopic eyes, and cylindrical values were -0.25 up to -4.50 in the FS-LASIK group and -0.25 and -2.25 in the SMILE group.

Table 2. Preoperative Refractive Status

Variable	FS-LASIK (n= 378 eyes) (%)	SMILE (n= 112 eyes) (%)
UCVA		
≥6/12	50 (13.2%)	3 (2.7%)
<6/12-6/18	29 (7.7%)	0 (0%)
<6/18-6/60	99 (26.2%)	17 (15.2%)
<6/60-3/60	161 (42.6%)	82 (73.2%)
<3/60	39 (10.3%)	10 (8.9%)
Myopia		
Low	205 (54.2%)	39 (34.8%)
Moderate	104 (27.5%)	56 (50%)
High	68 (18%)	17 (15.2%)
Hyperopia		
Low to Moderate	1 (0.3%)	0 (0%)
High	0 (0%)	0 (0%)
SE (D)		
Median (Min-Max)	-2.75 (-11.75−1.38)	-3.8125 (-8.88−-1.13)

FS-LASIK = *femtosecond laser-assisted in situ keratomileusis*, SMILE = *small incision lenticule extraction,* UCVA = *uncorrected visual acuity,* SE= *spherical equivalent*

Postoperative UCVA were recorded in both groups and summarized in figure 1. Visual acuity values were written in decimal notations, as written on the medical records. At 1 day postoperatively, 176 (46.6%) eyes in the FS-LASIK group and 51 (45.5%) eyes in the SMILE group achieved a UCVA of 1.0. At 1 week postoperatively, 273 (72.2%) eyes in the FS-LASIK group and 93 (83%) eyes in the SMILE group achieved a UCVA of 1.0. At 1 month postoperatively, 326 (86.2%) eyes in the FS-LASIK group and 106 (94.6%) eyes in the SMILE group achieved a UCVA of 1.0.

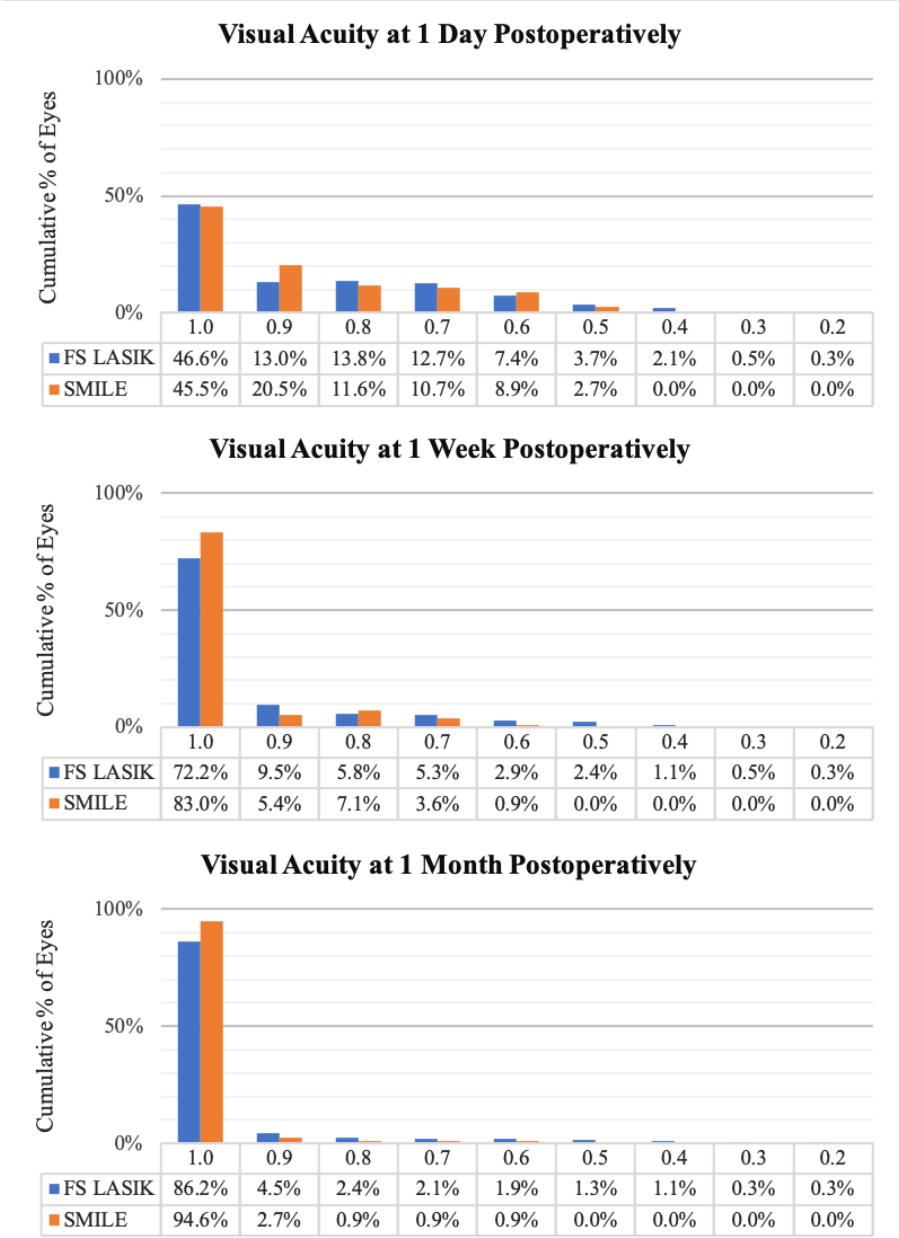

Figure 1. Uncorrected Visual Acuity Results at 1 Day, 1 Week, and 1 Month Postoperatively in FS-LASIK and SMILE

Postoperative refractive status of all eyes at 1 month postoperatively in terms of residual refractive error (RRE) are summarized in table 3. RRE were recorded according to the spherical equivalent (SE) value of the lenses needed to correct the eyes that had yet to achieve a postoperative UCVA of 1.0. Although, there were 4 eyes and 2 eyes in the FS-LASIK and SMILE group that did not achieve a postoperative UCVA of 1.0 yet had no record of lens correction at 1 month postoperatively, which resulted in 48 and 4 eyes in the FS-LASIK and SMILE groups that had RRE. The mean and median of RRE in both groups are presented on the table. As previously mentioned, myopia is defined as having a SE of ≥ −0.50 D and hyperopia as a SE of ≥ +0.50 D, which will help to determine whether any eyes are still or no

longer defined as such postoperatively. In the FS-LASIK group there were 25 eyes with a RRE of ≥ −0.50 D and none ≥ +0.50 D. Whereas in the SMILE group, there were no eyes with an RRE of ≥ −0.50 D or ≥ +0.50 D. BCVA values were recorded according to the best visual acuity achieved with lenses at 1 month postoperatively. Sixteen (4.2%) eyes and 3 (2.7%) eyes in the FS-LASIK and SMILE groups did not achieve a BCVA of 1.0.

Table 3. Postoperative Refractive Status

Variable	FS-LASIK (n= 48 eyes)	SMILE (n= 4 eyes)
Residual Refractive Error		
+ 0.5 - − 0.5 D	23 (47.9%)	4 (100%)
Mean ± SD (D)	-0.6146 ± 0.3608	-0.1563 ± 0.3590
Median (Min-Max) (D)	-0.625 (-1.63−0.25)	-0.3125 (-0.38−0.38)

FS-LASIK = *femtosecond laser-assisted in situ keratomileusis*, SMILE = *small incision lenticule extraction,* UCVA = *uncorrected visual acuity,* SE= *spherical equivalent*

DISCUSSION

The goal of refractive surgery is to improve the visual ability of patients with ametropia and restore normal vision without the help of glasses nor contact lenses. In corneal refractive surgery, adjustment of the shape and thickness of the cornea is what alters the refractive power of the eyes. FS-LASIK and SMILE are two of the most popular corneal refractive surgery methods currently used. Both procedures differ in their techniques, as FS-LASIK creates a flap using femtosecond laser and stromal ablation using excimer laser, while SMILE is a flapless procedure in which a lenticule is formed and extracted through a small incision, both created by the same femtosecond laser.

In this study, UCVA at 1 day postoperatively showed a slightly higher percentage in the FS-LASIK group (46.6%) than in the SMILE group (45.5%). Previous studies have also shown that FS-LASIK tend to have better visual acuity results in the early postoperative phase, such as the study conducted by T. Liu et al. and M. Liu et al.[5,7] This is caused by the difference in the healing response in both procedures which creates muddiness of the refractive media associated with the formation of interface haze during the SMILE procedure.[7] Another reason suggested by Agca et al were the surgical maneuvers in SMILE that are more challenging than those of FS-LASIK, such as the creation of two lamellar cuts (superficial and deep) rather one flap cut and an increased number of surgical steps needed to separate the lenticule. In terms of the effects of the laser treatment, the total energy applied to the corneal stroma in SMILE is also higher compared to the stroma in FS-LASIK. These differences may contribute to the varying inflammatory response.[11]

UCVA results at 1 week and 1 month postoperatively in this study showed superior results in the SMILE group. These results align with those of a study conducted by Ganesh et

al., in which 96% of eyes in SMILE achieved a UCVA of 20/20 or better meanwhile FS-LASIK had only 88%, and Lin et al. in which 85% of eyes in SMILE achieved a UCVA of 20/20 or better meanwhile FS-LASIK had only 84%.[4,6] Although in those studies, UCVA results were recorded at 3 months, which are different to this study. In a systemic review conducted by Guo et al., corneal biomechanical strength in SMILE was preserved significantly better than in FS-LASIK.[12] This was thought to be caused by the fact that the SMILE procedure only makes a small incision, rather than a flap, which creates preservation of stronger anterior corneal lamellae. As a result, the recovery effect of a patient's visual ability is further improved and is a contributing factor to the superior results of SMILE in this study.[1,13]

Regarding residual refractive error, this study also showed better results in the SMILE group which were similar to those of a study conducted by Ganesh et al. This was believed to be caused by an intraoperative difference between the two procedures that creates a variation in hydration, thus creates a possibility of under ablation or over ablation. The process of lifting the flap in FS-LASIK exposes the stroma, causing hydration changes before creating refractive correction with the excimer laser. Meanwhile, in SMILE, lenticule creation by the femtosecond laser is done before any disturbance of the stroma. As a result, SMILE is thought to have better predictability.[6] Although, at Cicendo Eye Hospital, the temperature and humidity of each operating rooms are controlled to minimize the possibility of this phenomenon. SMILE also showed better results in terms of BCVA, with less eyes achieving a postoperative BCVA of less than 1.0 at 1 month.

One case recorded in this study showed the results between FS-LASIK and SMILE done to the same patient in different eyes. The patient had originally come in to undergo SMILE on both eyes, although during the procedure, black spots developed in the left eye leading to the decision of the surgeon to postpone the procedure on that eye. There were no complications on the right eye. The patient came in 3 months later to undergo FS-LASIK on the left eye. The results were excellent in both eyes, which achieved a UCVA of 1.0 at one month postoperatively.

Six eyes in the FS-LASIK group had yet to achieve a UCVA of ≥6/12 at 1 month postoperatively. Three out of the six eyes had a BCVA value of 1.0, while the other 3 eyes had a BCVA value of 0.8, 0.6, and 0.4. Although, 2 out of the 3 eyes that had a BCVA value of less than 1.0 had a much more satisfactory result at 3 months postoperatively, which indicated a slower recovery. No intraoperative complications were reported in the six eyes. Another contributing factor to poorer results in the FS-LASIK group is due to the fact that two of the six eyes had high myopia preoperatively, one being the eye with the highest SE in this study. This

may also be another reason to the overall superiority of the SMILE results, in which more eyes, 68 (18%) eyes, had high myopia in FS-LASIK than in SMILE, which had 17 (15.2%) eyes. Eyes with a higher degree of ametropia are more likely to experience under correction and will require more time to reach refractive stability.[1]

This study had its limitations such as the difference in the number of subjects included from each group, in which more patients who came to Cicendo Eye Hospital chose to undergo FS-LASIK rather than SMILE. Duration of postoperative follow up in this study were also limited to 1 month as most patients did not come in for a follow up at 3 and 6 months or longer.

CONCLUSION

In conclusion, this study found slightly better results of UCVA in FS-LASIK than SMILE at 1 day postoperatively. A more significant difference was found at 1 week and 1 month postoperatively, in which UCVA of the SMILE group showed superior results. Residual refractive error recorded at 1 month was also shown to be better in SMILE than FS-LASIK. In terms of BCVA, less eyes in the SMILE group had a loss of lines. For future studies, a prospective method should be considered with better control of confounding variables between the two groups, such as the degree or type of ametropia included in the study, surgeons operating on the procedures, as well as comparing data before and after both procedures.

