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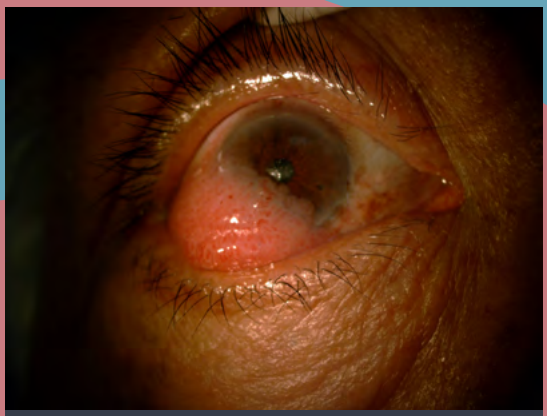

ABOUT THE COVER IMAGE

Berry-licious but malicious features an anterior segment photo of squamous cell carcinoma. The image was taken by Dr. Low Chun Heng and Dr. Chandramalar T. Santhirathelagan, Hospital Sungai Buloh, Selangor, Malaysia.

Malaysian Journal of Ophthalmology

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Malaysian Journal of Ophthalmology

Editorial
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Corneal changes in patients with diabetes mellitus: clinical implications

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Abstract

Diabetes mellitus (DM) is a major chronic disease and currently a 'public health priority' in most countries in the world.[1] India is home to the second-largest population of diabetics in the world with 77 million people in 2019, which is expected to rise to 134.2 million by the year 2045. With continued improvement in health care delivery, the life expectancy is also set to increase in people with DM by about 33% by 2050.[2] The cost involved in the management of DM and its associated complications exerts a great stress on the health care system.[3] DM affects nearly all ocular tissues—the tear film, cornea, crystalline lens, optic nerve, and retina—and is currently the leading cause of legal blindness in adults globally. Although diabetic retinopathy (DR) is usually more prominent and highlighted compared to other ocular complications, corneal issues appear to be more frequent with approximately 70% of examined patients being affected.[4]

DM-induced corneal alterations include low tear secretion leading to dry eye, epithelial fragility, recurrent erosions, superficial punctate keratitis, epithelial defects, neuropathy manifested by reduced corneal sensitivity and delayed epithelial healing, oedema, increased corneal thickness, increased hysteresis, and endothelial changes.[5]

In patients with chronic DM, the cell adhesion mechanism is impaired, leading to recurrent epithelial erosion and delayed wound healing. The corneal neuropathic changes of the sub-basal nerve plexus include decreased density, length, and branch density with increased nerve tortuosity and thickness, leading to epitheliopathy and delayed wound healing. Corneal stroma has shown to have abnormal collagen bundles of variable thickness, advanced glycation end products, and upregulation

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of matrix metalloproteinases 3 and 10, leading to altered stromal remodelling. The alteration of corneal stroma, poor epithelial barrier function, and, rarely, decreased endothelial cells can lead to accumulation of fluid in the stroma causing corneal oedema.[6,7]

Alterations in corneal thickness, transparency, and hysteresis seen in diabetic patients have clinical and surgical implications. In chronic deranged glycaemic status (measured by glycated haemoglobin A1c [HbA1c] levels), there is alteration of corneal thickness, which is an important measure used in planning for cataract and keratorefractive procedures. In recent years, there has been a greater demand for improved precision in these surgeries; thus, understanding thickness changes and having DM under control prior to surgery would improve precision. Corneal thickness and hysteresis do have an impact on the measurements of intraocular pressure (IOP). Hence, understanding the magnitude of change in these parameters compared to age-matched controls would help in adjusting the measured IOP.[8,9]

The article titled "Effect of glycaemic control on cornea among type 2 diabetes mellitus" in the current issue analyses very important findings pertinent to the Indian subcontinent. There is a correlation between glycaemic control and corneal parameters, *i.e.*, corneal thickness and anterior corneal curvature. It is interesting to see a clear correlation between the magnitude of change in HbA1c with corneal thickness and anterior corneal curvature. The findings in this paper provide vital information that could impact clinical decision by anterior segment specialists. We look forward to future publications on this relevant topic from this part of the region, as diabetic ocular complications are becoming increasingly common.

References

1. Kumpatla S, Kothandan H, Tharkar S, Viswanathan V. The costs of treating long term diabetic complications in a developing country: a study from India. JAPI. 2013;61:1–17.
2. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr. 2010 Oct 22;8:29.
3. Akari S, Mateti UV, Kunduru BR. Health-care cost of diabetes in South India: a cost of illness study. J Res Pharm Pract. 2013;2:114–7.
4. Calvo-Maroto AM, Perez-Cambrodí RJ, Albarán-Diego C, Pons A, Cerviño A. Optical quality of the diabetic eye: A review. Eye (Lond) 2014;28:1271-80.
5. Ljubimov AV. Diabetic complications in the cornea. Vision Res. 2017;139:138-152.
6. Shih KC, Lam KS, Tong L. A systematic review on the impact of diabetes mellitus on the ocular surface. Nutr Diabetes. 2017;20;7:e251.
7. Zhao H, He Y, Ren YR, Chen BH. Corneal alteration and pathogenesis in diabetes mellitus. Int J Ophthalmol. 2019;18;12:1939-1950

8. Luo XY, Dai W, Chee ML, et al. Association of Diabetes with Central Corneal Thickness Among a Multi-ethnic Asian Population. JAMA Netw Open. 2019;2(1):e186647.
9. Kim YJ, Kim TG. The effects of type 2 diabetes mellitus on the corneal endothelium and central corneal thickness. Sci Rep. 2021;15;11:8324.

Malaysian Journal of Ophthalmology

Editorial
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From my laptop

Dear readers,

Finally, many countries are now moving toward the endemic phase of Covid-19. Borders are now opening, and we are allowed to roam the earth again. Freedom at last but not quite yet, Omicron is everywhere.

March is for World Glaucoma Week (WGW), the global initiative to create public awareness on glaucoma, the major cause of irreversible blindness worldwide. WGW this year was celebrated with a 'bang' in Malaysia. Many activities were organised to create awareness not only among the public but also among the medical fraternity. One of the highlights this year was the Ministry of Health Annual Glaucoma Symposium (MAGS), which attracted many participants with an interesting scientific program. Kudos to the organizer and Ministry of Health, Malaysia! Malaysian Journal of Ophthalmology (MYJO) was given the opportunity to publish the abstracts submitted to MAGS in a supplement. Please check it out.

This year, Kuala Lumpur will be hosting the Asia-Pacific Glaucoma Congress as a hybrid event. I hope to reconnect with many of our friends and colleagues at the Kuala Lumpur Conference Centre in August! Take care and stay safe.

Till we meet again.

Professor Dr Liza Sharmini Ahmad Tajudin

Editor in Chief

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Surgical outcome of retropupillary iris-claw lens implantation: a retrospective review

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Abstract

Introduction: Intraocular lens (IOL) selection, especially in cases with insufficient capsular and/or zonular support has increasingly become a challenge to surgeons. Retropupillary iris-claw IOLs (RP- ICIOL) have gained popularity in recent years.
Purpose: This study aimed to review the outcomes of RP-ICIOL implantation in two tertiary eye centres.
Study design: Retrospective review.
Methods: This is a retrospective study of 14 eyes of 14 patients who underwent Artisan RP-ICIOL implantation between November 2018 and December 2020 in two tertiary eye centres in Malaysia.
Results: The mean age of patients was 51.5 ± 17.4 years with the range between 18 and 77 years old. There were ten (71.4%) males and four (28.6%) females. The IOL was implanted primarily in three eyes (21.43%) and as a secondary procedure in eleven eyes (78.6%). Mean preoperative best-corrected visual acuity (BCVA) was logMAR 1.32 ± 0.82, while mean postoperative BCVA was logMAR 0.56 ± 0.42 (p = 0.010). Visual improvement of two or more lines in BCVA was observed in nine eyes (64.3%), no improvement in two eyes (14.3%), and worsening in three eyes (21.4%). There were no complications observed during the surgery. All our patients had a well-centred IOL at the 1-month postoperative follow-up. Mean preoperative

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intraocular pressure was 16.8 ± 2.0 mmHg and postoperative intraocular pressure was 15.7 ± 5.1 mmHg (p = 0.430).
Conclusion: RP-ICIOL implantation is safe and provides the optical advantage of a more biologically appropriate retropupillary position, ensuring a favourable functional visual outcome with low risk of complications.

Keywords: Artisan intraocular lens, capsular support, cataract surgery, retropupillary iris-claw intraocular lens

Penghasilan pembedahan katarak dengan implantasi kanta cakar iris retropupillari: tinjauan retrospektif

Abstrak

Pengenalan: Pemilihan kanta intraokular (IOL) kini semakin mencabar kepada pakar oftalmologi, terutamanya dalam kes dimana terdapat kekurangan sokongan kapsul dan/atau zonular. Kanta cakar iris retropupillari (RP-ICIOL) menjadi popular sejak kebelakangan ini.
Tujuan: Tujuan kajian ini adalah untuk mengkaji penghasilan pembedahan katarak dengan implantasi RP-ICIOL di dua pusat perubatan tertiari.
Reka bentuk kajian: Tinjauan retrospektif.
Kaedah: Tinjauan retrospektif ini melibatkan 14 mata daripada 14 pesakit yang menjalani pembedahan katarak dengan implantasi Artisan RP-ICIOL di antara November 2018 dan Disember 2020 di dua pusat perubatan tertiari di Malaysia.
Keputusan: Purata umur pesakit yang terlibat adalah 51.5 ± 17.4 tahun dengan julat antara 18 hingga 77 tahun yang terdiri dari sepuluh (71.4%) lelaki dan empat (28.6%) perempuan. Implantasi RP-ICIOL sebagai prosedur primer telah melibatkan tiga mata (21.43%) dan sebagai prosedur sekunder dalam sebelas mata (78.6%). Purata ketajaman penglihatan terbaik (BCVA) sebelum pembedahan ialah logMAR 1.32 ± 0.82 berbanding dengan purata BCVA selepas pembedahan ialah logMAR 0.56 ± 0.42 (p = 0.010). Sembilan mata (64.3%) menunjukkan penambahbaikan BCVA sebanyak dua garisan atau lebih, dua mata (14.3%) tiada menunjukkan peningkatan BCVA dan tiga mata (21.4%) menunjukan kemerosotan penglihatan. Tiada komplikasi diperhatikan semasa pembedahan. Kesemua RP-ICIOL didapati berkedudukan stabil selepas pembedahan dan semasa rawatan susulan. Purata tekanan intraokular (IOP) sebelum pembedahan ialah 16.8 ± 2.0 mmHg, dan IOP selepas pembedahan ialah 15.7 ± 5.1 mmHg (p = 0.430).
Kesimpulan: Pembedahan katarak dengan implantasi RP-ICIOL adalah selamat dan

mengekalkan kedudukan kanta pada ruang retropupillari, memberikan ketajaman penglihatan yang baik selepas pembedahan serta mempunyai risiko komplikasi yang rendah.

Kata kunci: kanta intraokular artisan, kanta intraokular cakar iris retropupillari, pembedahan katarak, sokongan kapsul

Introduction

Intraocular lens (IOL) selection, especially in cases with insufficient capsular and/or zonular support, has increasingly become a challenge to surgeons. It is one of the main determining factors that influence a patient's final visual outcome.[1]

Loss of capsular or zonular support can be due to congenital or secondary causes, which include trauma: ocular pathologies such as pseudoexfoliation syndrome, Marfan syndrome, and lens coloboma; complicated cataract surgery such as iatrogenic zonulodialysis: and intraoperative posterior capsule rupture.[2] Choices for IOL implantation in these cases include angle-supported anterior chamber IOL (ACIOL), scleral-fixated IOL (SFIOL), and iris-claw IOL (ICIOL).[3]

Conventionally, ACIOL and SFIOL implantation are commonly practiced in Malaysia in cases of insufficient capsular and/or zonular support. The ACIOL was first introduced by Baron in 1952.[4] Closed-loop ACIOLs gained popularity in the 1970s due to their various flexible designs that were thought to alleviate problems with sizing.[5] However, the sharp edges eroded uveal tissue and released inflammatory mediators, causing a variety of complications such as pseudophakic corneal decompensation, pigment dispersion, chronic iritis, cystoid macular oedema (CMO), and uveitis glaucoma hyphaema syndrome.[6] Subsequent generations of ACIOLs in the 1990s with improved design in terms of reducing fixation to three or four points, well-polished, and haptic without holes have demonstrated good surgical outcomes and a reduction in the above-mentioned complications.[7] However, IOL sizing is still one of the major drawbacks of angle-supported ACIOLs.[8] Complications associated with incorrect ACIOL sizing are common due to the limited availability of different diameters. A small-diameter ACIOL increases the risk of rotation and dislocation, which may lead to corneal endothelial and anterior chamber angle damage. A large-diameter ACIOL poses a risk of peripheral anterior synechiae formation, raised intraocular pressure (IOP), and glaucoma due to excessive pressure on the angle structures.[9,10]

The sutured SFIOL was first described by Girard in 1981 and later modified by Malbran and colleagues in 1986.[11] This method can be used in patients who are contraindicated for ACIOL implantation, such as glaucoma patients or patients with inadequate iris support or low corneal endothelial cell count. However, SFIOL is technically challenging and requires longer operative times. Besides, it is associated

with complications such as suture breakage, resulting in IOL tilt or decentration, dislocation of the IOL into the vitreous, suture erosion and exposure, CMO, retinal detachment, and endophthalmitis.[12] In addition, this method is limited by the availability of surgical skills and steep learning curve.