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ORIGINAL ARTICLE

CLINICAL FEATURES OF VERNAL CONJUNCTIVITIS IN CICENDO NATIONAL EYE HOSPITAL

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ABSTRACT

Introduction: *Vernal conjunctivitis is a chronic, recurrent form of allergic conjunctivitis that occurs mainly in children and is commonly found in warm and humid climates or tropical countries, including Indonesia. Although vernal conjunctivitis is a self-limiting disease, it often leads to visual impairment and significantly affects the patient's quality of life.*

Methods: *This retrospective descriptive study was conducted in Cicendo National Eye Hospital from March to April 2023 using the total sampling method to obtain the clinical features of vernal conjunctivitis patients.*

Result: *This study took 117 patients (234 eyes) registered in electronic medical records from January to December 2022 with an age range of 7-18 years. The mean age of the patients was 10.73 ± 3.69 years, with total of 78 patients (66.67%) being male. A total of 30 patients (25.64%) had a history of atopic allergies. All patients in this study had a bilateral condition. The palpebral type was diagnosed in 85 patients (72.64%). Red eyes were the most prominent symptom experienced in 89 eyes (76.06%). Papillary signs were seen in 203 eyes (86.75%), with an uncorrected visual acuity of 6/6 to 6/18 were found in 163 eyes (69.66%). A small proportion of patients experienced complications in 93 eyes (39.74%).*

Conclusion: *The clinical features of vernal conjunctivitis patients in Cicendo National Eye Hospital are similar to those in other tropical countries. Most patients were male and complained of itching and red eyes. The palpebral type is the most common type. Few distinct features were noted indicating a low association with atopy.*

Keywords: *pediatrics, allergy, conjunctivitis, vernal conjunctivitis*

INTRODUCTION

Vernal conjunctivitis is a chronic, recurrent form of allergic conjunctivitis caused by an inflammatory condition of the conjunctiva, usually bilateral, which often occurs in childhood.[1] Globally, the prevalence of vernal conjunctivitis is between 0.1 – 0.5% with an incidence rate that tends to be higher in developing countries. Vernal conjunctivitis is generally found in warm and humid climates or tropical countries such as Asia, Africa, or the Middle East. This condition is commonly found in male patients who are starting to enter the prepubertal period and can last around 5-10 years until it slowly disappears at the age of 18 years.[2,3]

Most of the patients have presented symptoms of severe itching and redness of the eyes, the presence of a foreign body sensation, recurrent burning and pain, mucous discharge, lacrimation, to photophobic reactions in some patients. There are two characteristics of the clinical manifestations that distinguish the types of vernal conjunctivitis. The palpebral type is

characterized by the presence of giant papillae on the superior tarsal conjunctiva, known as Cobblestone papillae. Meanwhile, the limbal type is represented by a thickening of the limbus and a gray nodule filled with eosinophils called Horner-Trantas dot.[4,5]

Vernal conjunctivitis usually does not cause blindness; it is more commonly known as a self-limiting disease. However, this disease can cause visual impairment if it spreads to the other part of the eye. In some cases, vernal conjunctivitis may involve the patient's corneal epithelium, identified by the development of superficial punctate keratitis due to inflammation. Repeated episodes of allergic reactions in some patients can also induce another complication like shield ulcers in the upper third of the patient's cornea.[4,6] If it worsens, vernal conjunctivitis often leads to visual impairment and significantly affects the patient's quality of life due to limitations in daily activities, schooling, as well as potential psychological issues.[3,7,8] This surely has a substantial impact on the patient's well-being, necessitating a better understanding of the disease's nature and it's predisposing factors.

As a tropical country, Indonesia has various risk factors causing vernal conjunctivitis, ranging from various allergens to seasonal factors. Interestingly, the clinical features and severity of the disease may also change according to the geographical condition of the patient. Considering the lack of studies and evidence on this disease in warmer climates such as Indonesia, studies on vernal conjunctivitis have great potential to continue to be researched. Knowing the clinical features of vernal conjunctivitis also helps in the early diagnosis of the patient's manifestations as well as the other threatening complications. Thus, this study is aimed to describe clinical features of vernal conjunctivitis in Cicendo National Eye Hospital.

METHODS

A retrospective, descriptive study was conducted from March to April 2023 and approved by Cicendo National Eye Hospital Research Ethics Committee with protocol number LB.02.01/2.3/2827/2023. Subjects were selected using the total sampling method. All vernal conjunctivitis patients who came in for their first or follow-up visits in the Pediatric Ophthalmology and Strabismus Unit in Cicendo National Eye Hospital from January to December 2022 with an age range of 7 to 18 years were included in this study. Exclusion criteria include patients with incomplete electronic medical records, especially those with incomplete data variables that have been listed.

Variables in this study were based on anamnesis of electronic medical record data, including age, gender, atopic history, visit history, patient's residence, clinical symptoms, clinical signs, type of vernal conjunctivitis, uncorrected visual acuity (UCVA), and complications. Age was determined based on data recorded when the patient registered for their

first visit and assessed by calculating the average age obtained in years. Patient's visit history was grouped into first and follow-up visits. Follow-up visits were taken based on the patient's last control visit in 2022. Patient's residence was classified into Bandung, consisting of Bandung City, Bandung Regency, and West Bandung Regency, and outside Bandung.

Clinical symptoms are subjective complaints of patients written on anamnesis. Clinical signs are the findings on ophthalmological examination that the examiner observes. Vernal conjunctivitis types are classified into palpebral, limbal, and mixed types. Uncorrected visual acuity (UCVA) result is a measurement of the degree of visual acuity of the patient, which is recorded in the electronic medical record data. Complications in this study included the presence of shield ulcers, superficial puncture keratitis, and treatment-related complications, such as glaucoma and cataract. Data obtained were processed using Microsoft® Excel 2022.

RESULTS

Based on electronic medical record data, 117 vernal conjunctivitis patients were obtained with an average age of 10.73 ± 3.69 years and dominated by males (66.67%). A total of 30 patients studied had a history of atopic (25.64%). Most of the patients lived in Bandung (77.78%) and went as follow-up patients (76.07%). The clinical profile of vernal conjunctivitis patients is listed in Table 1.

Table 1. Vernal Conjunctivitis Patient Characteristics

	Patients (n=117)	Percentage (%)
Age (years old)		
Mean ± SD	10.73 ± 3.69	
Range	7 – 18	
Gender		
Male	78	66.67
Female	39	33.33
Atopic history		
Atopic	30	25.64
Non atopic	87	74.36
Patient's residence		
Bandung	91	77,78
Outside Bandung	26	22.22
Visit history		
First	28	23.93
Follow-up	89	76.07

All patients in this study were presented with a bilateral condition and most of them were diagnosed with palpebral types (72.64%), followed by mixed and limbal types. Patient symptoms were dominated by redness eyes (76.06%), followed by itching (63.24%) and

burning (29.91%).

Distinctive papillae on the tarsal conjunctiva were seen in 203 eyes (86.75%) and Horner-trans dots in 39 eyes (16.67%). Most of the uncorrected visual acuity (UCVA) had the range of 6/18 to 6/6 (69.66%) and was measured using the Snellen chart.

Table 2. Vernal Conjunctivitis Clinical Characteristics

	Patients (n=117)	**Percentage (%)**
Types		
Palpebral	85	72.64
Limbal	3	2.56
Mixed	29	24.8
Clinical symptoms		
Redness eyes	89	76.06
Itching	74	63.24
Burning sensation	35	29.91
Foreign body sensation	1	0.85
Discharge	20	17.09
Photophobia	7	5.98
Blurry eyes	29	24.78
Lacrimation	33	28.21
	Eyes (n=234)	**Percentage (%)**
Clinical signs		
Papillae	203	86.75
Giant papillae	10	4.27
Hyperemia	36	15.38
Hornes-Trantas dot	39	16.67
Limbal hypertrophy	18	7.69
Conjunctival hyperpigmentation	43	18.37
Blepharospasm	10	4.27
Crust	14	5.98
Uncorrected visual acuity		
6/6 – 6/18	163	69.66
< 6/18 – 6/60	42	17.94
< 6/60 – 3/60	11	4.71
<3/60	18	7.69
Complications		
Yes	93	39.74
No	141	60.26

Table 3 shows the complications involving the cornea, with superficial punctate keratitis being the most common complication in patients (32.48%), followed by shield ulcers (5.12%). In addition, a small proportion of patients experienced treatment-related complications, such as glaucoma (9.41%) and cataract (3.01%).

Table 3. Vernal Conjunctivitis Patient Complications

	Eyes (n=234)	Percentage (%)
Complications		
Shield ulcers	12	5.12
Superficial punctate keratitis	76	32.48
Treatment-related Complications		
Glaucoma	22	9.41
Cataract	7	3.01

DISCUSSION

Vernal conjunctivitis is a chronic recurrent bilateral allergic condition that is generally caused by seasonal factors. This condition usually occurs in school-aged children, with prepubertal onset or before ten years of age in 80% of cases.[2,3] In this study, it was presented that the average age of 117 vernal conjunctivitis patients was 10.73 years, with an age range of 7 to 18 years old. The result of our study is similar to a previous study conducted by Roumeau et al. that stated the average age of vernal conjunctivitis patients was 11.2 years with an age range of 3 to 38 years old.[9] These two studies show the similarity that vernal conjunctivitis patients are mostly found in the first decades of life.[7]

Gender is one of the predisposing factors where the highest prevalence distribution of vernal conjunctivitis patients is male.[10] Ahmed et al. stated that sex differences had been observed and men represented 63.3% of all vernal conjunctivitis study subjects.[11] This result matches this study in that the majority of patients were male, with a proportion of 66.67% or two-thirds of all research subjects. Significant differences between sexes confirm that hormonal factors play a major role in causing vernal conjunctivitis.[3]

Vernal conjunctivitis is a clinical form of allergic conjunctivitis in which IgE-mediated hypersensitivity mechanisms play an important role in its pathogenesis. This statement is also supported by previous studies which stated that patients with vernal conjunctivitis commonly have a family history of atopic or are influenced by other atopic conditions, for example house dust mites and pollen, or by other systemic allergic factors such as allergic rhinitis, eczema, and asthma. It is also related to the fact that systemic allergic factors have a similar immunopathology to vernal conjunctivitis.[12] However, the study of Sacchetti et al. showed that approximately half of the patients with vernal conjunctivitis have a negative allergic test, suggesting that other pathogenic mechanisms participate in the disease's inflammatory reaction.[13] This study's result aligns with the previous one, which found that a history of atopic allergies was not a significant factor in the appearance of vernal conjunctivitis exacerbations. Moreover, this study was found that 25.64% of patients had a history of atopic such as allergies

to sunlight and dust. Di Zazzo et al. also found that 23.07% of vernal conjunctivitis patients had a history of atopic allergies.[14] Although there is a possibility of patient cluelessness regarding the allergic history that is not registered in the electronic medical record data, several other factors that may be involved in the pathogenesis of vernal conjunctivitis can help clarify the result of this study, for example imbalance of innate immunity, hormonal changes, genetic susceptibility, and neurogenic factors.[13,15,16]

In this study, 77.78% of vernal conjunctivitis patients lived and came from Bandung. Cicendo Eye Hospital is a national referral hospital located in Bandung, West Java which makes it more accessible for patients living in Bandung compared to those referred from other cities. Environmental factors, including climate, temperature, or air pollution, in Bandung were also considered to play a significant role in the incident of vernal conjunctivitis. The results of the International Study of Asthma and Allergies in Childhood (ISAAC) studies indicated that the sunlight intensity, current of air, and other climate factors were mostly associated with a higher prevalence of this disease in each patient region.[17]

Vernal conjunctivitis has different types and characteristics in each country with various manifestations. The palpebral type is most often found in European and American countries, while the limbal type is more dominant in central and southern African countries.[11,15] This study shows that most of the patients with vernal conjunctivitis in tropical countries have the palpebral type, which is 72.64%, followed by the mixed type and the limbal type. The cobblestone papillae were found as the most common clinical sign in this study. These results were also mentioned by another study conducted by Nagrale et al. in India, also a tropical country, and stated that the palpebral type (48.75%) is also the most common type of vernal conjunctivitis.[3]

Red (76.06%), itchy eyes (63.24%) followed by a burning sensation (29.91%) were this study's three most common symptoms. A previous study by Ahmed et al. indicated that itching and burning sensations (100%) were observed in all cases.[11] Because most of the patients studied were follow-up patients, it was suspected that other complaints, such as watery, blurry eyes, or discharge, were no longer felt. In contrast to other forms of allergic conjunctivitis, the clinical symptoms of vernal conjunctivitis can cause complications that may threaten the patient's vision.[2,3,18]

Seeing that UCVA can be a parameter of the severity of vernal conjunctivitis, a study by Bangal et al. stated that 82% of vernal conjunctivitis cases have good UCVA ranging from 6/6 to 6/9 in the right and left eyes.[16] This study has a similar result in which 69.66% of eyes had good vision in the range of 6/6 to 6/18. Good visual acuity results might indicate that this study has more vernal conjunctivitis patients with no complications (60.26%).