In recent years, the iris-claw intraocular lens (ICIOL) has gained popularity in Malaysia. ICIOLs can be implanted either in the anterior chamber or the retropupillary space. Worst *et al.* first described the iris-clip IOL, which required sutures to be fixed to the iris, in 1972.[13] In the 1980s, Amar first proposed the fixation of an iris-claw lens at the posterior surface of the iris. The implantation of retropupillary ICIOLs (RP-ICIOL) is less invasive and requires a shorter surgical duration with faster visual recovery compared to SFIOLs.[14] Hence, RP-ICIOLs have emerged as a viable option for secondary IOL implantation in recent years. A recent meta-analysis by Liang *et al.* revealed that RP-ICIOL may perform better with greater IOP reduction and reduced incidence of CMO.[15]

The knowledge regarding outcomes of RP-ICIOL implantation is still limited in Malaysia. The purpose of this study was to evaluate the various indications, complications, and visual outcomes of RP-ICIOL implantation in eyes with insufficient or absent capsular/zonular support.

Material and methods

This is a retrospective review including 14 eyes of 14 patients who underwent Artisan aphakic IOL (Ophtec BV, Groningen, Netherlands) implantation between November 2018 and December 2020 in two tertiary eye centres in Malaysia. This study was conducted in accordance with the Declaration of Helsinki for human research. Informed consent was obtained from all individual participants included in the study.

We included both primary and secondary RP-ICIOL implantations performed during the study period. Eyes with dislocated/subluxated IOL or crystalline lens and post-lens aspiration aphakia for traumatic cataract were included in this study. Exclusion criteria were eyes with no light perception, corneal decompensation, advanced glaucoma, iris neovascularization, and aniridia. Snellen visual acuity values were expressed as the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Visual acuity of light perception was set at 2.9 logMAR, hand movement at 2.6 logMAR, and counting fingers at 2.3 logMAR.

Records and operative reports of patients who underwent RP-ICIOL implantation were reviewed.

Preoperative data collected were demographics, causes of aphakia, previous ocular surgeries, pre-existing ocular pathologies, IOP, and best-corrected visual acuity (BCVA). Postoperative data regarding BCVA, IOP, and complications were collected at 1 month postoperative. Patient evaluation comprised objective and

subjective refraction, BCVA, slit-lamp examination, IOP measurement by Goldmann applanation tonometry, indirect fundus examination, and A-scan ultrasound biometry.

All data were entered into the Statistical Program for Social Science (SPSS) version 26.0 software. Data were checked and cleaned to ensure accurate documentation and to eliminate any missing or erroneous values. The SPSS and Statistical Data Analysis (STATA) version 26.0 software was used for the statistical analysis.

Results

A total of 14 eyes were included in our study. The mean age of patients was 51.5 ± 17.42 years with a range between 18 and 77 years old. There were ten (71.4%) males and four (28.6%) females. Of the 11 patients, five were Malays, eight were Chinese, and one was Indian. There were six left eyes (42.9%) and eight right eyes (57.1%). The IOL was implanted primarily in three eyes (21.4%) and as a secondary procedure in eleven eyes (78.6%). The indications for primary surgery were subluxated/dislocated crystalline lens (*n* = 3, Marfan syndrome: 1, trauma: 2). For secondary IOL implantation, the indications were dislocated posterior chamber IOL (PCIOL) (*n* = 3), IOL exchange for subluxated PCIOL (*n* = 4), IOL exchange for subluxated SFIOL (*n* = 1), and post-lens aspiration aphakia for traumatic cataract (*n* = 3) (Fig. 1).

Four eyes had pre-existing primary open-angle glaucoma, four eyes had pre-existing high myopia and one of these had myopic maculopathy, one eye had pre-existing proliferative diabetic retinopathy with secondary glaucoma, one eye had pre-existing aphakic secondary glaucoma, one eye had ocular hypertension, and one eye had a corneal scar.

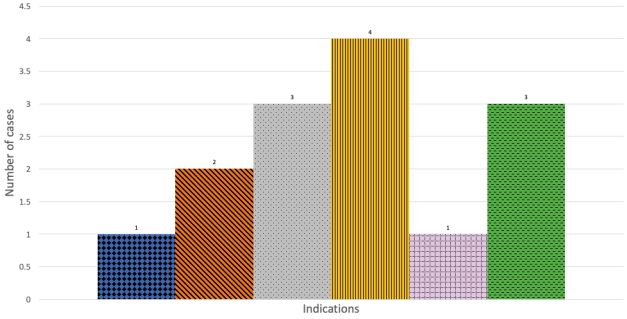

Fig. 1. Indications for retropupillary iris-claw intraocular lens implantation.

Table 1. Comparison of pre-operative and post-operative BCVA

Patient	Preoperative BCVA (logMAR)	Postoperative BCVA (logMAR)	BCVA difference
1	2.3	0.3	-2.0
2	1.0	0.2	-0.8
3	2.3	1.5	-0.8
4	2.6	0.5	-2.1
5	0.2	0.5	0.3
6	0.8	0.8	0
7	1.0	0.2	-0.8
8	2.3	0.1	-2.2
9	0.6	0.8	0.2
10	1.8	0.3	-1.5
11	0.7	1.3	0.6
12	0.5	0.2	-0.3
13	0.6	0.6	0
14	1.8	0.6	-1.2
		Mean of differences	-0.76
		Standard deviation of differences	0.936
		***p*-value**	0.010*

BCVA: best corrected visual acuity
**p*-value based on paired t-test

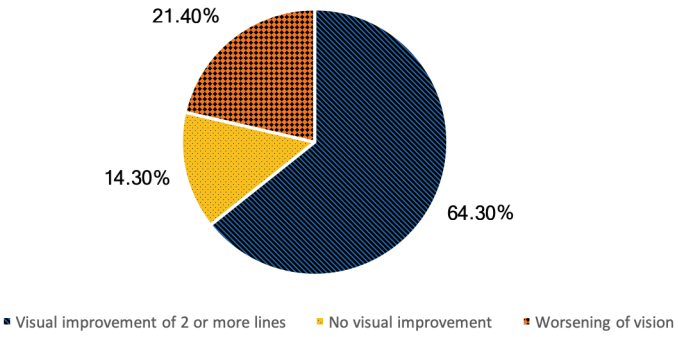

Fig. 2. Visual outcomes of retropupillary iris-claw intraocular lens implantation at 1-month follow-up.

Table 2. Comparison of preoperative and postoperative IOP

Patient	Preoperative IOP	Postoperative IOP	IOP difference
1	14	12	-2
2	20	8	-12
3	14	14	0
4	18	18	0
5	16	15	-1
6	17	20	3
7	18	29	11
8	16	12	-4
9	16	14	-2
10	16	14	-2
11	20	18	-2
12	14	12	-2
13	18	20	2
14	18	14	-4
		Mean of differences	-1.07
		Standard deviation of differences	4.922
		***p*-value**	0.430*

IOP: intraocular pressure
**p*-value based on paired t-test

Mean best-corrected visual acuity (BCVA) improved from logMAR 1.32 ± 0.823 preoperatively to logMAR 0.56 ± 0.420 postoperatively ($p = 0.010$) (Table 1). Visual improvement of two or more lines in BCVA was observed in nine eyes (64.3%), no improvement in two eyes (14.3%) and worsening in three eyes (21.4%) at 1 month postoperatively (Fig. 2). Causes of worsening of visual acuity were due to secondary glaucoma, pre-existing corneal scar, and diabetic retinopathy.

All surgeries were uneventful without complications. IOLs were noted to be well centred at the 1-month postoperative follow-up. Mean preoperative IOP was 16.8 ± 2.01 mmHg, and postoperative IOP was 15.7 ± 5.09 mmHg (Table 2); the difference was not statistically significant ($p = 0.430$). No serious complications were observed postoperatively except for one patient who developed secondary steroid-induced glaucoma requiring long-term IOP-lowering agents.

Discussion

IOL selection in cases with insufficient or absent of capsular/zonular support is an emerging surgical dilemma that presents a challenge to most ophthalmologists. To date, there is still no established consensus on the best choice of IOL selection for the treatment of eyes insufficient capsular/zonular support.[16] All available options have their own risks and complications.

In our study, 64.3% of the eyes had improved BCVA postoperatively, which is comparable to a study by Labeille *et al.* (68.8%).[17] Our study showed that RP-ICIOL provided statistically significant improvement in visual acuity with mean postoperative BCVA of logMAR 0.56 ± 0.420 compared to mean preoperative BCVA of logMAR 1.32 ± 0.823 (p = 0.010). Of 14 eyes, two eyes (14.3%) showed no improvement in BCVA while three eyes (21.4%) showed worsening visual acuity. Deterioration of vision was attributed to secondary glaucoma, pre-existing corneal scar, and diabetic retinopathy status.

RP-ICIOL implantation better preserves the anatomic characteristics of the anterior segment with respect to the iridocorneal angle, thus avoiding angle closure and pupillary block.[18] In our study, mean preoperative IOP was 16.8 ± 2.01 mmHg and mean postoperative IOP was 15.7 ± 5.09 mmHg (p = 0.430). Despite the concerns regarding IOP elevation after RP-ICIOL implantation, IOP was not elevated in most cases in our study. Postoperatively, only one eye developed secondary glaucoma (steroid-induced) requiring long-term IOP-lowering agents, similar to the study by Schallenberg *et al.* where one patient had raised IOP.[19]

Our study indicates that RP-ICIOL implantation is effective in the treatment of cases without sufficient capsular/zonular support by improving visual acuity without serious intraoperative or postoperative complications. There were no intraoperative complications noted in our cases. Postoperatively, none of our cases showed chronic anterior chamber inflammation, which is similar to the results of a study conducted by Forlini *et al.*[20] Iris ovalization and atrophy are common problems after RP-ICIOL implantation, but have no influence on visual or refractive outcomes or IOP.

The limitations of this study include its retrospective design, heterogeneous ophthalmic history and comorbidities, small sample size, and short follow-up. Further studies with larger sample sizes and longer follow-up are required to compare the results of primary RP-ICIOL implantation with those of other IOL implantation methods, with a focus on IOL stability and long-term outcomes such as postoperative chronic inflammation and corneal endothelial cell count reduction.

Conclusion

In conclusion, RP-ICIOL implantation provides optical and physiological advantages of more biologically appropriate retropupillary position, ensuring a good refractive outcome in patients with insufficient or absence of capsular/ zonular support. It is relatively less invasive and safe with minimal risk of complication. Therefore, this type of IOL implantation should be considered especially in patients who are contraindicated for angle-supported ACIOL implantation, such as glaucoma patients or patients with low corneal endothelial cell count.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki for human research. Informed consent was obtained from all individual participants included in the study. All patients provided their consent for the clinical information to be reported in the journal. Institutional review board approval was not required for the present study due to its retrospective nature.

Competing interests
None to declare.

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None to declare.

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None to declare.

References

1. Wagoner MD, Cox TA, Ariyasu RG, Jacobs DS, Karp CL, American Academy of O. Intraocular lens implantation in the absence of capsular support: a report by the American Academy of Ophthalmology. Ophthalmology. 2003;110:840-859.
2. De Silva SR, Arun K, Anandan M, Glover N, Patel CK, Rosen P. Iris-claw intraocular lenses to correct aphakia in the absence of capsule support. J Cataract Refract Surg. 2011;37:1667-1672.
3. Dajee KP, Abbey AM, Williams GA. Management of dislocated intraocular lenses in eyes with insufficient capsular support. Curr Opin Ophthalmol. 2016;27:191-195.
4. Hernandez Martinez A, Almeida Gonzalez CV. Iris-claw intraocular lens implantation: Efficiency and safety according to technique. J Cataract Refract Surg. 2018;44:1186-1191.

5. Sumitha CV, Pai V, Thulasidas M. Retropupillary iris-claw intraocular lens implantation in aphakic patients. Indian J Ophthalmol. 2020;68:597-602.
6. Moschos MM, Nitoda E. The Correction of Aphakia Using Anterior Chamber Intraocular Lens. In Vivo. 2016;30:733-738.
7. Shen JF, Deng S, Hammersmith KM, et al. Intraocular Lens Implantation in the Absence of Zonular Support: An Outcomes and Safety Update: A Report by the American Academy of Ophthalmology. Ophthalmology. 2020;127:1234-1258.
8. Thulasidas M. Retropupillary Iris-Claw Intraocular Lenses: A Literature Review. Clin Ophthalmol. 2021;15:2727-2739.
9. Weene LE. Flexible open-loop anterior chamber intraocular lens implants. Ophthalmology. 1993;100:1636-1639.
10. Evereklioglu C, Er H, Bekir NA, Borazan M, Zorlu F. Comparison of secondary implantation of flexible open-loop anterior chamber and scleral-fixated posterior chamber intraocular lenses. J Cataract Refract Surg. 2003;29:301-308.
11. Buckley EG. Hanging by a thread: the long-term efficacy and safety of transscleral sutured intraocular lenses in children (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc. 2007;105:294-311.
12. Luk AS, Young AL, Cheng LL. Long-term outcome of scleral-fixated intraocular lens implantation. Br J Ophthalmol. 2013;97:1308-1311.
13. Worst JG. Iris claw lens. J Am Intraocul Implant Soc. 1980;6:166-167.
14. Teng H, Zhang H. Comparison of Artisan iris-claw intraocular lens implantation and posterior chamber intraocular lens sulcus fixation for aphakic eyes. Int J Ophthalmol. 2014;7:283-287.
15. Liang IC, Chang YH, Hernandez Martinez A, Hung CF. Iris-Claw Intraocular Lens: Anterior Chamber or Retropupillary Implantation? A Systematic Review and Meta-Analysis. Medicina (Kaunas). 2021;57.
16. Toro MD, Longo A, Avitabile T, et al. Five-year follow-up of secondary iris-claw intraocular lens implantation for the treatment of aphakia: Anterior chamber versus retropupillary implantation. PLoS One. 2019;14:e0214140.
17. Labeille E, Burillon C, Cornut PL. Pars plana vitrectomy combined with iris-claw intraocular lens implantation for lens nucleus and intraocular lens dislocation. J Cataract Refract Surg. 2014;40:1488-1497.
18. Baykara M, Ozcetin H, Yilmaz S, Timucin OB. Posterior iris fixation of the iris-claw intraocular lens implantation through a scleral tunnel incision. Am J Ophthalmol. 2007;144:586-591.
19. Schallenberg M, Dekowski D, Hahn A, Laube T, Steuhl KP, Meller D. Aphakia correction with retropupillary fixated iris-claw lens (Artisan) - long-term results. Clin Ophthalmol. 2014;8:137-141.
20. Forlini M, Soliman W, Bratu A, Rossini P, Cavallini GM, Forlini C. Long-term follow-up of retropupillary iris-claw intraocular lens implantation: a retrospective analysis. BMC Ophthalmol. 2015;15:143.