Complications usually have different rates in each case of vernal conjunctivitis. In the present study, shield ulcers were found in 12 eyes (5.12%) and superficial punctate keratitis in 76 eyes (32.48%). Other studies show a little bit lower frequency of corneal complications. Ahmed et al. stated that superficial punctate keratitis was present in 6.7% of the cases, whereas there were no cases with shield ulcers.[11] Prolonged use of topical steroids, with a duration of use exceeding 6 months, can also lead to serious treatment-related complications, such as glaucoma, cataract, and secondary infections. This could be due to develop acute rise in intraocular pressure (IOP) and permanent trabecular meshwork damage.[10,19] Persistent elevated IOP may occur depending on the duration of use, the route of administration, and the type of steroid. This study uncovered 22 eyes (9.41%) with secondary glaucoma and 7 eyes (3.01%) with cataract associated with previous long-term steroid use.

CONCLUSION

After conducting a study on 117 vernal conjunctivitis patients at Cicendo National Eye Hospital in 2022, clinical features were found with complaints of red and itchy eyes due to manifestations of allergic reactions. The palpebral type is the most common type. However, this study did not assess the severity of vernal conjunctivitis as a variable. Further research is needed to assess patient's varying degrees of severity, the correlation between certain specific genetics related to the disease, as well as other factors in more detail with vernal conjunctivitis recurrence in Indonesia.

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ORIGINAL ARTICLE

BEVACIZUMAB VS RANIBIZUMAB IN MACULAR EDEMA DUE TO RETINAL VEIN OCCLUSION: SHORT-TERM OUTCOMES

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ABSTRACT

Introduction: *Bevacizumab or Ranibizumab was widely used as therapy for macular edema (ME) in retinal vein occlusion (RVO) and diabetic retinopathy. The purpose of this study was to comparing short-term outcomes for patients who received intravitreal Bevacizumab (IVB) injection or Ranibizumab (IVR) for ME due to RVO*
Methods: *This was observational, cross sectional study comparing patients received IVB or IVR. Primary outcomes data (visual acuity and central macular thickness/CMT) and secondary outcomes data (number injection and intra ocular pressure/IOP) were collected at baseline and 3 months after injection*
Discussion: *There were 4 eyes in each group. There were no significant difference in mean change of visual acuity (-0.275±0.25 vs -0.15±0.5 logMAR; p=0.676) and CMT (-171.50 ±129.08 vs -98.25±37.67 um; p=0.345) in IVB vs IVR groups. There were also no significant difference in mean change of IOP (2±2.16 vs 2±4.69 mmHg; p=1) and number of injection (2.25±0.50 vs 1.75±0.9; p=0.401) in both groups.*
Conclusion: *In short-term both IVB and IVB have relative similar outcomes on increasing visual acuity and decreasing CMT in ME due to RVO*

Keywords: *vein occlusion, macular edema, macular thickness, visual acuity*

INTRODUCTION

Retinal vein occlusion is the second most prevalent retinal vascular disease, after diabetic retinopathy, affecting an estimated 16 million people worldwide.[1] Branch retinal vein occlusion (BRVO) is the most prevalent type compared to central retinal vein occlusion (CRVO) which is 0.44% vs 0.08%.[1,2] CRVO is caused due to thrombosis in the central retinal vein as it passes through the lamina cribrosa, whereas BRVO is caused due to venous thrombosis in the artery venosus crossing where arteries and veins have the same vascular membrane.[3,4]

The development of ME is the most important cause of visual impairment in all forms of RVO. Retinal ischemia resulting from circulatory stasis because of venous obstruction promotes the production of VEGF-A, leading to increased vascular permeability and, finally edema.[5,6]

Intravitreal injections for anti-VEGF therapy are the standard care for ME occurring after RVO. Ranibizumab (Patizra) [0.5 mg/0.05 mL] and bevacizumab (Avastin) [1.25 mg/0.05 mL] are anti-vascular endothelial growth factor inhibitors given by a repeated intravitreal injection to treat MO due to RVO. Bevacizumab, a humanized fulllength antibody,

currently available off-label for this indication; while ranibizumab, a humanized high-affinity antibody fragment that targets all isoforms of VEGF-A, has the clearence for ME cases.[7,8] Several study demonstrated that intravitreal injection of Bevacizumab or Ranibizumab resulted in significant functional and anatomical improvements in patients with RVO.[9-11] There are two points of ME therapy in RVO which are improving visual acuity and reducing macular thickness. The purpose of anti-VEGF therapy is to decreasing the levels of VEGF resulting decreasing the macular edema and consequently improving visual function.

Whereas other study comparing Bevacizumab and Ranibizumab for ME in RVO in long term outcome,[13-15] our study focusing on short-term outcome, particularly in 3 moths after first intravitreal injection of anti VEGF.

METHODS

This was a retrospective study of macular edema patients due to RVO treated with intravitreal bevacizumab or ranibizumab injection. The data collected from 2021 until 2022 at Santosa Hospital and Karisma Cimareme Hospital.

The inclusion criteria for this study were foveal-involved macular edema due to RVO, onset of symptoms not more than 6 months duration, and at least 30 years old. Exclution criteria were injection of any other intravitreal drug during study period, history of intraocular surgery in the study eye during the study period, prior anti VEGF or corticosteroid intravitreal use in the study eye within 3 months, presence of any other macular pathology (diabetic retinopathy, myopic choroidal neovascularization, age-related macular degeneration), senile cataract that resulted in poor image quality, coexisting ocular disease (i.e., epiretinal membrane or glaucoma)

Patients were divided into 2 groups, bevacizumab and ranibizumab injection therapy. Patients were follow up for a period of 3 months. All patients received a complete ocular examination, including visual acuity, intraocular pressure (IOP) examination, slit lamp biomicroscopy examination, indirect funduscopy, and CMT measurements by spectral-domain optical coherence tomography (SD-OCT) (Zeiss Cirrus). BCVA was measured with a standard Snellen chart at 6 m and converted to logMAR visual acuity for statistical analysis.

The primary outcomes after 3 months folow up were the mean change from baseline of visual acuity and CST assessed by SD-OCT from both groups. The secondary outcomes were the difference of mean number injections and the difference of mean change from baseline of IOP from 2 groups.

Statistical analyses performed using R Statistical Software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria).

There was no statistical difference between Bevacizumab group and ranibizumab group in baseline data, including age, gender, duration of symptoms, diabetes, hypertension, hypercholesterol, smoking habits, lens, diagnosis, additional laser retina and number of injection. There was also no statistical difference in baseline of visual acuity, intraocular pressure and central macular thickness between two groups. (Table 1)

Table 1. Patients demographics and characteristics

	Bevacizumab Group (N=4)[1]	**Ranibizumab Group (N=4)[1]**	***p* value [2]**
Age, years	50 (8.16)	43.25 (9.03)	0.310
Sex,			1
Male	3 (75%)	2 (50%)	
Female	1 (25%)	2 (50%)	
Duration of symptoms, week	3.50 (1)	2 (1.41)	0.139
Diabetes	0 (0%)	0 (0%)	1
Hypertention	4 (100%)	4 (100%)	1
Systolic	164 (15.17)	158.75 (14.68)	0.637
Diastolic	101.75 (7.27)	96.75 (9.07)	0.424
Hypercholesterol	0 (0%)	1 (25%)	1
Smoking	3 (76%)	1 (25%)	0.486
Lens			1
Phakic	3 (75%)	4 (100%)	
Pseudophakic	1 (25%)	0 (0%)	
Diagnosis			1
BRVO	2 (50%)	3 (75%)	
CRVO	2 (50%)	1 (25%)	
Additional Laser Retina	1 (25%)	0 (0%)	1
Visual acuity baseline, logMAR	0.73 (0.33)	0.70 (0.23)	0.906
IOP Baseline, mmHg	14.25 (1.26)	14.75 (1.50)	0.628
CMT baseline, *u*m	430.50 (137.01)	395.25 (46.93)	0.654
Number of injection	2.25 (0.50)	1.75 (0.96)	0.401

[1]Mean (SD); n/N (%); [2]Calculated using t-test for continous variable and Fisher-test for categorical variable; [3]Hypertension if systolic ≥140 mmHg and diastolic ≥90 mmHg;
[4]CMT=central macular thickness

Mean visual acuity at baseline and month 3 in IVB group was 0.73±0.33 LogMAR (range: 1.2-0.5 LogMAR) and 0.45 ±0.24 LogMAR (range: 0.7-0.2 LogMAR) repectively. Mean visual acuity at baseline and month 3 in IVR group was 0.70±0.23 LogMAR (range:

0.9-0.5 LogMAR) and 0.55±0.41 LogMAR (range: 0.9-0.1 LogMAR) respectively. There was no statistical significant difference change in visual acuity between 2 groups. (Table 2)

Although there was a decrease in CMT in the 3rd month, there was no significant difference in the change in CMT between 2 groups (-171.50±129.08 um vs -98.25±37.67 um). (Table 2) Mean CMT at baseline and month 3 in IVB group was 430.50±137.01 um (range: 336-632 um) and 259±18.30 um (range: 240-280 um) respectively. Mean CMT at baseline and month 3 in IVR group was 395±46.93 um (range: 336-445 um) and 297±59.12 um (range: 248-325 um) respectively.

Table 2. Clinical Outcome

	Bevacizumab Group (N=4)[1]	**Ranibizumab (N=4)[1]**	***p* value[2]**
Change in visual acuity, (logMAR)	-0.275 (0.25)	-0.15 (0.5)	0.676
Change in CMT, (um)	-171.50 (129.08)	-98.25 (37.67)	0.345
Change in IOP, (mmHg)	2 (2.16)	2 (4.69)	1

[1]Mean (SD); [2]calculated using t-test

The same thing happen with change in IOP between 2 groups. There was only 2 mmHg increase in IOP in IVB or IVR groups (Table 2) without significant difference among 2 groups.

Figure 1. Graphs of mean changes in visual acuity and mean change in CMT from baseline to 3 months from IVB and IVR groups

DISCUSSION

Although the prevalence of RVO is more prevalent at the age of more than 65 years, in this study a younger age was obtained.[16] The Beijing Eye Study conclude that patients under 45 years old can also develop an RVO.[17] RVO is also more common in males and BRVO is 4-6 times more common than CRVO in other study the BRVO. Both condition were seen in this study.

There are several systemic diseases as risk factors for RVO such as hypertension, diabetes, and hypercholesterolemia.[18] In this study it appears that hypertension and hypercholesterolemia are risk factors for RVO. Cigarete smoking increases risk of RVO and most of the participants in this study were active smooker.[18,19]

There were 3 Randomized Controlled Trial (RCT) study comparing bevacizumab and ranibizumab in macular edema due to RVO, BRVO or CRVO or both. The final results of all of the study were 6 months (change in visual acuity and change in CMT in 6 months of therapy).[20-22] Our study concluded the final result in just 3 months after intravitreal injection. IVB is noninferior to IVR for patients with DME resulting from RVO after 6 months treatment in The Bevacizumab to Ranibizumab in Retinal Vein Occlusions (BRVO) sudy. The VA improved for IVB and IVR were 15.3±13 letters and 15.5±13.3 respectively. Change in CMT were 287±231.3 $\boldsymbol{u}$m and 300.8±224.8 $\boldsymbol{um}$ respectively.[20]

Similar conclusion from the Bevacizumab versus Ranibizumab in Branch Retinal Vein Occlusion (MARVEL) study and the Bevacizumab versus Ranibizumab in Treatment of Macular Edema From Vein Occlusion (CRAVE) study.[21-22] Both study found a similar effect on improving visual acuity after 6 months therapy. Mean CMT reduction between IVB and IVR in CRAVE study were 212.6 $\boldsymbol{u}$m and 243.8 $\boldsymbol{u}$m respectively while in MARVEL study were 201.7±166.2 $\boldsymbol{u}$m and 177.1±122.3 $\boldsymbol{u}$m respectively. In CRAVE study the VA gain were 0.33 logMAR for IVB and 0.34 logMAR for IVR, while in MARVEL study the mean gain BCVA were +15.6 letters for IVB and +18.1 letters for IVR.[21-22]

Increase in ocular volume or pharmacologic drug properties of anti VEGF injection could elevate the IOP wheither acute or sustained rise in IOP. Although the incidence of this ocular hipertension is low after a single or multiple IVB and/or IVR, clinician must aware cause it could end up as glaucoma or impair retinal blood flow.[23-25] In this study there was no significant changes in IOP between IVB and IVR eventhough we didn't check the effect on the mean ocular perfusion pressure (MOPP).

In BRAVO and CRUISE study, IVR was given monthly for 6 months then given as needed for 1 year which were 2.8 addittional injection and 3.6 additional injection for BRAVO and CRUISE respectively.[26-28] In real-world study, anti-vegf wheither bevacizumab or ranibizumab or aflbercept was administered 5-7 times yearly.[29] Our research cut-off point was the first 3 months after the first anti-VEGF injection. In those 3 months it was found that only about 2 anti-VEGF injections were given both in IVB and IVR. The next injection will still be given according to the development of macular edema.

This study, although both showed a decrease in CMT for the IVB and IVR groups, showed a lower decrease in CMT compared to the other three studies. This is reasonable because the CMT measurement was carried out only within 3 months after the injection. The same result of this study also occurred in the measurement of visual acuity after 3 months after the IVB or IVR injection. There was an increase in visual acuity but not as dramatic as the other three studies above.

Major limitation of this study included the small sample size. To overcome this problem, future studies should include more subjects in each group or conduct the RCT studies.

CONCLUSION

As the conclusion from this study that in the initial 3 months after injection, IVB and IVR gave the same results in terms of increasing visual acuity and decreasing CMT in patients with macular edema due to RVO.

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ORIGINAL ARTICLE

INSIGHTS INTO PRIMARY OPEN-ANGLE GLAUCOMA PATIENTS: UNVEILING DEMOGRAPHIC, CLINICAL, AND THERAPEUTIC PROFILES IN A LEADING TERTIARY REFERRAL HOSPITAL IN YOGYAKARTA

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ABSTRACT

Introduction: *Primary open-angle glaucoma (POAG) is the primary cause of irreversible blindness in adults worldwide. The characteristics of glaucoma patients and their response to therapy may differ by institution, region, and country. This study aimed to describe the demographic, clinical, and therapeutic aspects of POAG patients at Dr. Sardjito General Hospital Yogyakarta.*

Methods: *This study included POAG patients who underwent full clinical ophthalmologic evaluations at Dr. Sardjito General Hospital Yogyakarta from January to December 2021. Characteristics such as age at presentation, sex, residence, visual acuity, intraocular pressure (IOP), cup-to-disc ratio (CDR), laterality of affected eyes, Humphrey field analyzer-measured mean deviation (MD), and pattern standard deviation (PSD), medical and surgical treatment were recorded retrospectively.*

Results: *Data from 253 POAG patients were collected, the mean age was 52±17.15 years old and the female sex was more common at 58%. The mean IOP was 16.49±8.02 mmHg, and the mean CDR was 0.68±0.18. The mean refractive errors of all eyes were -0.64±0.22 dioptres (D), with 63% of eyes had good visual acuity (6/12 or better), 19% had moderate visual acuity (6/15 to 6/50), and 18% had poor visual acuity (count fingers to no light perception). Furthermore, the mean MD and PSD were -8.89±12.01 dB and 4.73±3.52 dB, respectively. Of all patients, 81% received medication only while 19% received medication and surgical intervention. Trabeculectomy was the most common surgery performed (94%).*

Conclusion: *POAG is generally a bilateral disease and occurs mostly in middle age population. Overall, trabeculectomy was the most common surgery performed in POAG patients.*

Keywords: *glaucoma, epidemiology, intraocular pressure*

INTRODUCTION

Visual impairment is one of the health problems causing huge burden globally. Glaucoma is the third cause of blindness after cataracts and refractive disorders.[1] The number of glaucoma patients are approximately 76 million worldwide, according to data from population-based studies.[2]

Glaucoma is a type of optic neuropathy in which the retinal ganglion cells are progressively destroyed in a distinctive pattern, leading to increased loss of optic nerve fibers in a typical pattern, resulting in a distinctive pattern of optic nerve head cupping and visual field loss. [3,4] Primary open-angle glaucoma (POAG) is the predominant subtype of glaucoma and

affects 68.56 million individuals worldwide. POAG tends to be idiopathic. The patient has gradual visual field loss but does not appear with acute pain, red eyes, or rapid visual loss.[5]

Treatment for glaucoma patients currently relies on maintaining low intraocular pressure (IOP), an effective method of preventing glaucoma progression. However, recent investigations have shown that glaucoma is a multifactorial disease, and that its complicated causes and progression can affect treatment efficacy. Therefore, decisions on treatment for patients with progressive glaucoma must take into consideration the background of the patient and the type of glaucoma.[6]

Epidemiological data regarding the POAG patients in Yogyakarta is still limited. Therefore, there is a need for more sources of information on the profiles of glaucoma patients in order to better understand patient characteristics. This study was conducted to investigate the characteristics of POAG patients in Dr. Sardjito General Hospital Yogyakarta from January to December.

METHODS

This study used a retrospective descriptive design. Data on POAG patients who underwent full clinical ophthalmologic evaluations to Outpatient Clinic of Dr. Sardjito General Hospital from January to December 2021 were collected in this study. These ophthalmologic evaluations included testing for visual acuity, refractive error and intraocular pressure, as well as slit lamp and fundus examinations. Standard automated perimetry was performed with the Humphrey field analyzer (HFA; SITA standard 24-2 or 30-2). Best-corrected visual acuity was measured with a decimal visual acuity chart. The spherical equivalent, determined as spherical power plus half the cylindrical power, was used to represent refractive error.

The data were obtained from medical records, including age at presentation, sex, residence, visual acuity, intraocular pressure (IOP), cup-to-disc ratio (CDR), laterality of affected eyes, Humphrey field analyzer-measured mean deviation (MD), and pattern standard deviation (PSD), medical and surgical treatment. This study used secondary data in the form of medical records. The exclusion criteria were medical records with incomplete data.

RESULTS

The demographic characteristics of 253 patients with POAG included in this study are shown in Table 1. The patients had a mean age of 52±17.15 years old. The sex ratio was 107:146 (male:female). Sixty five percent patients were originated from Yogyakarta, 25% were from Central Java, and 10% from outside Yogyakarta and Central Java. According to the location of

the eyes affected by these disorders, in most cases, both eyes were affected (bilateral).

Table 1. Demographic data of POAG patients

Variable	
Age (years)	
Mean±SD	52±17.15
Gender, number of patients (% of total)	
Male	107 (42)
Female	146 (58)
Residence, number of patients (% of total)	
Yogyakarta	164 (65)
Central Java	64 (25)
Others	25 (10)
Laterality of affected eyes (% of total)	
Unilateral	21 (8)
Bilateral	232 (92)

Note: POAG, primary open-angle glaucoma.

Table 2 shows that the mean IOP was 16.49±8.02 mmHg, and the mean CDR was 0.68±0.18. Furthermore, the mean MD and PSD were - 8.89±12.01 dB and 4.73±3.52 dB, respectively. The mean refractive errors of all eyes were -0.64±0.22 dioptres (D).

Table 2. Clinical characteristics of POAG patients

Variable	(Mean±SD)
IOP (mmHg)	16.49±8.02
CDR	0.68±0.18
MD (dB)	-8.89±12.01
PSD (dB)	4.73±3.52
Refractive errors (D)	-0.64±0.22

Note: IOP, intraocular pressure; CDR, cup-to-disc ratio; MD, mean deviation; PSD, pattern standard deviation; D, dioptres.

Table 3 shows that 63% of eyes had good visual acuity (6/12 or better), 19% had moderate visual acuity (6/15 to 6/50), and 18% had poor visual acuity (count fingers to no light perception). Of all patients, 81% received medication only while 19% received medication and surgical intervention. Trabeculectomy was the most common surgery performed (94%) (Table 4).

Table 3. Best-corrected visual acuity of POAG patients

Visual acuity	Number of eyes (%)
6/12 or better	319 (63)
6/15-6/60	96 (19)

CF-NLP	91 (18)

Note: CF, count fingers; NLP, no light perception;

Table 4. Treatment modality and ocular surgeries performed in POAG patients

Treatment	Number of patients (%)
Modality	
Medication only	206 (81)
Medication + surgery	47 (19)
Type of ocular surgery	
Trabeculectomy	44 (94)
Cyclocryotherapy	2 (4)
GDD Implant	1 (2)

Note: GDD, glaucoma drainage device

DISCUSSION

POAG is a chronic, progressive, anterior optic neuropathy accompanied by cup-to-disc atrophy, decreased field of view, and systemic conditions. Increased intraocular pressure is the main risk factor for the occurrence of POAG. Higher IOP is more likely increasing the progression of optic disc damage.[7]

Demographic consideration shows that POAG is predominantly seen in older people as seen in this study with a mean age of 52 years. Study found older age to be a risk factor for this disease.[2,8] Age group of 40 years and above should be targeted for public enlightenment and screening for glaucoma especially in low-resource countries as this will enhance early detection and subsequent management of POAG. A study in India on the characteristics of glaucoma obtained a comparison between men and women of 1.03:1. There was no significant differences by sex.[9] It can be concluded that POAG can affect all genders.

POAG is generally a bilateral disease that attacks adulthood. At least one eye must have typical damage to the optic nerve or changes in visual field characteristics.[7] From the study, the data on the number of affected eyes in POAG were mostly bilateral. POAG usually occurs bilaterally but has a different degree of severity in each eye.[3]

The CDR findings showed a mean of 0.68. This means that advanced optic nerve loss had occurred before presentation. Besides papillary and peri-papillary changes, CDR is the most important parameter in the evaluation of glaucoma. Even though CDR assessment is useful in characterizing damage from glaucoma, it could manifest inter-observer variations and even variations by the same observer in asserted value on repeat observations.[10]

This study obtained the results of the visual range of POAG patients were normal to mild visual impairment. It was because POAG slowly affected peripheral vision where visual acuity could be normal and furthermore central vision disturbance could occur in the final stage

of the disease. [11] Global indices such as MD and PSD allow clinicians to determine easily whether visual field deterioration has occurred. MD is the weighted mean value of all test points in the total deviation plot, which is based on the deviation from age-matched normal values. PSD values are calculated based on the variation from the normal, age-corrected hill of vision involving the total deviation plot. PSD is a metric that indicates a difference in the sensitivity of adjacent tested points. In glaucoma patients, as irregular depression of visual field sensitivity progresses, PSD values increase. [12] From visual field assessment using HFA, this study showed that the mean MD and PSD were -8.89 dB and 4.73 dB, respectively. Thus, the number of glaucoma patients with normal visual acuity have possibility in decreasing of visual field.

Intraocular pressure lowering can be achieved by medication, laser or surgery (either alone or in combination).[13] Topical IOP-lowering medications have long been the primary POAG treatment and widely used.[14] While topical medications are effective, there are potential pitfalls associated with their use. A significant proportion of patients require more than one type of drop. As glaucoma is a chronic progressive disease, instillation of medication becomes a lifelong commitment, and patient compliance becoming essential for successful management.[15] Trabeculectomy was the most common surgery performed in this study, Trabeculectomy remains the most common initial operation for patients with advanced glaucoma in most countries Trabeculectomy lowers IOP by creating a new drainage site for aqueous humour outflow underneath the conjunctiva. Glaucoma drainage device, or tube surgery, has traditionally been reserved to treat patients with refractory cases of glaucoma or at high risk of failure. [13,16]

Limitations of this study are the difficulties to access the medical record and limited time. Further and more complete research is needed with a larger sample population.

CONCLUSION

POAG is generally a bilateral disease and occurs mostly in middle age population. Overall, trabeculectomy was the most common surgery performed in POAG patients. It is imperative to provide reliable and integrated knowledge about eye diseases, especially glaucoma, to increase public awareness of this disease.