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Effect of glycaemic control on corneal parameters among type 2 diabetes mellitus

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Abstract

Purpose: To study the effect of glycaemic control as demonstrated by the change in HbA1c on corneal parameters among patients with type 2 diabetes mellitus (T2DM).
Study design: Prospective study analysing corneal parameters among patients with T2DM along with fluctuations in HbA1c.
Methods: A prospective, single-centre, cohort study was carried out on T2DM patients with HbA1c > 6.5% from Kasturba Hospital, Manipal, India. The subjects underwent a comprehensive eye examination. One-hundred and twenty-two subjects who fulfilled the inclusion criteria were analysed using the Huvitz 9000A to measure anterior corneal curvature followed by ultrasound pachymetry to measure central corneal thickness (CCT) at baseline and after 3 months. A simple linear regression was used to compare the mean corneal parameters, CCT and anterior corneal curvature, for each group with the mean HbA1c. The mean difference was considered statistically significant only if the value was $p < 0.05$.
Results: We observed a significant difference between baseline and follow-up levels of HbA1c ($t = 2.487$; $df = 53$; $p < 0.05$). Simple linear regression analysis showed a positive correlation and revealed a mean increase in CCT of 1.893 µm ($p < 0.001$) and a mean increase in anterior corneal curvature of 0.069 D ($p < 0.005$) for every unit increase in HbA1c.
Conclusions: The present study showed that changes in CCT and anterior corneal curvature occur with respect to changes in HbA1c level. Thus, careful attention is

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required in considering HbA1c status when performing comprehensive eye examinations in diabetic patients.

Keywords: central corneal thickness, corneal curvature, diabetes mellitus type 2, HbA1c

Kesan kawalan glisemik pada parameter kornea di kalangan diabetes mellitus jenis 2

Abstrak

Tujuan: Untuk mengkaji kesan kawalan glisemik seperti yang ditunjukkan oleh perubahan HbA1c pada parameter kornea di kalangan pesakit diabetes mellitus jenis 2 (T2DM).
Reka bentuk kajian: Kajian prospektif menganalisis parameter kornea di kalangan pesakit dengan T2DM bersama-sama dengan perubahan turun naik dalam HbA1c.
Kaedah: Kajian kohort prospektif, pusat tunggal, telah dijalankan ke atas pesakit T2DM dengan HbA1c > 6.5% dari Hospital Kasturba, Manipal, India. Subjek menjalani pemeriksaan mata yang komprehensif. Seratus dua puluh dua subjek yang memenuhi kriteria inklusi dianalisis menggunakan Huvitz 9000A untuk mengukur kelengkungan kornea anterior diikuti oleh pachymetry ultrasound untuk mengukur ketebalan kornea pusat (CCT) pada garis dasar dan selepas 3 bulan. Regresi linear mudah digunakan untuk membandingkan parameter kornea min, CCT dan kelengkungan kornea anterior, bagi setiap kumpulan dengan min HbA1c. Perbezaan min dianggap signifikan secara statistik hanya jika nilainya adalah $p < 0.05$.
Keputusan: Kami melihat perbezaan yang ketara antara tahap asas dan susulan HbA1c ($t = 2.487$; $df = 53$; $p < 0.05$). Analisis regresi linear mudah menunjukkan korelasi positif dan mendedahkan peningkatan purata dalam CCT sebanyak 1.893 μm ($p < 0.001$) dan peningkatan purata kelengkungan kornea anterior sebanyak 0.069 D ($p < 0.005$) bagi setiap peningkatan unit dalam HbA1c.
Kesimpulan: Kajian ini menunjukkan bahawa perubahan dalam CCT dan kelengkungan kornea anterior berlaku berkenaan dengan perubahan dalam tahap HbA1c. Oleh itu, perhatian yang teliti diperlukan dalam mempertimbangkan status HbA1c apabila melakukan pemeriksaan mata yang komprehensif dalam pesakit diabetes.

Kata kunci: diabetes mellitus jenis 2, HbA1c, kelengkungan kornea, ketebalan kornea pusat

Introduction

India is the diabetes capital of the world with 65.1 million diabetic individuals in 2013, which is expected to rise to 1.9 million by the year 2035. Several studies have reported the growth of the type 2 diabetes mellitus (T2DM) epidemic in India.[1] A standardized, quality measure for diabetes mellitus (DM) is glycosylated haemoglobin, type A1c (HbA1c). When comparing venous plasma to HbA1c, the latter is much more accurate. HbA1c of 6.5% has a good sensitivity of 65% and specificity of 88% in detecting DM. Hence a cut-off value of 6.5% for HbA1c is a reliable diagnostic factor for classifying a person as DM.[2,3]

Multiple factors such as lifestyle modification, living standards, genetic factors, and an upsurge in urban migration contribute to the aetiology of diabetes among the Indian population. Even though Western countries have risk factors such as high obesity and overweight rates compared to the Indian population—which has a lean body mass index—the Indian population is prone to have a higher rate of DM. One of the causes for this discrepancy could be a genetic predisposition for the development of coronary artery disease, which in turn is due to low levels of high-density lipoproteins and dyslipideamia. Consequently, Indians tend to develop complications of DM in much earlier stages of life.[4]

DM can affect all ocular structures. It is well established that DM plays a crucial role among the leading causes of blindness,[5] and leads to ocular diseases such as diabetic retinopathy (DR), glaucoma, diabetic keratopathy, cataract, eye muscle palsy (especially lateral rectus), and retinal vascular occlusion.[6]

Sukla *et al.* and Huntjens *et al.* have shown a correlation between central corneal thickness (CCT) and HbA1c in 2016 and 2012, respectively.[7,8] Similarly, in 2005 Sonmez *et al.* demonstrated a weak positive correlation between anterior corneal curvature and HbA1c.[9] While the published literature has found an association between corneal parameters and HbA1c, the same is not true regarding the amount of change in corneal parameters with each unit change in HbA1c. Fluctuations in HbA1c may alter corneal thickness and curvature, and these changes may lead to visual degradation. The purpose of this research was to study the effect of glycaemic control as demonstrated by the change in HbA1c on corneal parameters, CCT and anterior corneal curvature, among patients with T2DM invariable of diabetic retinopathy status in the Indian population.

Methods

The study protocol was approved by the Institutional Ethics Committee (IEC) of Kasturba Hospital and Manipal (IEC-227/2016). The study conformed to the tenets of the Declaration of Helsinki. A prospective cohort-observational study was done by including DM patients from Kasturba Hospital. Following an explanation of the

procedure in plain terms the subjects could understand and obtaining written informed consent, 160 subjects whose HbA1c was greater than 6.5% underwent a compressive eye examination.

The comprehensive eye examination started with previous ocular history, vision assessment (using logMAR chart), and refraction. Undilated retinal examination was carried out for all the study participants with the help of a Smart scope (Bosch Private Limited, Bangalore, India). Subjects with a history of any previous ocular surgery, chronic use of any ocular medications, contact lens use, retinal photocoagulation within 1 month of the study, and any other ocular diseases such as pterygium, entropion, or ocular conditions interfering with tearing, such as dry eye, were excluded from the study as they may alter the corneal parameters. Subjects with systemic conditions influencing HbA1c such as anaemia, hemoglobinopathy, pregnancy, hepatic or renal disease, and hypothyroidism were also excluded.

By using the formula $n = [\sigma^2 (Z_{1-\alpha/6} + Z_{1-\beta})^2] / d^2$, we calculated the sample size as 116 along with a dropout percentage of 20%, as this was a prospective study [where, $Z_{1-\alpha/6} = 2.39$ for 5%; $Z_{1-\beta} = 0.84$ for 80% power, σ = SD of the observation (from a previous study)[10] d = clinically significant difference). Among the 160 subjects approached, 122 were shortlisted according to the inclusion and exclusion criteria and went on to evaluation. Anterior corneal curvature was measured with the Huvitz 9000A (Huvitz Bldg, Gyeonggi-DO, South Korea). An average of three values was taken for anterior corneal curvature and from that value, the average of flat and steep meridians was considered for analysis. CCT was measured using ultrasound pachymetry. Ten readings were obtained on continuous contact of the probe with the anterior surface of the cornea, two extreme high values and two extreme low values were excluded, and an average of the six readings was taken as one reading. The same procedure was repeated thrice and an average of these three readings recorded for analysis. Since ultrasound pachymetry is a contact procedure that may alter anterior corneal curvature readings, it was performed last. All the readings were taken between 09:00 and 17:00 hours. Intraocular pressure (IOP) was measured only after CCT measurement, as it may alter CCT values.

Although standard protocols outline follow-ups for DM every 6 months, HbA1c values are valid for only 3 months. Therefore, follow-up was shortened to 3 months in our study. In the follow-up visit, after HbA1c was measured, the subjects again underwent the same procedures, namely, Huvitz 9000A and ultrasound pachymetry for anterior corneal curvature and CCT, respectively.

Statistical analysis

Data analysis was done using SPSS software version 16. Paired t-test was used to evaluate the difference in baseline and follow-up values of HbA1c. A simple linear regression was used to compare the mean corneal parameters, CCT and anterior corneal curvature, for each group with the mean HbA1c. The mean difference was considered statistically significant only if the value was $p < 0.05$.

Results

Table 1 shows the demographic details and retinal status between OD and OS. Subjects had a median (interquartile range) spherical equivalent (SE) of 0.13 D (-0.25 to +1.16) and 0.34 D (+0.00 to +1.25) for OD and OS, respectively.

Our study classified DR based on the Internal Classification of Diabetic Retinopathy (ICDR). As shown in Table 1, 7.38–8.20% of eyes had mild non-proliferative diabetic retinopathy (NPDR), 4.10–5.47% of eyes had moderate NPDR, 1.64–2.46% of eyes had severe NPDR, and 0.82–0% of eyes had proliferative diabetic retinopathy (PDR) among the 122 subjects recruited. As the recruited subjects had DM for less than a decade, with a mean duration of DM of 5.59 ± 0.44 years, most eyes were only in the early stages of DR, corresponding to mild and moderate NPDR.

Pearson's correlation between OD and OS was strong for both variables, CCT and anterior corneal curvature (r = 0.957 and 0.939, respectively), with a statistical significance of $p < 0.001$. Hence, only OD was considered for analysis. Paired t-test was done between baseline and follow-up HbA1c levels, which was statistically significant (t = 2.487; df = 53; $p < 0.05$). The correlation between CCT with age, and CCT with DM duration, both were not statistically significant, as it was in the case of anterior corneal curvature with age, and anterior corneal curvature with DM duration, respectively ($p < 0.05$).

Table 1. Demographic details and retinal status between OD and OS

Parameter	OD	OS
Age*	54 ± 9 years	
Sex (M:F)	1.3:1 [male: 57% (n = 69); female: 43% (n = 53)]	
Duration of DM*	5.59 ± 0.44 years	
LogMAR visual acuity*	0.17 ± 0.18	0.16 ± 0.18
Refractive error SE**	+1.28 D (-0.19 to +1.09)	+1.25 D (+0.00 to +1.25)
IOP*	13.93 ± 2.14	14.07 ± 2.13
Retina WNL	69.67% (n = 85)	68.85% (n = 84)
Tessellated retina	22.95% (n = 28)	23.77% (n = 29)
Mild NPDR	7.38% (n = 9)	8.20% (n = 10)
Moderate NPDR	4.10% (n = 5)	5.47% (n = 7)
Severe NPDR	1.64% (n = 2)	2.46% (n = 3)
PDR	0. 82% (n = 1)	0.00% (n = 0)

DM: diabetes mellitus; SE: spherical equivalent; IOP: intraocular pressure; WNL: within normal limits; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy

*Mean ± standard error of the mean

**Interquartile range

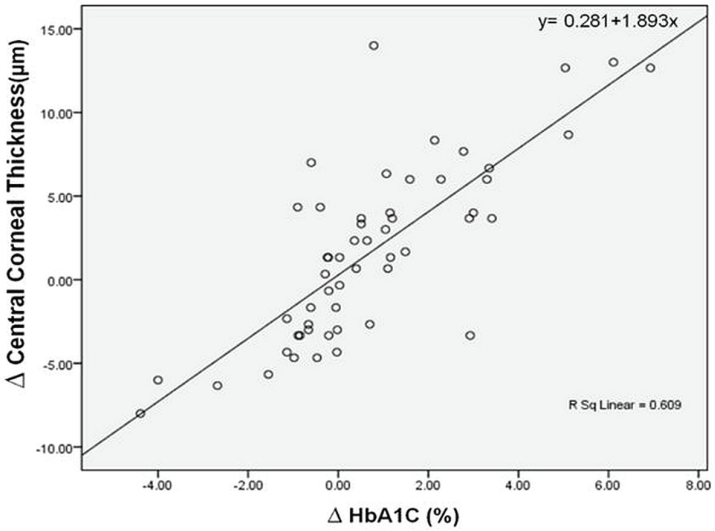

Fig. 1. Scatter plot showing the relationship between ΔCCT and ΔHbA1c.

A simple linear regression analysis was done along with adjustment for mean difference of baseline and follow-up HbA1c levels and the mean difference of baseline and follow-up of CCT for OD. A positive correlation was found between the mean difference of CCT and the mean difference of HbA1c. On average, for every unit increase in difference of HbA1c, there was an increase of 1.893 μm in the difference of CCT ($p < 0.001$), as shown in Figure 1.

To understand the relationship between CCT and HbA1c in depth, further detailed analysis was performed in subgroups based on HbA1c values. Hence, based on the median value of HbA1c (8.605) from the baseline visit, two groups were subdivided: a low HbA1c group (< 8.065) and a high HbA1c group (> 8.065). A simple linear regression analysis was carried for the two groups separately which found that, on average, for a unit increase of difference in HbA1c, CCT increased by 2.563 μm, provided the HbA1c value was less than 8.065. Likewise, on average, for a unit increase of difference in HbA1c, CCT increased by 1.949 μm, provided the HbA1c value was greater than 8.065, as shown in Figure 2.

Even though there was a strong positive correlation between the high HbA1c group and CCT ($r = 0.901$, $p < 0.001$) when compared to the correlation between low HbA1c group and CCT ($r = 0.510$, $p < 0.05$), the amount of change with a unit change in HbA1c was greater in the low HbA1c group than in the high HbA1c group.

The simple linear regression for anterior corneal curvature and HbA1c revealed a weak positive correlation ($r = 0.349$). On average, for every unit increase in difference of HbA1c, there was an increase of 0.069 D in the difference of anterior corneal curvature ($p < 0.05$), as shown in Figure 3.

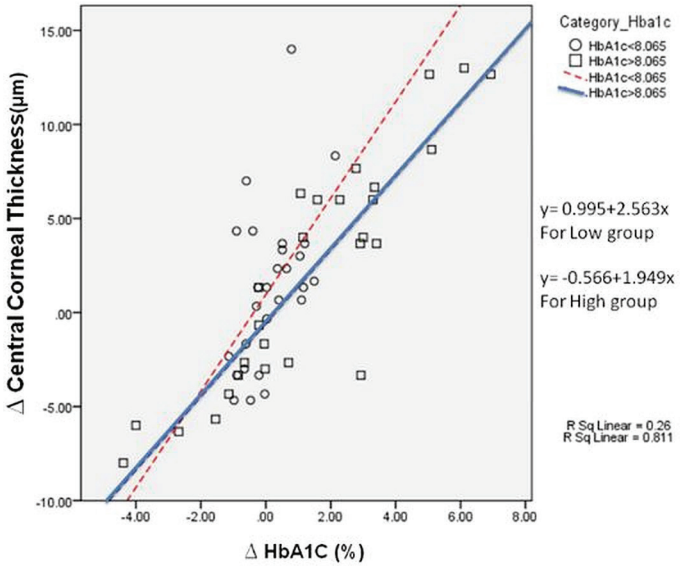

Fig. 2. Scatter plot showing the relationship between ΔCCT and ΔHbA1c among the low and high HbA1c groups.

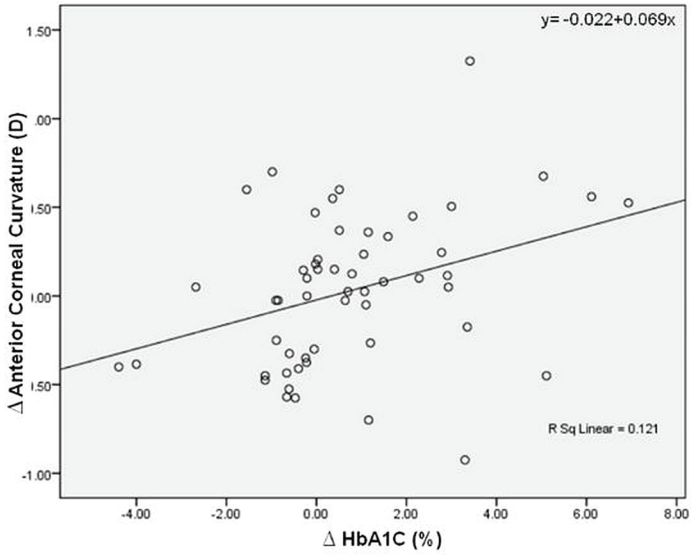

Fig. 3. Scatter plot showing the relationship between Δanterior corneal curvature and ΔHbA1c.

Discussion

The main outcomes of this study demonstrate that both CCT and anterior corneal curvature increase when there is an increase in HbA1c values. Reports have shown an overestimation of IOP in DM patients. This could be due to corneal stiffening caused by high levels of glucose.[5,11] Since our study found a strong positive correlation between CCT and HbA1c, measurement of glucose levels and CCT are necessary to avoid imprecise measurements of true IOP in DM patients.

A study by Shukla *et al.* found a strong correlation between mean CCT and HbA1c values ($r = 0.85$, $p < 0.05$), where analysis was done with only one visit. Our study found a strong correlation between mean difference of CCT (baseline and follow-up) and mean difference of HbA1c ($r = 0.78$, $p < 0.001$). The difference noted between Shukla *et al.* and our study may be due to intrasubject and intersubject variation, where confounding factors such as age and gender might play a role.[7]

Huntjens *et al.* conducted a study with type 1 DM (T1DM) and T2DM patients and found that an increase of 4.5 mM/l would consecutively increase 10 µm of CCT (approximately, a 1% increase in HbA1c corresponds to a 2.2 µm increase in CCT).[8] Our results revealed a mean increase of 1.9 µm in CCT for every unit increase in HbA1c. Given that the clinical features and complications of T1DM and T2DM are different, the discrepancy between our results and those of Huntjens *et al.* may be due to the inclusion of both types of DM in the latter study while we only included T2DM.

While a study by Su *et al.* found an average decrease in CCT of 5.13 µm per decade increase in age,[12] our study found no statistically significant correlation between age and CCT.

Our study found a weak correlation between CCT and DM duration, similar to the findings of Shukla *et al.*[7] Whereas our study found no statistical significance between DM duration and CCT, Lee *et al.*[13] and Pai *et al.*[14] found a statistically significant correlation between DM duration and CCT. The conflicting results between our study and Lee *et al.* and Pai *et al.* may be due to the different ranges of DM duration. Unlike our study, a few other studies found no statistical significance between CCT and glycaemic levels.[8,15,16]

Our study observed a weak positive correlation between anterior corneal curvature and glycaemic levels in DM patients, which is in concordance to Sonmez *et al.*, who noted a statistical difference only at the flattest meridian.[16] In our study, statistical significance was observed regarding the change in average anterior corneal curvature and change in HbA1c levels. In contrast to the present study, Rico *et al.* reported no significant change in anterior corneal curvature with changes in glycaemic levels.[15]

Whereas Huntjens *et al.* did not find a statistically significant change in anterior corneal curvature and glycaemic level,[8] our study found that, on average, a unit increase in HbA1c gives rise to a 0.069 D increase in anterior corneal curvature,

which is statistically significant. However, their study considered venous plasma levels for analysis, which could be influenced by medication, diet, and exercise.

The main limitations of the present study were its short duration and not accounting for diurnal variation of corneal thickness for the ease of the study. Further studies should address the comparison of corneal thickness with HbA1c fluctuations in accordance with different types of treatment modalities and a wider range of DM duration, since few studies have found morphological changes in the cornea mostly after 10 years of onset of DM.

Conclusion

We found that blood glucose levels measured in terms of HbA1c have a significant impact on corneal thickness. The present study showed that changes in CCT and anterior corneal curvature occur in correspondence to changes in HbA1c levels. Thus, careful consideration of HbA1c status is required when conducting comprehensive eye examinations in diabetic patients.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Institutional Ethics Committee (IEC) of Kasturba Hospital and Manipal (IEC-227/2016). The study conformed to the tenets of the Declaration of Helsinki. A prospective cohort-observational study was done by including DM patients from Kasturba Hospital. After an explanation of the procedure in plain terms the subjects could understand, written informed consent was obtained from all participants.

Competing interestes
None to declare.

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None to declare.

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References

1. Yesudian CAK, Grepstad M, Visintin E, Ferrario A. The economic burden of diabetes in India: A review of the literature. Global Health. 2014;10(1).
2. Choo MM, Prakash K, Samsudin A, Kadir AJ. Corneal changes in type ii diabetes mellitus in malaysia. Int J Ophthalmol. 2010;3(3):234–6.
3. Kumar PR, Bhansali A, Ravikiran M, Bhansali S, Dutta P, Thakur JS, et al. Utility of glycated hemoglobin in diagnosing type 2 diabetes mellitus: A community-based study. J Clin Endocrinol Metab. 2010;95(6):2832–5.
4. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australas Med J. 2014;7(1):45–8.
5. Toygar O, Sizmaz S, Pelit A, Toygar B, Kiziloğlu ÖY, Akova Y. Central corneal thickness in type ii diabetes mellitus: Is it related to the severity of diabetic retinopathy? Turkish J Med Sci. 2015;45(3):651–4.
6. Chous P. Diabetes and eye disease : what people with diabetes and healthcare professionals need to know. Diabetes Voice. 2009;54(3):30–3.
7. Shukla E, Nicholson A, Agrawal A, Rathod D. Correlation between severity of Type 2 diabetes mellitus and corneal morphology using specular microscopy in Indian population: A case–control study. Sudan J Ophthalmol. 2016;8(1):30.
8. Huntjens B, Charman WN, Workman H, Hosking SL, O'Donnell C. Short-Term Stability in Refractive Status Despite Large Fluctuations in Glucose Levels in Diabetes Mellitus Type 1 and 2. PLoS One. 2012;7(12).
9. Sonmez B, Bozkurt B, Atmaca A, Irkec M, Orhan M, Aslan U. Effect of glycemic control on refractive changes in diabetic patients with hyperglycemia. Cornea. 2005;24(5):531–7.
10. Altay Y, Burcu A, Ornek F. The change in central corneal thickness after successful control of hyperglycemia in diabetic patients. Int Eye Sci. 2014;14(4):575–8.
11. Krueger, Ramos-Esteban. How might corneal elasticity help us understand diabetes and intraocular pressure. J Refract Surg. 2007;23(3):85–8.
12. Su DHW, Wong TY, Wong WL, Saw SM, Tan DTH, Shen SY, et al. Diabetes, Hyperglycemia, and Central Corneal Thickness. The Singapore Malay Eye Study. Ophthalmology. 2008;115(6):964–9.
13. Lee JS, Oum BS, Choi HY, Lee JE, Cho BM. Differences in corneal thickness and corneal endothelium related to duration in Diabetes. Eye. 2006;20(3):315–8.
14. Pai SG, Vasuraj. Correlation Between Central Corneal Thickness In Diabetics And Non Diabetics When Measured With Spectral Domain Optical Coherence Tomography. Int J Sci Res. 2016;5(4):670–2.
15. Pérez-Rico C, Gutiérrez-Ortíz C, González-Mesa A, Zandueta AM, Moreno-Salgueiro A, Germain F. Effect of diabetes mellitus on Corvis ST measurement process. Acta Ophthalmol. 2015;93(3):e193–8.
16. Inoue K, Kato S, Inoue Y, Amano S, Oshika T. The corneal endothelium and thickness in type II diabetes mellitus. Jpn J Ophthalmol. 2002;46(1):65–9.

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Lack of perceived social support contributes to depression and anxiety in patients with glaucoma

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Abstract

Purpose: To determine the prevalence and associated factors for depression and anxiety among glaucoma patients in a tertiary referral centre. Their relationship with perceived social support is also explored.
Study design: Cross-sectional study involving 176 glaucoma patients.
Methods: Patients with known psychiatric illness, physical limitations, and other visually debilitating ocular conditions were excluded. Measurement tools included the Hospital Anxiety and Depression Scale (HADS) and Multidimensional Scale of Perceived Social Support (MSPSS). Ocular examination parameters such as LogMAR visual acuity, mean deviation (MD) on standard automated perimetry, and intraocular pressure (IOP) were recorded along with sociodemographic and clinical history. Multivariate linear regression analysis was carried out to identify predictive factors for depression and anxiety.
Results: The prevalence of depression and anxiety among glaucoma patients was 6.8% and 9.1% respectively. MSPSS scores were significantly lower in patients with depression ($p = 0.019$) and anxiety ($p = 0.016$). Patients with depression and anxiety had significantly worse visual acuity and MD values. After adjustment with multiple regression analysis, depression or anxiety were still significantly associated with MD values (depression b = -0.13, $p < 0.001$, whereas anxiety b = -0.10, $p = 0.001$) and MSPSS scores (b = -0.08, $p < 0.001$). IOP of the worse eye

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was associated with anxiety (b = 0.2, P = 0.002), whereas widowed status was associated with depression ($p < 0.005$).
Conclusions: Analysed HADS scores in this study show depression and anxiety rates among glaucoma patients in this population are relatively low. Severe glaucoma and lack of perceived social support are significant predictive factors. The findings underline the importance of screening for depression and anxiety in glaucoma patients to provide psychosocial intervention where needed.