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CASE REPORT

INTERNUCLEAR OPHTHALMOPLEGIA IN MULTIPLE SCLEROSIS PATIENT

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ABSTRACT

Introduction: *Internuclear ophthalmoplegia (INO) characterized by impaired adduction of the affected eye caused by a lesion in the medial longitudinal fasciculus (MLF). The common cause of INO is demyelinating disease including multiple sclerosis. INO arguably the most discrete localizing sign in medicine, has considerable value in predicting multiple sclerosis. Due to its high spatial resolution, MRI has allowed us to depict in vivo the anatomic organization of the human oculomotor nerve complex, the MLF, and related structures in the brainstem.*
Case Report: *A 48-year-old female presented with blurred vision of both eyes for 2 weeks, but then slowly resolved. Best corrected visual acuity presentation on both eyes were 20/20 with normal intraocular pressure (IOP). Adduction deficit observed on the left eye with no nystagmus. Convergence are not impaired in both eyes. Anterior segments was normal except minimal lens cloudiness in both eyes. Funduscopic examination result also within normal limit. Patient had undergone Computerised Tomography (CT-Scan) and the result was normal, no ischemic area or Space occupied lesion (SOL) or intracranial bleeding were found. Brain MRI showed bilateral optic perineuritis and multiple lesion in bilateral frontoparietalis and in the left side of the pons suggested multiple sclerosis.*
Discussion: *Impairment of adduction movement on the patient's left eye caused by demyelinating plaque related multiple sclerosis on the left side of the pons as shown MRI imaging. Management in this patient is based on the underlying condition.*
Conclusion: *Internuclear ophthalmoplegia in this cases maybe caused by lesion in the medial longitudinal fasciculus could be related with multiple sclerosis.*
Keywords: *Internuclear ophthalmoplegia, Medial longitudinal fasciculus, Multiple sclerosis*

INTRODUCTION

Internuclear ophthalmoplegia (INO) is a specific gaze abnormality characterized by impaired adduction of the affected eye with abduction nystagmus of the contralateral eye. It results from a lesion in the MLF in the dorsomedial brainstem, tegmentum of either the pons or the midbrain. The INO can be unilateral or bilateral and can be an isolated finding or may be associated with other brainstem signs and symptoms.[1]

As the MLF is a highly myelinated tract within the brainstem, the most common cause of INO in young people is demyelinating disease secondary to multiple sclerosis (41-54%). Other etiologies can include cerebral/brainstem vascular accidents (23-27%), infection (5-14%), head trauma (6%), brainstem tumour (4-5%), systemic lupus erythematosus (<5%),

nutritional and metabolic disorders, or degenerative disorders.[2]

Internuclear ophthalmoplegia, arguably the most discrete localizing sign in medicine, has considerable value in predicting multiple sclerosis or stroke, depending on whether the INO is bilateral or unilateral and on whether the patient is young or old.[3] Multiple sclerosis is a chronic inflammatory disease characterized by Central nervous system (CNS) plaques composed of inflammatory cells and their products, demyelinated and transected axons, and astrogliosis in both white and gray matter.[4]

We present a case of a patient with left eye Internuclear ophthalmoplegia (INO) in multiple sclerosis patient

CASE ILLUSTRATION

A 48-year-old female referred from Neurology department with blurred vision on both eyes for 2 weeks. The patient have been treated by neurologist with Gamma aminobutyric acid, Calcium channel blockers (CCBs), Angiotensin receptor blockers (ARB), and Biguanide. No history of trauma. The patient has uncontrolled Diabetes Mellitus since 2 years ago and uncontrolled hypertension since 10 years ago.

Best corrected visual acuity on both eyes were 20/20 with normal IOP. Slit lamp examination of both eyes were within normal except minimal lens cloudiness ODS. Eye movement was unremarkable on right eye, while left eye had adduction deficit with no restrain while convergence. there was no nystagmus observed. Other neuro ophtalmology examination including color test dan visual field were normal.

Figure 1. Photographs of eye movement show adduction limitations of the left eye

Patient had undergone Computerised Tomography (CT-Scan) and the result was normal, no ischemic area or Space occupied lesion (SOL) or intracranial bleeding were found.

Thus, we ordered MRI brain and showed bilateral optic perineuritis, multiple lesion in bilateral periventricular lateralis, juxtacortical region, bilateral frontoparietalis and in the left side of the pons suggested multiple sclerosis.

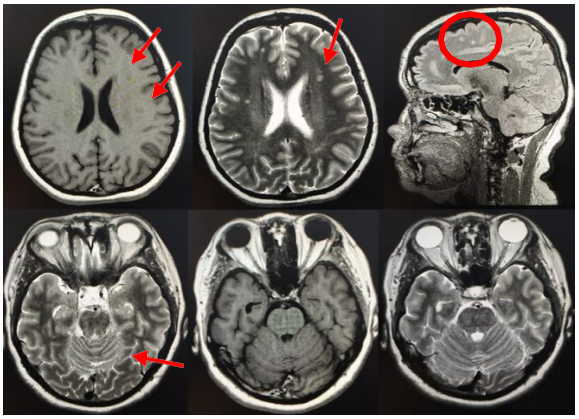

Figure 2. Brain MRI showed multiple lesions suspect multiple sclerosis (red arrows)

The patient then diagnosed OS Internuclear Ophthalmoplegia with multiple sclerosis and we collaborate Neurology department for Multiple sclerosis treatment.

DISCUSSION

The brainstem pathways for horizontal eye movements start from the abducens nucleus as the horizontal gaze center taking signal from the Paramedian Pontine Reticular Formation (PPRF). These pathways continue to the ipsilateral abducens nerve (cranial nerve VI) and the contralateral oculomotor nerve (cranial nerve III) through the MLF and end in conjugate horizontal eye movement in the ipsilateral direction to the side of the abducens nucleus (figure 3).[7]

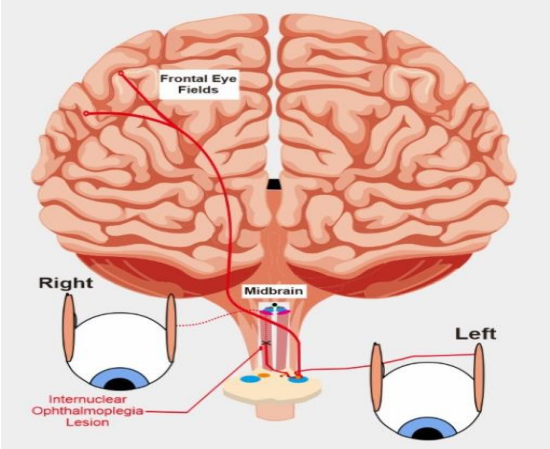

Figure 3. Neurological pathway for INO

INO is the clinical finding most commonly associated with lesions affecting the MLF on brain MRI. Thus, a lesion confined to the MLF disrupts the signal to the contralateral oculomotor nucleus and its activation of the medial rectus muscle.

Clinically, this results in preserved abduction of the contralateral eye with nystagmus, and weak or absent adduction of the ipsilateral eye.[8] However, depending on lesion location within the MLF, several specific neurologic manifestations may result.[9]

Our patient had an adduction under action on the left eye which was seen in eye movement test when she failed to move her eye to nasal. The affected eye adducts normally in convergence eye movement.[9] The ability to converge despite the absence of voluntary adduction indicates a more caudal lesion, with preservation of the medial recti subnuclei in the midbrain.[11] This finding distinguishes INO from the oculomotor nerve palsy.[12]

Patients with unilateral INO may have vertical diplopia due to a non-evident skew deviation, which can be relieved by using a small vertical prism. Skew deviation and Ocular tilt reaction (OTR) can be seen also with lesions independent of the MLF, for example, in the cerebellum or the thalamus. Tilt of the subjective visual vertical, the inner perception of verticality, is very often found in patients with MS.[13] In our patient, there is no vertical diplopia was found during examination.

Several pathologic studies have shown a clear anatomic relationship between the presence of lesions along the ipsilateral MLF and the presence of INO. Due to its high spatial resolution, MRI has allowed us to depict in vivo the anatomic organization of the human oculomotor nerve complex, the MLF, and related structures in the brainstem (typically white matter tracts have low signal intensity and nuclei have higher signal intensity). In patient with INO, MRI shown hyperintense lesions in the origin of the MLF on T-2 weighted images that were not detected using CT.[10]

In our patient, according to brain MRI that showed multiple lesion in bilateral periventricular lateralis, juxtacortical region, bilateral frontoparietalis and in the left side of the pons. This location could indicate damage to the abducens nucleus and the MLF it self. This finding consistent with the found in the patient which is ipsilateral adduction deficit of which the lesion was found (left side of the pons) and the multiple lession suggested to multiple sclerosis.[7]

Multiple sclerosis is a progressive central nervous system inflammatory disorder characterized by the accrual of white and gray matter lesions that exhibit varying degrees of inflammatory cell infiltration, demyelination, gliosis and neuroaxonal loss.[14]

The clinically isolated syndrome (CIS) is one of the most common presentations of MS and is characterised by an acute or subacute neurologic syndrome due to a solitary white matter lesion. INO is a brainstem CIS seen in approximately one-third of MS patients and can lead to a break in binocular fusion, diplopia, loss of depth perception, and reduction in quality of life.[14,15]

Treatment depends on the underlying cause. Acute strokes require hospitalization and neurological evaluation. Other pathologies require management by a physician (MS, infections, SLE). Most patients with demyelination, infectious, and traumatic etiologies show complete recovery. Patients with cerebrovascular disorders had a less favorable recovery. Recovery is said to be more likely if INO is isolated than if other neurological signs accompany it. According to some studies, recovery is also said to be less likely if there was a visible lesion causing internuclear ophthalmoplegia.[18] In our patient, we collaborate neurology departement to treat the multiple sclerosis as the underlying cause and no specific treatment from neuro ophthalmology division.

The majority of patients with persistent INO have minimal symptoms. Those with diplopia may benefit from botulinum toxin injections or Fresnel prisms. Surgical correction of strabismus may be used for patients with wall-eyed bilateral internuclear ophthalmoplegia.[18]

CONCLUSION

Internuclear ophthalmoplegia caused by lesion in the medial longitudinal fasciculus result in an adduction deficit could be related with multiple sclerosis. Management based on neurologist for multiple sclerosis treatment.

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CASE REPORT

CHALLENGE IN TREATING OPTIC NEURITIS IN PATIENT WITH CEREBRAL TOXOPLASMOSIS RELATED TO IMMUNOCOMPROMISED CONDITION

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ABSTRACT

Introduction: *This study aimed to discuss challenge in treating optic neuritis in a patient with cerebral toxoplasmosis related to an immunocompromised condition.*

Case Report: *A 28-year-old female complained of blurred vision and double vision 2 weeks before admission, accompanied by headache, low extremities weakness, dysphonia, and dysphagia. The visual acuity of both eyes was 6/30 and worsened to 6/60 in a couple of days. Anterior segment examination revealed anisocoria pupil, and RAPD was positive in the left eye. Funduscopic examination showed a blurry margin and hyperemia of the optic nerve head. There was impaired eye movement, indicating oculomotor and abducens nerve palsies. High titer of IgG Antibody Toxoplasma (264) and very low titer of CD4 (<50) with non-reactive HIV rapid test were found in laboratory findings. Multiple ring enhancement was shown in MRI finding. Unfortunately, the patient passed away during hospitalization due to respiratory failure.*

Discussion: *Toxoplasmosis-associated optic neuritis is rare and usually becomes potentially serious. Although parasite detection by microscopy and bioassay is considered the gold standard for the diagnosis of toxoplasmosis, clinical diagnosis relies more on serological examination methods. The high proportion of deaths from this disease is mostly caused by late diagnosis of the infection.*

Conclusion: *Optic neuritis that is accompanied by systemic disorders needs special attention and comprehensive treatment among multidisciplinary divisions, especially in the immunocompromised condition. Early detection and primary prevention are important to improve prognosis and survival rate.*

Keywords: *optic neuritis, cerebral toxoplasmosis, immunocompromised state*

INTRODUCTION

Optic neuritis is an important cause of potentially irreversible visual impairment.[1] Optic neuritis refers to inflammation of the optic nerve, which is a frequent cause of acute optic nerve injury in children and adults. Optic neuritis can affect any part of the nerve. When affecting the posterior portion of the optic nerve, the optic nerve papillae appear normal when the patient experiences vision loss (retrobulbar optic neuritis); when inflammation involves the anterior portion, the optic nerve papillae appear edematous (papillitis).[2,3]

The exact mechanism of acute optic neuritis has yet to be clearly identified. Optic nerve infiltration usually occurs along with neurological or systemic signs and symptoms.[4,5] Infections from bacteria, spirochetes, viruses, fungi, and protozoa (Bartonella, Rickettsia, Coxsackievirus B, human immunodeficiency virus (HIV), histoplasmosis, and toxoplasmosis) in the optic nerve

can cause optic neuritis.[2]

Toxoplasmosis is a central nervous system (CNS) infection caused by *Toxoplasma gondii* (*T. gondii*), and it can spread throughout the body.[6] Toxoplasmosis is a common infection whose prevalence is estimated at 30% worldwide.[7] Clinical manifestations that can arise in cerebral toxoplasmosis are headache, fever, hemiparesis, ataxia, cranial nerve disorders involving impaired ocular movement, seizures, as well as involuntary and rigidity movements. Clinical features of ocular toxoplasmosis are retinal scars, vitritis, optic neuritis, and retinal detachment. Toxoplasmosis is generally benign but has the potential to be severe in immunocompromised patients.[8]

The purpose of this case report is to discuss the diagnosis and prognosis of patients with bilateral optic neuritis with partial ophthalmoplegia caused by paresis of N.III and paresis of N.VI (multiple cranial nerve palsy) due to suspected cerebral toxoplasmosis with immunocompromised condition.