Keywords: anxiety, depression, glaucoma, perceived social support, prevalence

Kekurangan Persepsi Sokongan Sosial Menyumbang Kepada Kemurungan Dan Keresahan Pesakit Glaukoma

Abstrak

Tujuan: Untuk menentukan kadar kelaziman dan faktor-faktor yang menyumbang kepada kemurungan dan keresahan di kalangan pesakit glaukoma yang dirawat di hospital tertiari. Hubungkait dengan persepsi sokongan sosial yang diterima pesakit juga dikaji.
Jenis kajian: "Cross-sectional study" melibatkan 176 pesakit glaukoma.
Kaedah: Pesakit yang menghidap masalah psikiatrik, kekurangan upaya fizikal dan mempunyai masalah mata jenis bukan glaukoma tidak dijemput untuk menyertai kajian. Soal selidik yang digunakan termasuklah Skala Gejala Kemurungan Dan Keresahan di Hospital (HADS) dan Skala Multidimensi Persepsi Sokongan Sosial (MSPSS). Pemeriksaan mata yang diuji termasuklah tahap penglihatan, markah purata pesongan (Mean Deviation) di mesin yang mengukur medan penglihatan dan tekanan bola mata. Rekod kesihatan dan demografik pesakit juga dicatit. Analisa 'Multivariate linear regression' telah dijalankan untuk mengenalpasti penyumbang utama kemurungan dan keresahan pesakit.
Keputusan: Kadar kelaziman kemurungan dan keresahan adalah masing-masing 6.8% dan 9.1% di kalangan pesakit glaukoma. Markah MSPSS ketara lebih rendah di kalangan pesakit yang murung (p = 0.019) dan pesakit yang resah (p = 0.016). Pesakit yang murung dan resah mempunyai tahap penglihatan yang lebih teruk dan medan penglihatan yang lebih tertutup (nilai MD rendah). Setelah analisa "multiple regression" diselaraskan, pesakit yang murung dan resah masih lagi menunjukkan keputusan yang ketara untuk dikaitkan dengan nilai MD (kemurungan b = -0.13, $p < 0.001$, manakala keresahan b = -0.10, p = 0.001) dan markah MSPSS (b = -0.08, $p < 0.001$). Tekanan bola mata pula turut dikaitkan

dengan perasaan resah (b = 0.2, P = 0.002), manakala status janda atau duda dikaitkan dengan perasaan kemurungan ($p < 0.005$).
Kesimpulan: Markah HADS yang telah dianalisa dalam kajian ini menunjukkan kadar kemurungan dan keresahan di kalangan pesakit glaukoma rendah berbanding dengan negara lain. Glaukoma yang diperingkat akhir dan kekurangan persepsi sokongan sosial yang diterima adalah antara faktor penentu. Kajian ini telah mencerminkan kepentingan membuat saringan kemurungan dan keresahan dikalangan pesakit glaukoma supaya intevensi awal dapat dilakukan.

Kata kunci: glaukoma, kadar kelaziman, kemurungan, keresahan, persepsi sokongan sosial

Introduction

Glaucoma is a chronic eye condition and the second leading cause of blindness worldwide.[1] The number of individuals estimated to be blind from glaucoma is 4.5 million, accounting for more than 12% of all global blindness.[2] In Malaysia, the 2014 National Eye Survey II showed an estimated prevalence of blindness in those aged 50 and above was at 1.2%, of which 6.6% was caused by glaucoma.[3]

The latest report released by Malaysia's National Health Morbidity Survey in 2015 revealed that the prevalence of mental health problems among adults aged 16 years and above shows an increasing trend, escalating from 10.7% in 1996 to 29.2% in 2015.[4] These increasing trends are similarly found in other Asian nations such as Singapore and India.[5,6] At the same time, a meta-analysis conducted by Yajing *et al.* of 28 pooled selected studies reported the prevalence of depression or depressive symptoms with any ocular disease was 25% (1,502/6,589 individuals, 95% CI, 0.20–0.30), with values ranging from 5.4% to 57.0%.[7] The highest prevalence was among patients with dry eye disease (29%), followed by glaucoma (25%), age-related macular degeneration (24%), and cataracts (23%).[7]

Psychiatric problems such as depression and anxiety are often present in glaucoma patients receiving treatment.[7-12] Previous studies also reported that patients with glaucoma often have coexisting anxiety disorder, with the prevalence between 13.0% and 33.0%.[7-10,13,14] For depressive disorders, the reported prevalence is between 10% and 57%.[8-10,12,16-18] These conditions often lead to unreliable Humphrey Visual Field tests and reduce quality of life for the patient.[8,9,19,20] Depression and anxiety may arise in glaucoma patients due to the fear of potential blindness, heavy economic burden caused by multiple medications and surgeries, and impaired ability to perform daily activities such as driving and reading.[8,21,22] The majority of the studies have concluded that the severity of visual field defects has a direct association with depression and anxiety among glaucoma patients.[8,12,17,23,24]

Perceived social support refers to the perceived availability and adequacy of social connections.[25] Previous studies have shown the importance of social support and how it contributes to good mental health and improved quality of life among different medical conditions.[26-29] The aim of this study was to determine the prevalence and associated factors for depression and anxiety among glaucoma patients in a tertiary referral centre. Their relationship with perceived social support was also explored. To our knowledge, this is the first study linking depression and anxiety with perceived social support among glaucoma patients in Malaysia.

Methods

This was a cross-sectional, observational study undertaken in the Ophthalmology Clinic in a tertiary referral hospital in Malaysia. The study was conducted from August 2018 to August 2019. It was approved by the institution's Medical Research Ethics Committee (MREC 201873-6439). All participants signed an informed consent form before starting the interview session. The study adhered to the tenets of the declaration of Helsinki.

Patients with glaucoma were diagnosed based on European Glaucoma Society criteria, *i.e.*, patients who showed signs of progressive optic neuropathy characterised by morphological changes of the optic nerve head and retinal nerve fibre layer with corresponding visual field defect.[15] We included all patients diagnosed with any type of glaucoma, primary or secondary. Other inclusion criteria were participants aged 18 years old and above, diagnosed to have glaucoma at least 1 month before the interview, able to consent for the interview, and able to communicate in Bahasa Malaysia or English. We excluded patients diagnosed with any psychiatric disorders or physical disabilities other than visual disability, such as being mute, deaf, amputees, and those with total life dependency under treatment with systemic beta-blockers for hypertension or any other conditions deemed likely to contribute to mental health problems. To ensure that the visual impairments were only attributable to glaucoma, we also excluded patients with other causes of blindness including severe macular disease, dense cataract, any retinal disorders, and amblyopia.

Questionnaire

The interview session was carried out in a private quiet room in the eye clinic by a trained interviewer (MFH). The measurement tool used is the Hospital Anxiety and Depression Scale (HADS).[9,12,31] This scale was developed by Zigmond and Snaith to identify and quantify the two most common forms of psychological disturbances, namely depression and anxiety, in physically ill patients in a non-psychiatric setting.[31] The original HADS was translated into Bahasa Malaysia and

validated.[32] The scale consists of seven items for depression and seven items for anxiety, which are scored using the Likert scale from 0 to 3. The calculation is by summation of the scores for all items. The cut-off scores used in the current study is ten, by which 0–10 indicates lack of depression/anxiety and 11–21 indicates that depression/anxiety are present.

Another measurement tool used in the study is the Multidimensional Scale of Perceived Social Support (MSPSS). This scale includes a scoring system for social support that patients receive from family, friends, and significant others.[33] The mean value of 12 components was used to categorize the subjects into low, moderate, and high perceived social support. Scores of 1.0–2.9 indicate low support, 3.0–5.0 indicate moderate support, and 5.1–7.0 indicate high social support.[33]

Statistical analysis

Using a sample size calculator to estimate a single proportion with a level of confidence of 0.95 and based on a prevalence of 10–57% for depression and 13–33% for anxiety, 13% was taken as a factor of interest.[8,9,12,16-18] By assuming 13% of the subjects in the population have the factor of interest, the study required a sample size of 174 patients for estimating the expected proportion with 5% absolute precision and 95% confidence. Data were collected and analysed using SPSS software version 25 (SPSS, Inc., Chicago, IL, USA). Numerical variables were presented using mean, standard deviation, median, interquartile range, and range. Categorical variables were presented as frequency and percentage. The median score of each numerical variable between normal patients and depression/anxiety patients was compared using the Mann-Whitney test. The association of categorical variables and severity of disease was determined using Pearson's chi-squared test with exact *p*-value or Fisher's exact test if the previous test did not hold its statistical assumption. For models with a continuous outcome, we used a linear rather than a logistic regression model to determine the influence of risk factors on depression and anxiety. Factors that were of statistical significance in the univariate analysis were included for multivariable linear regression analysis. The distribution of residuals in these models are less likely to diverge from normality. Additionally, linear models provide a robust estimate of the difference even when the data are not normally distributed.[34] Statistical significance was defined by a *p*-value of less than 0.05.

Results

A total of 190 eligible patients were approached but only 176 patients consented to participate in the study (93% response rate). The sociodemographic characteristics of the patients are presented in Table 1. The majority of patients were

male (56.8%), married (68.8%), and had completed at least secondary education (81.8%). Two-thirds were retired (66.5%) and had perceived high social support with MSPSS median score of 5.58. For clinical characteristics, most participants

Table 1. Sociodemographic characteristics of the study population (*N* = 176)

Variable	**Mean (SD)**
Age, years (SD)	67.5 (13.3)
Gender, *n* (%)	
Male	100 (56.8)
Female	76 (43.2)
Ethnicity, *n* (%)	
Malay	57 (32.4)
Chinese	77 (43.8)
Indian	37 (21.0)
Other	5 (2.8)
Marital status, *n* (%)	
Single	22 (12.5)
Married	121 (68.8)
Divorced/widowed	33 (18.8)
Education, *n* (%)	
No formal education	3 (1.7)
Primary education	29 (16.5)
Secondary education	74 (42.0)
Tertiary education	70 (39.8)
Occupation, *n* (%)	
Unemployed	29 (16.5)
Working full time	23 (13.1)
Working part time	7 (4.0)
Retired	117 (66.5)
MSPSS mean score	
Mean (SD)	5.53 (1.12)
Median (IQR)	5.58 (1.57)
Range	1.58–7.00

MSPSS: Multidimensional Scale of Perceived Social Support; SD: standard deviation; IQR: interquartile range

had a severe level of glaucoma in the worse eye (mean MD -13.93 dB), more than half had been diagnosed for more than 3 years (51%), and most had bilateral disease (89.2%). The study patients had an average HADS-D score of 4.41 and HADS-A score of 4.43 (Table 2).

There was no statistical difference in demographic factors between patients with and without depression or those with and without anxiety. Participants with depression or anxiety had significantly lower MSPSS scores (Table 3). For ocular factors, patients with anxiety had significantly worse LogMAR visual acuity in the worse eye, while both arms of patients had lower MD values on standard automated perimetry (Table 4).

Table 2. Clinical characteristics of study population (*N* = 176)

Variable	**Mean (SD)**
LogMAR VA worse eye	0.59 (0.62)
MD in worse eye, dB	-13.93 (9.95)
IOP worse eye, mmHg	16.49 (6.11)
Type of glaucoma, *n* (%)	
Primary	140 (79.5)
Secondary	36 (20.5)
Duration, *n* (%)	
< 12 Months	19 (10.7)
12–60 Months	65 (36.5)
> 60 Months	92 (51.7)
Laterality, *n* (%)	
Unilateral	19 (10.8)
Bilateral	157 (89.2)
Number of glaucoma surgeries, *n* (%)	
Nil	114 (64.0)
1	42 (23.6)
> 1	20 (11.2)
Type of glaucoma surgery, *n* (%)	
Nil	112 (62.9)
Laser	20 (11.2)
Surgery	40 (22.5)
Surgery + laser	4 (2.2)

Variable	Mean (SD)
Number of glaucoma eyedrops, *n* (%)	
0	9 (5.1)
1	66 (37.5)
2	27 (15.3)
3	36 (20.5)
4	38 (21.6)
Use of topical beta-blockers	102(60%)
Mean HADS-D score	4.41 (3.57)
Frequency of depression, *n* (%)	12 (6.8)
Mean HADS-A score	4.43 (3.93)
Frequency of anxiety, *n* (%)	16 (9.1)

VA: visual acuity; MD: mean deviation on Humphrey Visual Field test; IOP: intraocular pressure; HADS-D: Hospital Anxiety and Depression Scale for Depression; HADS-A: Hospital Anxiety and Depression Scale for Anxiety

Table 3. Comparison of demographic factors associated with depression and anxiety among patients with glaucoma (*N* = 176)

Variable	Without depression *N* = 164	Depression *N* = 12	*p*-value	Without anxiety *N* = 160	Anxiety *N* = 16	*p*-value
Gender, n (%)						
Male	92 (56.1)	8 (66.7)	0.557*	90 (56.3)	10 (62.5)	0.793*
Female	72 (43.9)	4 (33.3)		70 (43.8)	6 (37.5)	
Age mean (SD)	68(13)	63(17)	0.774*	68(11)	68(14)	0.663*
Ethnicity, *n* (%)						
Malay	54 (32.9)	3 (25.0)	0.743**	52 (32.5)	5 (31.3)	0.747**
Chinese	72 (43.9)	5 (41.7)		71 (44.4)	6 (37.5)	
Indian	33 (20.1)	4 (33.3)		32 (20.0)	5 (31.3)	
Other	5 (3.0)	0 (0.0)		5 (3.1)	0 (0.0)	

Variable	Without depression *N* = 164	Depression *N* = 12	*p*-value	Without anxiety *N* = 160	Anxiety *N* = 16	*p*-value
Marital status, *n* (%)						
Single	19 (11.6)	3 (25.0)	0.303**	21 (13.1)	1 (6.3)	0.691**
Married	115 (70.1)	6 (50.0)		110 (68.8)	11 (68.8)	
Divorced/ Widowed	4 (2.4)	0 (0.0)		4 (2.5)	0 (0.0)	
Widow	26 (15.9)	3 (25.0)		25 (15.6)	4 (25.0)	
Education, *n* (%)						
No formal education	3 (1.8)	0 (0.0)	0.278**	3 (1.9)	0 (0.0)	0.334**
Primary education	27 (16.5)	2 (16.7)		24 (15.0)	5 (31.3)	
Secondary education	66 (40.2)	8 (66.7)		67 (41.9)	7 (43.8)	
Tertiary education	68 (41.5)	2 (16.7)		66 (41.3)	4 (25.0)	
Occupation, *n* (%)						
Unemployed	27 (16.5)	2 (16.7)	0.939**	25 (15.6)	4 (25.0)	0.249**
Working full time	21 (12.8)	2 (16.7)		23 (14.4)	0 (0.0)	
Working part time	7 (4.3)	0 (0.0)		6 (3.8)	1 (6.3)	
Retired	109 (66.5)	8 (66.7)		106 (66.3)	11 (68.8)	
Income, *n* (%)						
< 1000	25 (15.2)	3 (25.0)	0.628**	25 (15.6)	3 (18.8)	0.607**
1001–3000	49 (29.9)	3 (25.0)		47 (29.4)	5 (31.3)	
3001–5000	43 (26.2)	4 (33.3)		42 (26.3)	5 (31.3)	
5001–7000	25 (15.2)	2 (16.7)		24 (15.0)	3 (18.8)	
> 7000	22 (13.4)	0 (0.0)		22 (13.8)	0 (0.0)	
Household, *n* (%)						
1–2	61 (37.2)	3 (25.0)	0.559**	60 (37.5)	4 (25.0)	0.467*
3–5	78 (47.6)	6 (50.0)		74 (46.3)	10 (62.5)	
> 5	25 (15.2)	3 (25.0)		26 (16.3)	2 (12.5)	

Variable	Without depression *N* = 164	Depression *N* = 12	*p*-value	Without anxiety *N* = 160	Anxiety *N* = 16	*p*-value
MSPSS score						
Mean (SD)	5.60 (1.05)	4.52 (1.57)	**0.019*** **	5.60 (1.10)	4.87 (1.18)	**0.016****
Range	2.00–7.00	1.58–6.75		1.58–7.00	2.41–6.41	

VA: visual acuity; IQR: interquartile range; SD: standard deviation
*Pearson's Chi-Squared test with exact p-value
**Fisher's exact test
***Mann-Whitney test

Table 4. Comparison of clinical factors associated with depression and anxiety among patients with glaucoma (*n* = 176)

Variable	Without depression (*N* = 164)	Depression (*N* = 12)	*p*-value	Without anxiety (*N* = 160)	Anxiety (*N* = 16)	*p*-value
LogMAR VA in worse eye						
Median (IQR)	0.30 (0.60)	0.70 (1.30)	**0.082***	0.30 (0.60)	1.00 (1.20)	**0.001***
Mean deviation in worse eye (dB)						
Median (IQR)	-11.22 (16.23)	-28.46 (13.68)	**0.004***	-10.65 (16.63)	-17.45 (15.19)	**0.001***
IOP in worse eye (mmHg)						
Median (IQR)	15.00 (5.00)	16.00 (6.00)	0.883*	15.00 (5.00)	16.0 (7.00)	0.126*
Type of glaucoma, *n* (%)						
Primary	130 (79.3)	10 (83.3)	0.957***	126 (78.8)	14 (87.5)	0.531***
Secondary	34 (20.7)	2 (16.7)		34 (21.3)	2 (12.5)	
Duration of glaucoma						
< 12 Months	18 (11.0)	1 (8.3)	0.910***	17 (10.6)	2 (12.5)	0.934**
12–60 Months	60 (36.6)	5 (41.7)		60 (37.5)	5 (31.3)	
> 60 Months	86 (52.4)	6 (50.0)		83 (51.9)	9 (56.3)	

Variable	Without depression (*N* = 164)	Depression (*N* = 12)	*p*-value	Without anxiety (*N* = 160)	Anxiety (*N* = 16)	*p*-value
Laterality, *n* (%)						
Unilateral	18 (11.0)	1 (8.3)	0.982***	18 (11.3)	1 (6.3)	> 0.999**
Bilateral	146 (89.0)	11 (91.7)		142 (88.8)	15 (93.8)	
Number of glaucoma surgeries, *n* (%)						
Nil	106 (64.6)	8 (66.7)	0.535***	106 (66.3)	8 (50.0)	0.349***
1	38 (23.2)	4 (33.3)		36 (22.5)	6 (37.5)	
> 1	20 (12.2)	0 (0.0)		18 (11.3)	2 (12.5)	
Type of glaucoma surgery, n (%)						
Nil	104 (63.4)	8 (66.7)	0.857***	105 (65.6)	7 (43.8)	0.167***
Laser	18 (11.0)	2 (16.7)		16 (10.0)	4 (25.0)	
Surgery	38 (23.2)	2 (16.7)		35 (21.9)	5 (31.3)	
Surgery and laser	4 (2.4)	0 (0.0)		4 (2.5)	0 (0.0)	
Number of glaucoma eyedrops, *n* (%)						
0	9 (5.5)	0 (0.0)	0.939***	9 (5.6)	0 (0.0)	0.182***
1	60 (36.6)	6 (50.0)		63 (39.4)	3 (18.8)	
2	26 (15.9)	1 (8.3)		25 (15.6)	2 (12.5)	
3	34 (20.7)	2 (16.7)		32 (20.0)	4 (25.0)	
4	35 (21.3)	3 (25.0)		31 (19.4)	7 (43.8)	

VA: visual acuity; IQR: interquartile range

*Mann-Whitney test

**Pearson's chi-squared test with exact *p*-value

***Fischer's exact test

Univariate regression analysis showed that divorced status, lower MSPSS scores, visual acuity, and MD values were significantly associated with depression (Table 5). Whereas for anxiety, it was associated with lower income, lower MSPSS score, visual acuity, MD values, recent diagnosis, and a higher number of glaucoma surgeries. From the multivariable analysis, factors that remained associated with depression were MD values, MSPSS scores, and widowed status (Table 6). When MSPSS and marital status were controlled for, an increase in MD value by 1 unit resulted in a decrease of HADS-D score by 0.13 points on average (b = - 0.13, $P < 0.001$). When the MSPSS score increased by 1 point, the HADS-D score was reduced by 0.08 points (b = -0.08, $P < 0.001$). Widowed status was a significant factor for depression.

For anxiety, the multivariable analysis showed significant factors included MD values, MSPSS scores, and intraocular pressure (IOP) in the worse eye. With every increase in MD by 1 unit, the anxiety score decreased by 0.10 points on average (b = - 0.10, $P = 0.001$) with the adjustment of MSPSS and marital status. When the MSPSS score increased by 1 point, the HADS-A score was reduced by 0.08 points (b = -0.08, $P < 0.001$) when other factors were adjusted. With every unit increment in IOP, the patient had 0.20 units higher in HADS-A score on average, with adjustment of MD and MSPSS (b = 0.20, $P = 0.002$).

Table 5. Association factor of HADS-D AND HADS-A scores using univariate linear regression analysis ($N = 176$)

Variable	Depression (HADS-D)			Anxiety (HADS-A)		
	b (se)	95% CI	*p*-value	b (se)	95% CI	*p*-value
Gender						
Male	-0.10 (0.55)	-1.18, 0.97	0.849	-0.59 (0.60)	-1.78, 0.59	0.323
Female	Ref			Ref		
Age	-0.02 (0.02)	-0.06, 0.03	0.469	-0.02 (0.02)	-0.06, 0.03	0.394
Ethnicity						
Other	0.74 (1.68)	-2.58, 4.05	0.661	-2.07 (1.84)	-5.69, 1.56	0.262
Chinese	0.30 (0.63)	-0.95, 1.54	0.639	-0.58 (0.69)	-1.93, 0.78	0.404
Indian	0.01 (0.76)	-1.49, 1.51	0.993	0.33 (0.83)	-1.31, 1.97	0.689
Malay	Ref			Ref		

Variable	Depression (HADS-D)			Anxiety (HADS-A)		
	b (se)	95% CI	*p*-value	b (se)	95% CI	*p*-value
Marital status						
Single	-1.15 (1.00)	-3.14, 0.83	0.252	-0.84 (1.11)	-3.04, 1.35	0.45
Married	-1.27 (0.73)	-2.72, 0.18	0.086	-0.88 (0.81)	-2.48, 0.73	0.283
Divorced	-3.77 (1.89)	-7.51, -0.03	**0.048**	-3.21 (2.10)	-7.35, 0.94	0.128
Widow	Ref			Ref		
Education level						
No formal Education	0.07 (2.17)	-4.21, 4.35	0.975	-3.37 (2.39)	-8.08, 1.35	0.16
Secondary education	-0.22 (0.78)	-1.76, 1.33	0.784	-0.48 (0.86)	-2.18, 1.22	0.578
Tertiary education	-1.02 (0.79)	-2.58, 0.54	0.200	-0.93 (0.87)	-2.65, 0.79	0.286
Postgraduate	-4.93 (3.63)	-12.10, 2.24	0.177	2.97 (4.01)	-4.94, 10.87	0.46
Primary education	Ref			Ref		
Occupation						
Unemployed	0.50 (0.75)	-0.97, 1.97	0.501	0.60 (0.82)	-1.02, 2.22	0.468
Working full time	-0.07 (0.82)	-1.69, 1.54	0.929	0.42 (0.90)	-1.36, 2.20	0.641
Working part time	1.28 (1.40)	-1.48, 4.04	0.361	1.06 (1.54)	-1.98, 4.09	0.494
Retired	Ref			Ref		
Household income						
< 1000	1.87 (1.02)	-0.14, 3.88	0.068	2.35 (1.11)	0.15, 4.55	0.036
1001–3000	1.15 (0.91)	-0.64, 2.94	0.207	1.21 (1.00)	-0.75, 3.18	0.224
3001–5000	0.90 (0.92)	-0.92, 2.72	0.332	2.03 (1.01)	0.04, 4.03	**0.046**
5001–7000	1.73 (1.03)	-0.30, 3.75	0.094	1.88 (1.12)	-0.34, 4.10	0.097

Variable	Depression (HADS-D)			Anxiety (HADS-A)		
	b (se)	95% CI	*p*-value	b (se)	95% CI	*p*-value
>7000	Ref			Ref		
MSPSS score	-1.11 (0.23)	-1.55, -0.66	**< 0.001**	-0.80 (0.26)	-1.31, -0.29	**0.002**
LogMAR VA in worse eye	1.65 (0.42)	0.82, 2.49	**< 0.001**	1.28 (0.48)	0.35, 2.22	0.008
MD in worse eye	-0.13 (0.03)	-0.18, -0.08	**< 0.001**	-0.09 (0.03)	-0.15, -0.03	**0.004**
IOP in worse eye	0.04 (0.04)	-0.05, 0.13	0.386	0.09 (0.05)	-0.01, 0.19	0.062
Type of glaucoma						
Primary	-0.11 (0.67)	-1.43, 1.22	0.873	-0.83 (0.73)	-2.28, 0.62	0.262
Secondary	Ref			Ref		
Duration (months)	-0.06 (0.05)	-0.17, 0.04	0.234	-0.14 (0.06)	-0.25, -0.02	**0.019**
Laterality						
Unilateral	-0.35 (0.87)	-2.06, 1.37	0.691	0.11 (0.96)	-1.78, 2.00	0.907
Bilateral	Ref			Ref		
Number of glaucoma surgeries	0.65 (0.35)	-0.03, 1.33	0.059	0.76 (0.38)	0.01, 1.51	**0.047**
Number of eye drops	0.31 (0.21)	-0.10, 0.73	0.139	0.43 (0.23)	-0.03, 0.89	0.064
Use of topical beta-blockers	0.13 (0.54)	-1.2, 0.95	0.809	0.6 (0.601)	-0.59, 1.78	0.323

VA: visual acuity; MD: mean deviation on Humphrey Visual Field test; IOP: intraocular pressure; HADS-D: Hospital Anxiety and Depression Scale for Depression; HADS-A: Hospital Anxiety and Depression Scale for Anxiety; MSPSS: Multidimensional Scale of Perceived Social Support; REF: Reference

Table 6. Factors associated with depression (HADS-D) and anxiety (HADS-A) in patients with glaucoma by multivariable linear regression analysis (*N* = 151)

Variable	Depression			Anxiety		
	b (se)	**95% CI**	***p*-value**	**b (se)**	**95% CI**	***p*-value**
MD worse eye	-0.13 (0.03)	-0.18, -0.08	< 0.001	-0.10 (0.03)	-0.15, -0.04	0.001
MPSS score	-0.08 (0.02)	-0.12, -0.05	< 0.001	-0.08 (0.02)	-0.12, -0.04	< 0.001
IOP worse eye	-	-	-	0.20 (0.07)	0.08, 0.33	0.002
Marital status						
Single	-2.02 (0.94)	-3.88, -0.17	0.033	-	-	-
Married	-2.05 (0.70)	-3.44, -0.65	0.004	-	-	-
Divorcee	-3.99 (1.64)	-7.23, -0.75	0.016	-	-	-
Widow	Ref			-	-	-

MD: mean deviation on Humphrey Visual Field test MSPSS: Multidimensional Scale of Perceived Social Support; IOP: intraocular pressure; b: unstandardized regression coefficient; CI: confidence interval; se: standard error; Ref: reference Multivariable regression analysis was applied; adj. R^2 = 0.278; residual plot showed the residual was normally distributed and scattered around the band of 0.