CASE ILLUSTRATION

A 28-year-old female patient from the Neurology Department with diagnosis Multiple cranial nerve palsy due to suspected neuromyelitis optica spectrum disorder (NMOSD) with differential diagnosed infratentorial Cerebral space occupying process (SOP) due to Primary cerebral tumor and metastatic process was consulted to Ophthalmology department because the patient complained of double and blurred vision 2 weeks before hospital admission.

The patient complained there was double and blurred vision, which was only felt when looking far away and waking up for 2 weeks before admission followed by glare and pain when looking. One week later patient complained of difficulty swallowing, shortness of breath, and cough. There were no complaints of red eyes, tearing, or muttering. Initially, the patient complained of hoarse voice and sore face followed by headaches and weakness in both legs 1 month. In the last 1 month, the patient also experienced weight loss. The patient's weight decreased by 10 kg within 1 month. There was no history of ocular trauma, eye surgery and spectacle use. There was no history of systemic disease and family history with same complained was denied. The patient had a history of keeping cats and dogs since childhood.

From general condition, the patient was completely conscious with normal vital signs. Vesicular breath sounds throughout the lung fields. Glove and stocking-type hypesthesia were found.

An examination of the cranial nerve at N. V showed corneal sensibility and sensory examination within normal limits. An examination of N. VII demonstrated UMN-type paresis

on the right side of the face. An examination of N. IX and X in the patient yielded positive dysphonia results. On examination of N. XII, UMN-type parese dextra (tongue atrophy) was found.

From ophthalmological examination, visual acuity in both eyes was 6/30, using the Snellen chart. It was found that the pupil size of the right eye was 3mm and the left eye was 5mm, the light reflexes of both pupils were positive but slower in the left eye, and there was a relative afferent pupillary defect (RAPD) in the left eye.

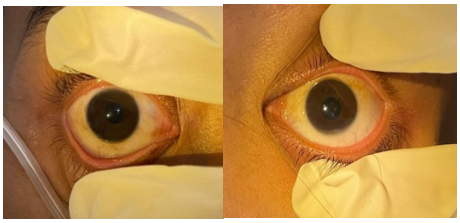

Figure 1. Anisocoria was noted. Dilated pupil in the left eye. No dyschromatopsia was noted.

Visual field using confrontation test revealed superotemporal defect on the left eye and superonasal in the right eye. The limitations of the eye movement of both eyes were seen on superotemporal, temporal, and inferotemporal directions.

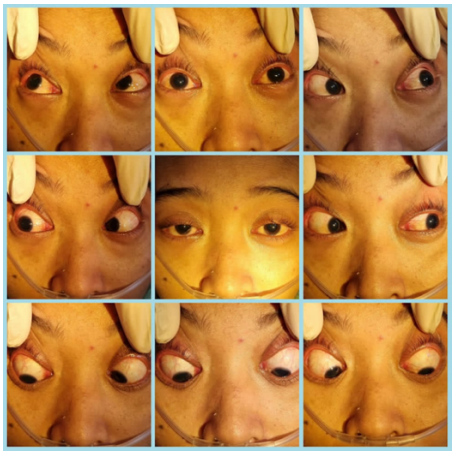

Figure 2. Eye movement examination: limitation of both eye movements seen on superotemporal, temporal, and inferotemporal directions

On funduscopic examination, fundus reflexes were positive in both eyes. The optic nerve got swelling and hyperemic in all quadrants, so the CD ratio was difficult to evaluate. There were no focal exudates, scar tissue, retinal hemorrhages, or vitritis in the vitreous.

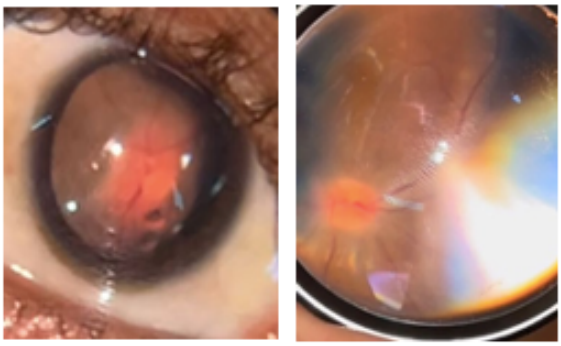

Figure 3. Fundus photos of both eyes. The margin of the N. II ODS optic nerve head appeared blurry.

Laboratory examination showed that Anti-CMV IgG was positive (95.7), Anti-HSV-1 IgM and IgG were positive (67/>200); Anti HSV-2 IgM was positive (110.5), Anti Rubella IgG was positive 32.55; VDRL was non-reactive, TPHA was non-reactive; Anti-Toxoplasma IgM was negative, Anti-Toxoplasma IgG was positive (0.488/264), and CD4 <50 but for HIV examination was non-reactive. This examination was carried out because there was a suspicion of an immunocompromised condition due to various infections found in the patient. The patient also underwent a chest X-ray examination, and an image of pneumonia was obtained.

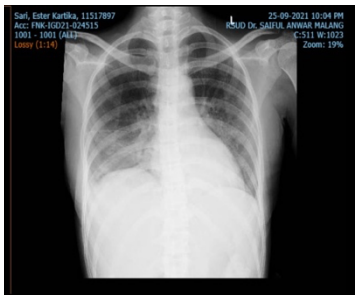

Figure 4. Chest X-ray image. Infiltrates were found in both lung fields.

A Head MRI with contrast on the 7th day of treatment showed the following results:

- Multiple intraaxial rim-enhanced lesions in bilateral fronto-temporoparietooccipital lobes, bilateral centrum semiovale, right corona radiata, bilateral external capsule, bilateral thalamus, mesencephalon, pons, cerebellum suspect et causa toxoplasmosis; and
- Looping of right AICA grade III with CHAVDA classification.

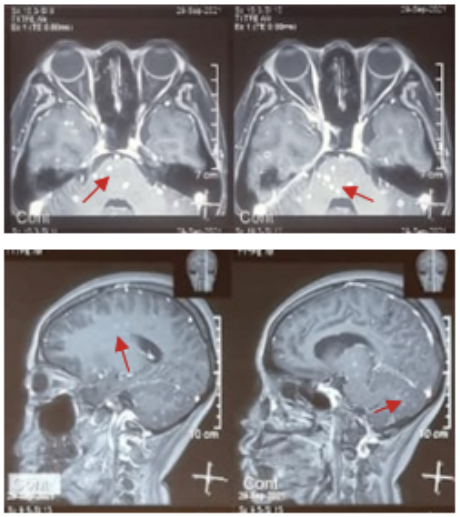

Figure 5. Head MRI examination result. Multiple ring enhancement was found in bilateral fronto-temporoparietooccipital lobes, bilateral centrum semiovale, right corona radiata, bilateral external capsule, bilateral thalamus, mesencephalon, pons, and cerebellum.

The patient's examination on the 10th day showed a decrease in visual acuity to 6/60 in both eyes. However, the other ophthalmologic status still showed the same results as the previous examination.

The patient was treated together with the neurology department and diagnosed with Multiple Cranial Nerve Palsy due to suspected Toxoplasmosis Cerebri dd Tuberculoma, Inferior paraplegia UMN Type due to suspected NMOSD dd Leptomeningeal Metastases, Hypokalemia, Leukocytosis and Immunocompromised state. The patient was given WidaKN2 infusion therapy for 2 cycles, followed by maintenance of Normal Saline 0.9 20 drops per minute, Paracetamol 3x500 mg orally, loading Pyrimethamine 200mg, and Clindamycin 4x600mg.

The patient was also consulted to Pulmonology and Respiratory Department and was diagnosed with Pneumonia (HAP) due to Acinetobacter baumannii and impending respiratory failure type 2. The patient was given oxygen via NRBM 8 lpm, Combivent nebulization 3x1, 2x80mg Gentamicin injection, methylprednisolone injection 1x31.25mg, Cefixime 2x200mg per oral for 7 days, Theophylline 2x1 per oral, and Codeine 3x10mg per oral.

Based on the history taking and examinations, the patient was diagnosed with ODS optic neuritis and optic neuropathy with partial ophthalmoplegia caused by paresis of N.III and paresis of N.VI (multiple cranial nerve palsy) with suspected toxoplasmosis and immunocompromised state with the differential diagnosis papiloedema due to increased intracranial pressure.

The patient received treatment of neuroprotectant from the neuro-ophthalmology division along with other therapies from the neurology and pulmonary disease department. The patient passed away on the 11th day of treatment, allegedly due to respiratory failure.

DISCUSSION

Optic neuritis a rare and uncommon manifestation of toxoplasmosis, which is characterized by a gradual loss of vision and enlargement of the optic nerve. In certain cases, it may also be accompanied by a macular star, known as neuroretinitis. Treatment typically leads to a favorable prognosis for optic neuritis. However, the presence of systemic abnormalities in the patient, such as cerebral abnormalities, toxoplasmosis cerebri, or immunocompromised conditions, can exacerbate the condition. The degree of visual impairment in patients with optic neuritis can range from near-normal acuity to no light perception.

This study demonstrates anisocoric pupil size in the right eye and relative afferent pupillary defect (RAPD) in the left eye. RAPD is a clinical indicator utilized to identify abnormalities in the pupillary pathway on the afferent side. Optic neuritis is one of the possible causes of this condition.[15]

Cranial nerve dysfunction can occur due to lesions in its course from the intrinsic brainstem to its peripheral pathways. Multiple cranial nerve dysfunction is defined as the condition where two or more cranial nerves are affected. Mehta et al. discovered that the abducens cranial nerve (VI) had the highest occurrence of involvement among cranial nerve, followed by the oculomotor (III) and trigeminal (V) cranial nerves. The most common cause of involvement was found to be infection.[16]

Optic disc swelling may be seen on funduscopic examination in some patients during the active phase.[3] If a clinician observes substantial inflammation of the optic disc, hemorrhage in the optic disc, or ocular inflammation, they should examine the possibility of infection. [1]

Toxoplasmosis-associated optic neuritis is uncommon and typically has the potential to be severe. A retrospective study conducted by Eckert et al. explained that of 928 patients only 51 eyes (5.03%) had optic nerve involvement. Out of the 51 eyes, 22 eyes (43.1%) exhibited optic neuritis accompanied by active lesions located distant from the papillae, whereas 18 eyes (35.3%) with optic neuritis with lesions close to the papillae, 8 eyes (15.7%) showed more than one type of lesion simultaneously. Of these 8 eyes, 6 eyes (75%) demonstrated distant active lesions associated with neuroretinitis, while the remaining two (25%) displayed active lesions near the papillae associated with neuroretinitis. Pure papillitis without retinal lesions only occurred in 3 (5.9%) out of 51 eyes.[17]

A reduction in CD4 count (<50) in this patient signifies an immunocompromised condition and increases the risk factor for reactivation of latent tissue cysts containing toxoplasma parasites due to immune system deficiencies. This reactivation contributes to the emergence of *T. gondii* infection which manifests as neurological symptoms, including headache, disorientation, drowsiness, reflex changes, seizures, and hemiparesis.[18] Examination of the cranial nerves in this patient showed a lesion in N. VII due to paresis on the right side of the face. In HIV, clinical manifestations occur when the CD4 lymphocyte count is <100 cells/ml. The most common manifestation of HIV is encephalitis. Encephalitis occurs in approximately 80% of cases. The initial symptoms that appear are a headache and a focal neurological deficit.[19]

The patient's physical examination revealed the presence of hypesthesia with the glove and stocking type. Martinot et al. and Matsuura et al. have also reported cases of toxoplasma with patient symptoms in the form of hypesthesia.[12,13] Toxoplasmosis cerebri typically results in unifocal lesions, with diffuse lesions being a rare incidence. Clinical symptoms depend on the location and number of lesions. The most frequently complained of symptoms include headache (49-63%), fever (41-68%), focal deficit (22-80%), seizures (19-29%), confusion (15-52%), ataxia (15-25%), lethargy (12- 44%), cranial nerve weakening (12-19%), and visual disturbances (8-15%). Other manifestations may include dysarthria, cognitive impairment, increased intracranial pressure, and involuntary movements.[14]

Serological tests to determine the cause of infection must be carried out according to the suspected etiology.[20] The patient's serological examination yielded positive results for toxoplasmosis infection. Toxoplasmosis is a life-threatening opportunistic infection in immunocompromised patients. Diagnosing *T. gondii* infection in immunocompromised patients can be challenging. Although parasite detection by microscopy and bioassay is considered the gold standard for the diagnosis of toxoplasmosis, clinical diagnosis relies more on serological examination methods.[21]

Acute viral infection is a rare cause of isolated optic neuritis. Herpes simplex virus (HSV) may be involved in cases of acute optic neuritis, many of which coincide with inflammation of the retina, brain, or eye. HSV optic neuritis can occur concurrently with or following HSV encephalitis or retinal necrosis.[1]

Primary infection with *T. gondii* might lead to clinical manifestations in the eyes.[8] Toxoplasmosis usually manifests in the second to fourth decades of life.[9] Patients with optic neuritis usually range in age from 20 years to 50 years, with a higher prevalence in women. Common symptoms include acute loss of vision, scotoma, impaired color vision, and pain felt

when moving the eyeball.[4]

The patient has a long-standing history of pet ownership, specifically cats and dogs, dating back to their childhood. Toxoplasmosis has a complex epidemiology. This parasite is capable of infecting almost all warm-blooded animals and has a two-host life cycle. Domestic cats and other members of the *Felidae* family are the definitive hosts. Non-*Felidae* species, including dogs and humans, are intermediate hosts for *T. gondii*. However, *T. gondii* can also undergo asexual reproduction in *Felidae* animals that operate as intermediate hosts.[10]

Hosts can contract infections by ingesting tissue that contains cysts or by consuming water or food contaminated with oocysts.[10] Humans can also become infected through consuming raw or improperly cooked meat containing infectious tissue cysts or through the consumption of sporulated oocysts in fruits and vegetables or water contaminated with cat feces.[8]

Groups of severely immunocompromised patients are susceptible to developing cerebral toxoplasmosis.[22] Toxoplasma gondii infection induces strong innate and adaptive immune responses. While the innate immune response is important for controlling the early stages of infection, the adaptive immune response is critical for limiting parasite replication during later stages. Although CD8 T cells play an important effector role in controlling chronic infections, their maintenance depends on the essential help provided by CD4 T cells. [23,24]

Radiological imaging of the brain frequently shows multiple (67%) or single (33%) brain lesions often associated with edema. There is a tendency for involvement of the basal ganglia, corticomedullary junction or cerebral white matter.[25] CT scans usually demonstrate bilateral, multiple, hypodense ring enhancing lesions with surrounding edema in 60% to 70% of patients. The lesion may be solitary in 27% of patients. If the CT scan is normal during initial screening, MRI is recommended because it is more sensitive and can detect additional lesions in some cases.[21] On MRI examination, toxoplasmic encephalitis is often characterized by multiple ring-enhancing lesions in the cortex and/or basal ganglia. Although these are the two most common sites for *T. gondii* lesions, they can also be found both supra- and infra-tentorially.[25]

The patient was previously diagnosed with multiple cranial nerve palsy and suspected NMOSD. The cause of optic neuritis can be from demyelinating optic neuritis, which eventually progresses to clinically definitive Multiple Sclerosis (MS), or from an immune-mediated demyelinating disease affecting the optic nerve as part of Neuromyelitis Optica Spectrum Disease (NMOSD). [26] However, in this patient, the diagnosis was more likely to be Toxoplasma because the clinical condition was more suggestive of toxoplasmosis.

The results of trials by Petzold et al. recommend intravenous steroids, not to improve clinical outcomes, but to accelerate functional recovery of vision.[28] Methylprednisolone IV (1,000 mg daily for 3 days) followed by oral prednisone (1 mg/kg/day for 11 days) has been reported to improve vision and better short-term functional recovery.[29]

The combination therapy of pyrimethamine, clindamycin and steroids to this patient is expected to improve the clinical condition. Pyrimethamine is a drug that is specific for the tachyzoite stage of toxoplasma and can penetrate brain parenchyma. Pyrimethamine has a synergistic effect when combined with clindamycin and sulfadiazine. This combination is recommended as first-line therapy for toxoplasmosis cerebri in HIV patients. This patient received a loading dose of Pyrimethamine 200mg and Clindamicyn 4x600mg orally.[30]

Thus, a wide spectrum of clinical manifestations is possible with this disease, and radiological imaging of the brain is indicated to evaluate empiric therapy, including assessing for deterioration on neuroimaging, in addition to the clinical deterioration that occurs.[31]

Since the patient's CD4 counts were low and the disease progression was very rapid, especially for ocular disorders, special and comprehensive monitoring and evaluation is required across all patient-care departments. Quick coordination throughout divisions is also needed in treating toxoplasmosis cerebri patients who are immunocompromised.

Although respiratory failure was eventually identified as the cause of the patient's death, other theories contend that primary *Toxoplasma gondii* infection in immunocompromised patients can cause fatal clinical outcomes.[8] The high proportion of deaths in this disease is mostly caused by late diagnosis of the infection. Mortality related to Toxoplasmosis Encephalitis in HIV patients is almost 100% if there is a delay in therapy.[32]

CONCLUSION

Optic neuritis accompanied by systemic abnormalities requires special attention and comprehensive multidisciplinary treatment. Toxoplasmosis infection in immunocompromised states is a life-threatening opportunistic infection. Toxoplasmosis papillitis is a rare and potentially serious condition, so early detection and primary prevention in immunocompromised patients is important to improve prognosis and survival rates.

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LITERATURE REVIEW

EFFECT OF CAFFEINE CONSUMPTION ON INTRAOCULAR PRESSURE AND RISK OF GLAUCOMA: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: *Glaucoma is one of the leading causes of blindness worldwide with intraocular pressure (IOP) as its main risk factor. Several studies have investigated the association between IOP and caffeine consumption with mixed results. This study aims to review whether caffeine consumption increases IOP thus, increases the risk of glaucoma.*

Methods: *A comprehensive literature search was performed in 4 databases, including Pubmed, Proquest, ScienceDirect, and Cochrane. Last search was conducted on March 20, 2023. We include human studies investigating caffeine impact on IOP and/or glaucoma risk published in English with full text available from 2013 to 2023. The risk of bias was assessed with RoB 2.0 for crossover studies, NIH for cross-sectional and case-control studies. We present our results according to PRISMA guidelines.*

Discussion: *A total of 130.012 participants from 7 different studies were included in this review. Three crossover, 3 cross-sectional, and 1 case-control study were evaluated. This study involved a multi-racial population although Caucasian predominated. Five out of 7 studies exhibited a significant association (all p values <0.05) between caffeine consumption and increased risk of developing glaucoma.*

Conclusion: *Caffeine consumption generally shows a significant impact on developing risk of glaucoma and has been shown to increase IOP in acute settings, reported up to 90 minutes after consumption/ingestion. Limitations of this study include a small number of crossover participants and a high variability of participants (young healthy individuals and glaucoma patients). Further research is advised to investigate the association between caffeine consumption in a longer follow-up time and a more specific population.*

Keywords: *Caffeine, Coffee, Intraocular Pressure, Glaucoma, Ocular Hypertension*

INTRODUCTION

Glaucoma is a complex eye disease characterized by progressive damage to the optic nerve and visual field loss. It has become one of the leading causes of blindness worldwide. There are several different types of glaucoma, including primary open-angle glaucoma (POAG), primary angle-closure glaucoma (PACG), and secondary glaucoma. POAG is the most common type of glaucoma and is characterized by a gradual increase in IOP due to blockage of the drainage channels in the eye, which leads to optic nerve damage and visual field loss. PACG, on the other hand, is characterized by a sudden increase in IOP due to the closure of the drainage angle in the eye, which can lead to acute symptoms such as severe eye pain and

vision loss. Secondary glaucoma can occur as a result of other eye diseases or conditions such as uveitis or trauma. As seen on the mechanism of each type of glaucoma, elevated intraocular pressure (IOP) is the most significant risk factor, which can damage the optic nerve and lead to irreversible vision loss if left untreated.[1]

As caffeine has shown its impact on increasing blood pressure, recent studies have suggested that caffeine intake may also be associated with increased IOP which leads to the development and progression of glaucoma. The exact mechanism by which caffeine affects intraocular pressure and the pathogenesis of glaucoma is not yet fully understood. One possible mechanism is that caffeine may increase intraocular pressure by stimulating the production of aqueous humor, the fluid that nourishes the eye. This increase in pressure can damage the optic nerve and lead to glaucoma. Additionally, caffeine has been shown to decrease the flow of blood to the eye, which may further contribute to the development of glaucoma. Furthermore, caffeine has been found to have an impact on various biological pathways that may influence the development and progression of glaucoma. For example, caffeine intake has been shown to increase levels of cortisol, a stress hormone that has been associated with an increased risk of glaucoma. Caffeine may also affect the regulation of nitric oxide, a molecule involved in the control of intraocular pressure.[2]

While some studies have found a positive correlation between caffeine consumption and increased risk of glaucoma, others have also reported conflicting results. Since prevention of development and progression of glaucoma are critical to avoid the risk of irreversible vision loss and blindness, understanding the preventable risk factors such as caffeine consumption is essential to improve the diagnosis and management of this sight-threatening condition. Given the widespread use of caffeine-containing beverages and foods, understanding the potential impact of caffeine on glaucoma is a significant public health importance. In this systematic review, we aim to synthesize the available evidence on the association between caffeine intake with IOP and glaucoma, and to provide a comprehensive analysis of the findings. The results of this review may have implications for clinical practice, public health recommendations, and future research in the field.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[3] We conducted a comprehensive literature search across four databases, including Pubmed, Proquest, ScienceDirect, and Cochrane, using the following keywords: Caffeine OR Coffee AND Intraocular Pressure OR Glaucoma OR Ocular

Hypertension. Search was performed using adaptive search according to each database and MESH terms if available. The search was restricted to English articles published between 2013 to 2023, with the most recent search conducted on March 20, 2023. Article results from the databases then imported to Rayyan, a web-tool with artificial intelligence designed for systematic review.[4]

Inclusion and exclusion criteria were employed. Inclusion criteria included (1) Human studies (2) Studies involving caffeine intake (3) Studies describing the effect of caffeine on increased intraocular pressure and/or the risk of developing glaucoma. The exclusion criteria include (1) Studies that are not available in English (2) Studies that do not provide access to complete papers (3) review articles. The main outcome assessed in the included studies are IOP measurements and association to glaucoma prevalence.

After retrieving the articles from the search results, four authors independently reviewed them to determine their eligibility for inclusion. The risk of bias assessment was carried out by 4 independent reviewers in each study. Different assessment tools were determined for each type of research. The risk of bias was assessed with RoB 2.0 for crossover studies and NIH for cross-sectional and case-control studies. Evaluation of bias was performed at the study level, and any disagreements were resolved through discussion between the authors.

The process of data extraction involved first and second reviewers, who systematically collected information from the included articles. This information encompassed various aspects, including: (1) the author and year of publication of each study (2) Study design (3) Patients (4) Mean Age (5) Exposure (6) Control (7) Outcome. Subsequently, a thorough examination and verification of the extracted data were conducted by two additional reviewers, referred to as the third and fourth reviewers.

RESULTS

Following the removal of duplicates using the Rayyan automation tool and subsequent manual confirmation, each reviewer independently screened the abstracts with a blinded review process. Subsequently, the blind was turned off allowing discussion and resolution of conflicts between reviewers, aiming to achieve a consensus for the final analysis and data extraction. A total of 7 studies and 130.012 participants met the inclusion criteria (Figure 1).

Risk of bias for all crossover studies was low, while the risk of bias for the cross-sectional and case-control studies were fair. The characteristics of the studies are presented in Table 1. Among the evaluated studies were three crossover studies, three cross-sectional

studies, and one case-control study. Although the study included a multi-racial population, Caucasians were predominant.