Discussion

In the current study, the prevalence of depression and anxiety among glaucoma patients was 6.9% and 9.2%, respectively. For depression, this prevalence is slightly lower than the national average in Malaysia of 8–12%.[27] However, the prevalence of anxiety is slightly higher than the national average, which is quoted as 0.4–5.6%.[35] Our prevalence values are much lower (depression 6.9% *versus* 30%, anxiety 9.2% *versus* 64%) compared to a similar study done in Singapore, where cultural and ethnic distribution are similar to Malaysia.[8,36] Furthermore, compared to other Asian countries, the prevalence of anxiety disorders among glaucoma patients in Malaysia was much lower than in Pakistan (33.0%), China (22.92%), Turkey (13.5%), and Japan (13.0%).[9-12] Similarly, the prevalence of depression in our study was lower than in Pakistan (24.0%), Australia (19.9%), China (16.4%), America (10.9%), and Turkey (57.0%).[9,11,12,17,18]

The differences in prevalence may be attributed to the variety of study designs employed. Many of the studies focused on different types of glaucoma, for example, among primary glaucoma only.[8,10] Furthermore, the differences in prevalence can also be attributed to socioeconomic differences among other countries.[37,38] There have been no studies to determine which scale is superior as a screening tool for depression and anxiety among glaucoma patients. Questionnaires used by other studies include the Self Rating Depression Scale (SDS), Beck Depression Index (BDI II), Patient Health Questionnaire (PHQ 9), Geriatric Depression Scale (GDS 15), Hamilton Depression Rating Scale (HRDS), and Hamilton Depression/Anxiety Rating Scale (HAM-D and HAM-A).[7,8] However, the common assessment tools used in Malaysia are the Beck Depression Inventory (BDI), Depression, Anxiety and Stress Scale (DASS), and Patient Health Questionnaire 9 (PHQ-9), in addition to the Hospital Anxiety and Depression Scale (HADS) used in this study.[31] All these questionnaires were validated in Bahasa Malaysia, which is the national language.[27,32,39-41] We selected HADS as it was the most commonly used in clinical studies. The items used in the scales are also suitable for a non-psychiatric setting.

The findings in this study are in agreement with previous studies that found patients with more severe glaucoma are predisposed to a higher risk of depression and anxiety.[8,9,12,16,18] A lower MD value reflects the patient's functional visual status; several studies have shown that diminished functional vision affects their quality of life. Activities adversely affected include walking, standing, reading, sleep quality; impaired ability to perform these daily activities may eventually lead to depression.[8, 9,20,23]

Our study found that higher IOP in the affected eye is associated with increased anxiety, in contrast with other studies that did not find any association with IOP.[9,10,12,16] Uncontrolled or high IOP in glaucoma patients might lead to significant anxiety due to worry about the loss of sight in the affected eye. Physical manifestations of anxiety include fatigue, restlessness, and difficulty sleeping, which may mimic the

side effects of an antiglaucoma medication.[42-44] Thus, the treating physician should attempt to discern the root cause of the symptoms before stopping any topical antiglaucoma medication. If it is attributable to anxiety, the patient may require psychological intervention rather than cessation of medication or even surgery.

Lack of perceived social support was highly associated with depression and anxiety in this study. This is the first study to show its link with depression and anxiety in glaucoma patients. It is in agreement with many other studies conducted in Malaysia among the general population, where a lack of social support is a predisposing factor for depression.[27,43] Strong social support is also needed to improve the patients' quality of life and eventually leads to good adherence to antiglaucoma medications and compliance to follow-up in clinics.[46-48] In Malaysia, like most Asian nations, societal support is heavily dependent on close family ties or extended relatives. A systematic review by Tengku Mohd *et al.* concluded that the family institution plays a big role in addressing intervention programmes for depression in the Asian population.[49]

Interestingly, widowed status in glaucoma patients was found to be a significant risk factor for depression in our study. This contrasts with a study by Tastan *et al.* in Turkey that found unmarried glaucoma patients had higher levels of depression.[9] Yet another study in Singapore found no association between marital status and depression or anxiety.[8] This factor may be related to the level of perceived social support, as a widowed status implies a patient may have less immediate family support. Other sociodemographic variables such as age, occupation, financial status, and education level were not significantly associated with depression or anxiety among glaucoma patients in this study. This finding differs from those in the general population, where certain sociodemographic variables are risk factors for psychiatric conditions.[48]

Our study also found the use of topical beta-blockers was not found to be associated with depression. While there has been one study in India that reported an association between a self-reported measure of depression and the use of topical beta-blockers, many other studies found no significant association.[8,9,43,50,51] Thus, there is more evidence in the literature that proves that the use of beta-blockers in glaucoma patients does not seem to increase the risk of depression and anxiety.

This study has several strengths. This is the first study in Malaysia to report the prevalence and risk factors of depression and anxiety among patients with glaucoma. We also studied the relationship between depression and anxiety with perceived social support using the MSPSS questionnaire. It is the first time this scale has been used in a psychological study involving glaucoma patients. Our study also has several limitations. The psychological status of glaucoma patients is multifactorial and the independent variables in our study had limited explanatory effects. Other factors not included in our study should also be considered, such as other health comorbidities, side effects of treatment, and somatization. Another limitation is the study design itself, given that a cross-sectional study is unable to analyse behaviour over a specific period. The timing of the sampling is not guaranteed to be a true

representation. Future research should examine these relationships over a longer period in a larger sample size. Lastly, the nature of the assessment questionnaire, where patients may take time to recall the symptom and need to be prompted for answers, may result in recall bias.

In conclusion, the prevalence of depression and anxiety among glaucoma patients in our centre is relatively low compared to other countries.[52,53] Severe disease with low MD scores and lack of perceived social support are risk factors for both depression and anxiety. Additionally, widowed patients are more likely to suffer from depression compared to their married or single counterparts. Uncontrolled IOP constitutes an additional risk factor for anxiety disorder among glaucoma patients. Ophthalmologists and supporting staff should consider screening for depression and anxiety in glaucoma patients in order to provide psychosocial intervention where needed.

Declarations

Ethics approval and consent to participate
This study was approved by the institution's Medical Research Ethics Committee (MREC 201873-6439). All participants signed an informed consent form before starting the interview session. The study adhered to the tenets of the declaration of Helsinki.

Competing interests
None to declare.

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References

1. World Health Organization. Blindness and vision impairment prevention. Available from: https://www.who.int/blindness/causes/priority/en/index6.html
2. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006;90(3):262-267.
3. Chew FLM, Salowi MA, Mustari Z, et al. Estimates of visual impairment and its causes from the National Eye Survey in Malaysia (NESII). PloS One. 2018;13(6):e0198799-e0198799.

4. Ahmad NA, Mohamad Kasim N, et al. Prevalence and determinants of disability among adults in Malaysia: results from the National Health and Morbidity Survey (NHMS) 2015. BMC Public Health. 2017;17(1):756-756.
5. Subramaniam M, Abdin E, Sambasivam R, et al. Prevalence of Depression among Older Adults-Results from the Well-being of the Singapore Elderly Study. Ann Acad Med Singapore. 2016;45(4):123-133.
6. Poongothai S, Pradeepa R, Ganesan A, Mohan V. Prevalence of depression in a large urban South Indian population--the Chennai Urban Rural Epidemiology Study (CURES-70). PLoS One. 2009;4(9):e7185.
7. Zheng Y, Wu X, Lin X, Lin H. The Prevalence of Depression and Depressive Symptoms among Eye Disease Patients: A Systematic Review and Meta-analysis. Sci Rep. 2017;7:46453.
8. Lim NC, Fan CH, Yong MK, Wong EP, Yip LW. Assessment of Depression, Anxiety, and Quality of Life in Singaporean Patients With Glaucoma. J Glaucoma. 2016;25(7):605-612.
9. Tastan S, Iyigun E, Bayer A, Acikel C. Anxiety, depression, and quality of life in Turkish patients with glaucoma. Psychol Rep. 2010;106(2):343-357.
10. Mabuchi F, Yoshimura K, Kashiwagi K, Shioe K, Yamagata Z, Kanba S et al. High prevalence of anxiety and depression in patients with primary open-angle glaucoma. J Glaucoma. 2008;17(7):552-557.
11. Fasih U, Munir HM, Jafri A R, Riaz S U, Shaikh A. Assessment of anxiety and depression in primary open angle glaucoma patients (a study of 100 cases). Pak J Ophthalmol. 2010(26):143-147.
12. Zhou C, Qian S, Wu P, Qiu C. Anxiety and depression in Chinese patients with glaucoma: sociodemographic, clinical, and self-reported correlates. J Psychosom Res. 2013;75(1):75-82.
13. Bechetoille A, Arnould B, Bron A, Baudouin C, Renard JP, Sellem E et al. Measurement of health-related quality of life with glaucoma: validation of the Glau-QoL 36-item questionnaire. Acta Ophthalmol. 2008;86(1):71-80.
14. Hamelin N, Blatrix C, Brion F, Mathieu C, Goemaere I, Nordmann JP. [How patients react when glaucoma is diagnosed?]. J Fr Ophtalmol. 2002;25(8):795-798.
15. European Glaucoma Society. Terminology and Guidelines for Glaucoma (4th Edition). Savona: Publicomm; 2014.
16. Mabuchi F, Yoshimura K, Kashiwagi K, et al. Risk factors for anxiety and depression in patients with glaucoma. Br J Ophthalmol. 2012;96(6):821-825.
17. Skalicky S, Goldberg I. Depression and quality of life in patients with glaucoma: a cross-sectional analysis using the Geriatric Depression Scale-15, assessment of function related to vision, and the Glaucoma Quality of Life-15. J Glaucoma. 2008;17(7):546-551.
18. Wang SY, Singh K, Lin SC. Prevalence and predictors of depression among participants with glaucoma in a nationally representative population sample. Am J Ophthalmol. 2012;154(3):436-444.e432.
19. Tan K, Fhun, L, Yaakub, M, Chong, M, Ahmad-Tajudin LS. Stress and Repetitive Visual Field Assessment in Glaucoma Patients. Journal of Biomedical and Clinical Sciences (JBCS) 2018;2(2):35-41.
20. Quaranta L, Riva I, Gerardi C, Oddone F, Floriani I, Konstas AGP. Quality of Life in Glaucoma: A Review of the Literature. Adv Ther. 2016;33(6):959-981.
21. Ramulu PY, West SK, Munoz B, Jampel HD, Friedman DS. Driving cessation and driving limitation in glaucoma: the Salisbury Eye Evaluation Project. Ophthalmology. 2009;116(10):1846-1853.

22. Ramulu PY, Swenor BK, Jefferys JL, Friedman DS, Rubin GS. Difficulty with out-loud and silent reading in glaucoma. Invest Ophthalmol Vis Sci. 2013;54(1):666-672.
23. Agorastos A, Skevas C, Matthaei M, Otte C, Klemm M, Richard G et al. Depression, anxiety, and disturbed sleep in glaucoma. J Neuropsychiatry Clin Neurosci. 2013;25(3):205-213.
24. Kong X, Yan M, Sun X, Xiao Z. Anxiety and Depression are More Prevalent in Primary Angle Closure Glaucoma Than in Primary Open-Angle Glaucoma. J Glaucoma. 2015;24(5):e57-63.
25. Eagle DE, Hybels CF, Proeschold-Bell RJ. Perceived social support, received social support, and depression among clergy. Journal of Social and Personal Relationships 2018;36(7):2055-2073.
26. Kara S, Tan S, Aldemir S, Yılmaz A, Tatlı M, Dilmen U. Investigation of perceived social support in mothers of infants hospitalized in neonatal Intensive Care Unit. Hippokratia. 2013;17(2):130-135.
27. Ng CG, Mohamed S, See MH, et al. Anxiety, depression, perceived social support and quality of life in Malaysian breast cancer patients: a 1-year prospective study. Health Qual Life Outcomes. 2015;13:205-205.
28. Ioannou M, Kassianos AP, Symeou M. Coping With Depressive Symptoms in Young Adults: Perceived Social Support Protects Against Depressive Symptoms Only Under Moderate Levels of Stress. Front Psychol. 2019;9:2780-2780.
29. Gündüz N, Üşen A, Aydin Atar E. The Impact of Perceived Social Support on Anxiety, Depression and Severity of Pain and Burnout Among Turkish Females With Fibromyalgia. Arch Rheumatol. 2018;34(2):186-195.
30. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol. 2002;86(2):238-242.
31. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-370.
32. Yahya F, Othman Z. Validation of the Malay Version of Hospital Anxiety and Depression Scale (HADS) in Hospital Universiti Sains Malaysia. International Medical Journal (1994) 2015;22:80-82.
33. Zimet G. Multidimensional Scale of Perceived Social Support (MSPSS) - Scale Items and Scoring Information; 2016.
34. Lumley T, Diehr P, Emerson S, Chen L. The importance of the normality assumption in large public health data sets. Annu Rev Public Health. 2002;23:151-169.
35. Wong CH, Sultan Shah ZU, Teng CL, Lin TQ, Majeed ZA, Chan CW. A systematic review of anxiety prevalence in adults within primary care and community settings in Malaysia. Asian J Psychiatr. 2016;24:110-117.
36. Lim RBT, Zheng H, Yang Q, Cook AR, Chia KS, Lim WY. Ethnic and gender specific life expectancies of the Singapore population, 1965 to 2009 - converging, or diverging? BMC Public Health. 2013;13:1012-1012.
37. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health. 2013;34:119-138.
38. Ruscio AM, Hallion LS, Lim CCW, et al. Cross-sectional Comparison of the Epidemiology of DSM-5 Generalized Anxiety Disorder Across the Globe. JAMA Psychiatry. 2017;74(5):465–475.
39. Mukhtar F, Zulkefly NS. The Beck Anxiety Inventory for Malays (BAI-Malay): A Preliminary Study on Psychometric Properties. Malaysian Journal of Medicine and Health Sciences. 2011;7:73-79.