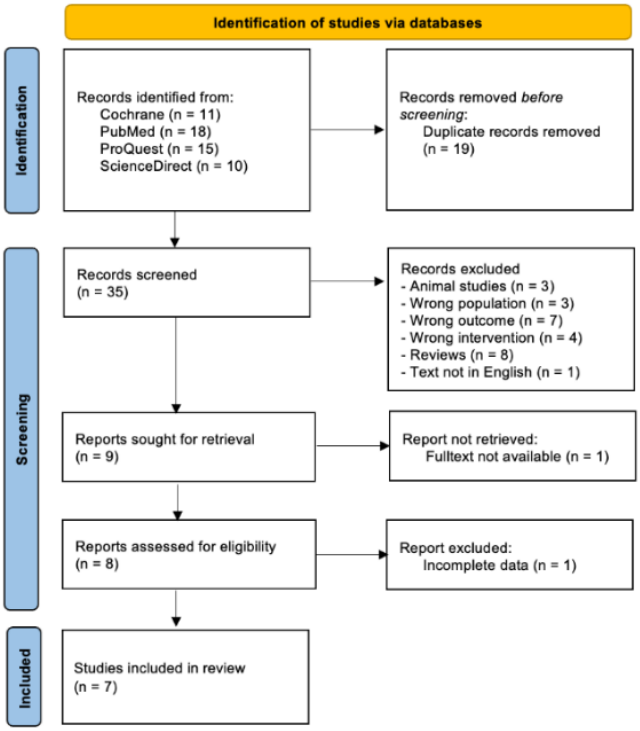

Figure 1. Study Selection Process

The effect of caffeine consumption was examined in healthy adults with both low and high caffeine consumption levels and in glaucoma patients. In healthy individuals, caffeine consumption at a dose of 4 mg/kg resulted in an acute increase in intraocular pressure (IOP) compared to placebo.[5–7] Furthermore, within the group of healthy individuals, a study comparing low-caffeine consumers to high-caffeine consumers found that the increase in IOP was more pronounced in the low-caffeine group influenced by tolerance level.[6] Caffeine consumption also has demonstrated an effect on patients with open-angle glaucoma (OAG). Two included studies, one cross-sectional and one case-control, revealed a significant association between coffee consumption and OAG.[8,9] Hun Bae, et al. suggested that coffee consumption may affect the risk of OAG, particularly in men compared to women.[8] However, two of the cross-sectional studies included in the analysis reported no significant association between caffeine consumption and either IOP or glaucoma ($p > 0.05$).[10,11] Although, a sub analysis Kim et al reported in individuals with high IOP genetic predispositions, consuming higher doses of caffeine was associated with a 0.35-mmHg higher IOP and a 3.90-fold higher glaucoma prevalence.[11]

Table 1. Characteristic and Outcomes of the Studies Included

Study (Year)	Settings	Study Design	Patients	Mean Age	Exposure	Control	Outcomes
Jiménez et al. (2020)	Spain	Placebo - controlled, double - blind, crossover study	22 healthy low caffeine consumers (≤ 1 cup/day)	22.4 years	Caffeine (~4 mg/kg)	Placebo (300 mg of corn starch)	**Caffeine intake caused an acute IOP rise ($p < 0.005$)**
Vera et al. (2018)	Spain	Placebo - controlled, double - blind, crossover study	40 university students (21 low- and 19 high - caffeine consumers)	22.1 years	Caffeine (~4 mg/kg)	Placebo (300 mg of corn starch)	**Caffeine intake caused an acute IOP rise particularly in low-caffeine consumers and in 90 minutes after ingestion ($p < 0.001$)**
Redondo et al. (2019)	Spain	Placebo - controlled, double - blind, crossover study	17 healthy low caffeine consumers (≤ 1 cup/day)	27.4 years	Caffeine (~4 mg/kg)	Placebo (300 mg of corn starch)	**Caffeine intake caused an acute IOP rise ($p = 0.005$)**
Wu et al. (2017)	Korean National Health and Nutrition Examination Survey (NHANES) Database in 2005 - 2006	Retrospective Cross - sectional	1.678 (84 glaucoma, 1593 non - glaucoma)	55.8 years (62.8 yrs for glaucoma, 55.4 yrs for non-glaucoma)	Consumption of various caffeinated beverages in the past 12 months including coffee, tea, and soft drinks: < 1 cup, 1-6 cups, and > 6 cups per week	-	No statistically significant association between consumption of coffee, tea and soft drinks, and glaucoma ($p > 0.05$). Consumption of at least one cup of hot tea daily had 74% decreased odds of having glaucoma compared with those who did not consume hot tea (adjusted OR=0.26, 95% CI 0.09 to 0.72, P=0.004). No statistically significant association existed for decaffeinated hot tea and glaucoma.
Bae et al. (2020)	Korean National Health and Nutrition Examination Survey	Cross - sectional	6.681 (323 glaucoma, 6358 non - glaucoma)	49.9 years for glaucoma, 41.8 years	Consumption of various caffeinated beverages in the past 12 months	-	**Participants who drank coffee had a higher risk of having OAG ([OR] 2.40; 95% [CI] 1.22–4.72; $p = 0.011$). In sex-stratified analyses, the robust association of coffee consumption with**

Study (Year)	Settings	Study Design	Patients	Mean Age	Exposure	Control	Outcomes
	(KNHANES) Database in 2010 - 2011			for non - glaucoma	including coffee, tea, and soft drinks: none, 6-11 cups/year, 1 cup/month, 2-3 cups/month, 1 cup/week, 2 cups/day, > 2 cups/day		**OAG was observed in men (OR, 3.98; 95% CI, 1.71–9.25; p = 0.001) but not in women. The OR comparing those who consumed coffee with those who did not consume coffee was 2.06 (95% CI, 1.11–3.82).**No significant association between tea consumption and OAG. Coffee consumption was not significantly associated with elevation of IOP.
Kim et al. (2021)	UK Biobank Database in 2006 - 2010	Cross - sectional	121.374 patients	56.8 years	Habitual tea and coffee consumption: nondrinkers (0 cup/day), low consumption (≤ 1 cup/day), and high consumption (> 1 cup/day)	-	No significant association between habitual tea and coffee consumption and IOP and glaucoma (p > 0.1). Greater caffeine intake was associated weakly with lower IOP (P=0.01). **Subanalysis in individuals with high IOP genetic predispositions, consuming higher dose of caffeine was associated with a 0.35-mmHg higher IOP (P = 0.01) and a 3.90-fold higher glaucoma prevalence (P = 0.0003).**
Mylona et al. (2019)	Outpatient services, Department of Ophthalmology, Aristotle University of Thessaloniki, Greece	Case - control	100 POAG patients, 100 healthy patients	68.63 years for POAG, 69.4 years for controls	Coffee consumption in POAG: 0-3/month, 1-6/week, 1-6/day	Coffee consumption in healthy patients: 0-3/month, 1-6/week, 1-6/day	**POAG patients had higher coffee consumption (p < 0.001)**

Significant results are written in bold

DISCUSSION

Within this review, all experimental crossover studies examining the impact of caffeine consumption on the rise of IOP in acute settings consistently yielded positive outcomes.[5–7] These findings are consistent with several studies reporting an IOP increase after administration of caffeine capsules compared to placebo. [12,13] Although the exact mechanism of IOP rise is not fully understood, several physiological processes may take part regarding these results. In animal studies, caffeine found to have an impact on epithelial cells of the ciliary body, promoting the production of aqueous humor, also reducing the tone of the smooth muscle cells in the chamber angle, causing the narrowing of fenestrae responsible for draining the aqueous humor, therefore increasing the resistance to its outflow.[14,15] This phenomenon also identified in human study by Redondo et al, where anterior chamber angle reduction after caffeine consumption has been causing an impair of the aqueous humor outflow.[7]

There are several suggested pathophysiological effects of caffeine on the risk of developing glaucoma. The meta-analysis of randomized controlled trials by Cai et al indicated that coffee intake is associated with elevated serum levels of triglycerides and low-density lipoprotein cholesterol, which increase the risk factors for development of glaucoma.[16] An experimental study also supports evidence regarding the ability of caffeine to elevate blood pressure resulting in an increase of total peripheral resistance that can lead to risk of developing glaucoma.[17] Moreover, caffeine is reported to have an impact on the posterior segment by reducing choroidal thickness, attributed to the vasoconstrictive property of caffeine on the choroid vascular structures.[18] Another possible mechanism is increasing plasma and aqueous levels of homocysteine, which is associated with development of pseudoexfoliation glaucoma and OAG.[19] Notably, these effects are observed to be attenuated in individuals who habitually consume caffeine.[20]

Our study revealed an adverse impact between coffee consumption and primary open-angle glaucoma primarily in men, while no significant association was found in women. The underlying reasons for this gender discrepancy are not yet fully understood but may be linked to physiological variances and differing hormone levels. Previous research has also highlighted disparities in OAG prevalence and risk factors between men and women, potentially influenced by factors such as serum glutamate levels, estrogen-progesterone levels, and tissue responses to glaucomatous insults. Estrogen-related effects, such as intraocular pressure reduction or neuroprotection, have been proposed as potential mechanisms explaining the sex-specific association. Interestingly, Kang et al. observed a significant positive relationship between caffeine intake and OAG risk in women, particularly those with high IOP.[11,21,22]

However, in a non-acute setting, the relationship between caffeine consumption with IOP and glaucoma-remained debatable. Li et al. reported minimal effects of caffeine on IOP in individuals without ocular abnormalities but noted significant elevation in IOP among patients with ocular hypertension or glaucoma.[23] Although a prospective cohort study by Kang et al. found no overall association between regular coffee consumption and OAG risk, subgroup analyses revealed a significant relationship between caffeine intake and the risk of OAG with elevated IOP in individuals with a family history of glaucoma.[22] It is considered that individuals with glaucoma may have heightened resistance to aqueous outflow compared to healthy individuals, explaining the IOP elevation following coffee consumption in individuals with OAG.[23] This may explain the investigated findings in the included studies that in individuals with high IOP genetic predispositions, consuming higher dose of caffeine was associated with a 0.35-mmHg higher IOP and a 3.90-fold higher glaucoma prevalence.[11]

Moreover, caffeine consumption from coffee or tea was weakly associated with decreased IOP and decreased risk of developing glaucoma in one of our included studies. These data are aligned with a Japanese study adjusting for multiple covariates found that male habitual coffee consumers had lower IOP compared to abstainers.[24] It is considered that individual with more habitual coffee consumption had a heightened tolerance level thus resulting in a decrease of caffeine effects. Additionally, The antioxidant compounds in coffee have been suggested as potential modifiers of blood pressure changes induced by caffeine consumption, which could partially explain the reduced responsiveness to caffeine observed in habitual consumers.[25] While tea, on the other hand, contains phytochemicals and flavonoids, which has been associated with anti-inflammatory, anticarcinogenic, antioxidant, and neuroprotective properties.[17] Flavonoids may play a protective role in individuals without glaucoma by promoting vasodilation, and caffeinated teas exhibit higher antioxidant capacity compared to decaffeinated teas.[26,27]

Conflicting results between studies may stem from differences in the study population and follow-up time. Additional studies are warranted to unravel the underlying pathophysiology and clarify these relationships.

This research has a few limitations that should be considered. Firstly, the number of samples included in crossover studies is limited, which may impact the generalizability of the findings. Additionally, the specific effects of caffeine on intraocular pressure (IOP) after a 90-minute period have not been extensively studied, leaving gaps in our understanding of the long-term impact of caffeine on IOP. Another limitation is the high variability in the characteristics of the study samples, including both healthy individuals and those with glaucoma, which may

introduce confounding factors. Furthermore, the limited representation of different ethnicities in the study population and the lack of assessment of the dose effect of caffeine on IOP may restrict the applicability of the results to diverse populations.

CONCLUSION

This review indicated that caffeine consumption has a significant impact on the risk of developing glaucoma and an acute effect on intraocular pressure (IOP), up to 90 minutes after consumption. This transient elevation emphasizes the need to consider caffeine intake when managing glaucoma or conducting an IOP assessment. It is important to note individual variations in caffeine response and other factors that may interact with caffeine consumption to influence glaucoma risk. Future research should focus on understanding the underlying mechanisms, long-term effects of chronic caffeine consumption, and more specific population characteristics in different ethnicities. This knowledge will inform clinical decision-making and interventions for individuals at risk of or diagnosed with glaucoma.

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