40. Rusli BN, Amrina K, Trived S, Loh KP, Shashi M. Construct validity and internal consistency reliability of the Malay version of the 21-item depression anxiety stress scale (Malay-DASS-21) among male outpatient clinic attendees in Johor. Med J Malaysia. 2017;72(5):264-270.
41. Sherina MS, Arroll B, Goodyear-Smith F. Criterion validity of the PHQ-9 (Malay version) in a primary care clinic in Malaysia. Med J Malaysia. 2012;67(3):309-315.
42. Jeong AR, Kim CY, Kang MH, Kim NR. Psychological Aspects of Glaucoma. J Nerv Ment Dis. 2016;204(3):217-220.
43. Bali SJ, Bali SJ, Parmar T, et al. Evaluation of Major Depressive Disorder in Patients Receiving Chronic Treatment with Topical Timolol. Ophthalmologica. 2011;226(3):157-160.
44. Schweitzer I, Maguire K, Tuckwell V. Antiglaucoma medication and clinical depression. Aust N Z J Psychiatry. 2001;35:569–571.
45. Saifuddin ABA, Tam CL, Lim PC, Bonn G. Examining social support and its relation to worry in Malaysia. Journal of Pacific Rim Psychology. 2019;13:e25.
46. Lunnela J, Kääriäinen M, Kyngäs H. The views of compliant glaucoma patients on counselling and social support. Scand J Caring Sci. 2010;24(3):490-498.
47. Khan TM, Sulaiman SA, Hassali MA, Tahir H. Attitude toward depression, its complications, prevention and barriers to seeking help among ethnic groups in Penang, Malaysia. Ment Health Fam Med. 2009;6(4):219-227.
48. Chan SLH, Hutagalung FD, Lau PL. A Review of Depression and Its Research Studies in Malaysia. International Journal of Education, Psychology and Counseling (IJEPC). 2017;2(4):44-55.
49. Tengku Mohd TAM, Yunus RM, Hairi F, Hairi NN, Choo WY. Social support and depression among community dwelling older adults in Asia: a systematic review. BMJ Open 2019;9(7):e026667.
50. Kaiserman I, Kaiserman N, Elhayany A, Vinker S. Topical beta-blockers are not associated with an increased risk of treatment for depression. Ophthalmology. 2006;113(7):1077-1080.
51. Wilson MR, Coleman AL, Yu F, Fong Sasaki I, Bing EG, Kim MH. Depression in patients with glaucoma as measured by self-report surveys. Ophthalmology. 2002;109(5):1018-1022.
52. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health. 2013;34:119-138.
53. Ruscio AM, Hallion LS, Lim CCW, et al. Cross-sectional Comparison of the Epidemiology of DSM-5 Generalized Anxiety Disorder Across the Globe. JAMA Psychiatry. 2017;74(5):465–475.

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Ganglion cell layer-inner plexiform layer thickness and vision loss in cerebral palsy

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Abstract

Purpose: To determine if measurements of macular ganglion cell layer-inner plexiform layer (GCLIPL) thickness can discriminate between cerebral palsy patients with and without vision loss using spectral domain optical coherence tomography (SDOCT).
Study design: Cross-sectional.
Materials and methods: Participants with cerebral palsy enrolled in a prospective study of SDOCT were included if they were cooperative for visual acuity (VA) testing and macular SDOCT images were acquired. Manual segmentation of the macular GCLIPL was performed using elliptical annuli with diameters of 4.5 mm. Subjects with VA < 6/9 were defined as having abnormal vision. Mann-Whitney U test was used to evaluate the relationship between vision and macular GCLIPL thickness. Data were analysed using SPSS version 22.0 software.
Results: Forty study eyes (normal vision = 17 eyes; abnormal vision = 23 eyes) from 21 participants with spastic cerebral palsy were included. Most subjects were male (61.90%, *n* = 13) and the median age was 13 years (range from 7 to 29 years). The median visual acuity was 0.1 logMAR for subjects with normal vision and 0.3 logMAR for subjects with abnormal vision. Eyes with normal vision had higher average GCLIPL thickness (mean = 106.3 ± 27.85 µm) compared to eyes with abnormal vision (mean = 96.6 ± 36.47 µm). However, a significant association between GCLIPL thickness and visual impairment could not be established in this study.
Conclusion: Our study demonstrated a reduction in macular GCLIPL thickness in

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cerebral palsy patients with visual impairment but did not fully support its use as surrogate marker of cerebral visual impairment due to study limitations. Future longitudinal studies are advised to elucidate the relationship between macular GCLIPL and cerebral visual impairment.

Keywords: cerebral palsy, ganglion cell layer, spectral domain optical coherence tomography, visual impairment

Ketebalan lapisan sel ganglion-pleksifom dalam dan ketajaman penglihtan di kalangan palsi serebrum

Abstrak

Tujuan: Bagi mengenalpasti samada pengukuran ketebalan lapisan sel-ganglion-pleksifom dalam (GCLIPL) menggunakan tomografi koheren optikal spektral domain (SDOCT) dapat mendiskriminasikan kehilangan penglihatan dalam kalangan pesakit cerebral palsi.
Bentuk kajian: Keratan-rentas
Metodologi dan bahan kajian: Pesakit cerebral palsi dipilih sekiranya mereka dapat memberi kerjasama dalam mengukur ketajaman penglihatan dan pengambilan pengukuran GCLIPL pada macula menggunakan SDOCT. Segmentasi GCLIPL dilakukan secara manual menggunakan annuli eliptikal yang bersaiz 4.5mm diameter. Pesakit yang mempunyai ketajaman penglihatan yang kurang dari 6/9 dikenaplasti sebagai pesakit mempunyai penglihatan yang tidak normal. Ujian Mann-Whitney U digunakan bagi memeriksa hubungkait di antara ketajaman penglihatan dan ketebalan GCLIPL pada makula. SPSS versi 22.0 digunakan bagi menganalisa data.
Keputusan: Sebanyak 40 mata (ketajaman penglihatan yang normal: 17, ketajaman penglihtan yang tidak normal: 23) daripada 21 pesakit cerebral palsi jenis spastik terlibat dalam kajian ini. Kebanyakan daripada mereka adalah lelaki (61.9%, n = 13) berumur median 13 tahun (julat umur 7 hingga 29 tahun). Median ketajaman penglihtan adalah 0.1 log MAR bagi penglihatan normal dan 0.3 logMAR bagi penglihatan tidak normal. Mata yang mempunyai ketajaman penglihatan yang normal mempunyai purata ketebalan GCLIPL yang lebih tinggi (106.3 ± 27.85 μm) berbanding dengan mata yang ketajaman penglihtan yang tidak normal (96.6 ± 36.47 μm). Walaubagaimanpun, tiada sebarang hubungkait yang signifikan antara ketebalan GCLIPL dan ketajaman penglihtan.
Rumusan: Berdasarkan kajian ini terdapat penurunan ketebalan GCLIPL pada

makula pesakit cerebral palsi yang mempunyai kecacatan penglihatan tetapi kegunaan GCLIPL sebagai penanda pengurangan tahap penglihatan tidak dapat dibuktikan disebabkan oleh limitasi kajian ini. Kajian secara membujur pada masa akan datang dapat membantu menjelaskan hubungkait antara GCLIPL macula dan kecacatan penglihatan serebrum.

Kata kunci: cerebral palsi, kecacatan penglihatan, lapisan sel-ganglion, tomografi koheren optikal spektral domain

Introduction

Cerebral palsy is defined as a range of nonprogressive syndromes of posture and motor impairment due to a defect or lesion of the developing brain. Worldwide population-based studies have reported a prevalence of 1.5 to more than 4 per 1,000 live births, but the rates vary from country to country and also within countries.[1,2] Cerebral palsy is chronically disabling and is often accompanied by co-occurring developmental disabilities, cognitive deficit, and perception disturbances. Visual disorders in children with cerebral palsy can be ocular or cerebral in origin.[3] Ocular defects associated with cerebral palsy encompass mainly refractive error, squint, squint with amblyopia, nystagmus, and ptosis. Cerebral visual impairment (CVI) is not uncommon in children with cerebral palsy. As the name implies, CVI occurs as a result of injury to the visual association cortices, their interconnecting pathways, and higher visual processing centres in a developing brain of the foetus and the newborn by a set of predisposing antenatal factors, perinatal, and postnatal aggravating events,[1,3,4] Damage to the visual association cortices can impair visual acuity, restrict the visual field, and cause oculomotor incoordination, whereas damage to higher visual processing centres often result in visual, cognitive, and perceptual impairment.[5,6]

The European Cerebral Palsy study has identified several neuropathologies in cerebral palsy.[7] White matter damage of immaturity or cerebral white matter injury, including periventricular leukomalacia and/or intraparenchymal haemorrhage, was the most common finding, followed by other pathologies such as basal ganglia lesions, cortical/subcortical lesions, malformations, and focal infarcts.[6,7] These neuropathologies, caused by various ischaemic and nonischaemic causative factors of cerebral palsy, result in axonal degeneration. Axonal degeneration in the manner of retrograde transynaptic degeneration (RTSD) has been demonstrated in cerebral palsy, which then results in CVI.[7-10]

Cerebral visual dysfunction is difficult to diagnose and is often incorrectly ascribed to apparent developmental disorders. Therefore, identification and measurement of visual dysfunction should be actively sought for early visual rehabilitation in children with cerebral palsy. Early on, the retinal nerve fibre layer thickness has

been widely opted as a biomarker for wide arrays of neurodegenerative disease and cerebral damage. With technological advancement and development of new software, optical coherence tomography now provides rapid, noninvasive, and objective measurement of the inner retinal layers of the macula, the ganglion cell layer, and inner plexiform layer (GCLIPL). Many studies have reported evidence of retinal GCLIPL reduction as a result of RTSD from cortical insult.[11-14] Herro and Lam demonstrated retrograde transynaptic retinal ganglion cell loss in patients with homonymous hemianopsias from ischaemic occipital injury.[15] Choi *et al.* and Garcia-Martin *et al.* have revealed the association between ganglion cell layer reduction with severity of Alzheimer's disease, suggesting that GCLIPL thickness could potentially be an early biomarker of neurodegeneration in Alzheimer's disease.[11,12] Therefore, the aim of this study is to illustrate the reduction of macular GCLIPL thickness in cerebral palsy patients with visual impairment. We hypothesize that said reduction is attributed to RTSD, which can lead to CVI in cerebral palsy patients.

Materials and methods

This cross-sectional study was conducted during an eye screening programme in Johor Cerebral Palsy School in February 2019. All participants underwent basic ocular examination, including visual acuity (VA) assessment, refraction, fundus examination, and spectral domain optical coherence tomography (SDOCT) macular assessment. Only subjects with intellectual and motor prerequisites to cooperate for ocular assessment and the ability to maintain fixation during SDOCT were included in this study via convenience sampling.

As a result of co-occurring developmental disabilities and cognitive impairment in cerebral palsy subjects, VA assessment was carried out using age-appropriate methods as in preverbal and preliterate subjects. Recognition acuity was assessed using Cardiff acuity test, LEA symbols chart, Sheridan Gardiner single letter optotypes, Bock's candy test, and miniature toy test, whereas resolution acuity was assessed with LEA grating paddles. VA assessment was carried out according to established protocol and the results obtained were converted to logarithm of the minimal angle of resolution (LogMAR) units. Subjects with VA < 6/9, LogMAR equivalence > 0.18, were labelled as having abnormal VA.

Retinal scans were obtained using the spectral domain optical coherence tomography from the HOCT-1/1F (HUVITZ Co., Ltd., Dongan-gu, Anyang-si, Gyeonggi-do, Republic of Korea). Macular scanning was conducted using scan protocol 3-D scan, which covers 9 mm x 12 mm of the retina with fovea centred in order to obtain GCLIPL thickness. The thickness maps were divided into six sectors representing the superior, superotemporal, superonasal, inferior, inferotemporal, and inferonasal of the elliptic GCLIPL layer. The outcome report illustrated GCLIPL thickness for each sector and a total average value (mean GCLIPL).

The demographic data and clinical characteristics were summarized by descriptive statistics, *i.e.*, continuous variables such as age and VA of subjects were not normally distributed and therefore were recorded as median and interquartile range; categorical data were recorded as percentages. The total average GCLIPL thickness and GCLIPL thickness by anatomic sectors were checked for Gaussian distribution by using skewness and kurtosis. GCLIPL thickness was normally distributed in subjects with normal and abnormal vision and was presented as mean value and standard deviation. To evaluate the relationship between total average GCLIPL thickness and GCLIPL thickness by anatomic sector with groups of normal and abnormal VA, nonparametric Mann-Whitney U-test was applied due to the small study group, regardless of data being Gaussian distributed. Statistical analyses were performed using the Statistical Package for the Social Sciences version 22 (SPSS, Inc., Chicago, IL, USA). *P*-values of < 0.05 were considered to indicate statistical significance.

Results

Twenty-one subjects met the inclusion criteria. Two subjects contributed only one study eye due to poor cooperation or poor image quality, resulting in a total of 40 study eyes. Demographic data and VA in LogMAR for subjects with normal and abnormal vision are summarized in Table 1. There were 17 eyes with normal vision and 23 eyes with abnormal vision. The eyes with normal vision had VA 0.1 LogMAR, whereas eyes with abnormal vision had VA 0.3 LogMAR. The GCLIPL

Table 1. Demographics and clinical characteristics of subjects with cerebral palsy

Demographics		
Age, *median (IQR)*	13 (7)	
Gender, *n (%)*		
Male	13 (61.90)	
Female	8 (38.10)	
Ethnicity, *n (%)*		
Malay	12 (57.1)	
Indian	5 (23.8)	
Chinese	4 (19.0)	
Clinical characteristics	**Normal vision** *N* = 17	**Abnormal vision** *N* = 23
Visual acuity (logMAR), *median* (IQR)	0.10 (0.10)	0.30 (0.40)
BCVA (logMAR), *mean* (*SD*)	0.04 (0.05)	0.27 (0.08)

BCVA: best-corrected visual acuity; IQR: interquartile range; SD: standard deviation

Table 2. Average macular GCLIPL thickness and GCLIPL thickness by anatomic sectors

GCLIPL (µm)	Vision			
	Normal (*n* = 16) SD (mean)	**Abnormal (*n* = 22) SD (mean)**	***Z***	***p*-value**
Average	106.3 (27.85)	96.6 (36.47)	-1.892	0.058
Superior	99.9 (23.79)	87.0 (22.79)	-1.686	0.092
Superotemporal	97.5 (12.50)	84.1 (18.62)	-2.264	0.024
Superonasal	109.7 (20.76)	94.8 (20.45)	-1.834	0.067
Inferior	107.8 (16.15)	94.0 (20.58)	-1,894	0.058
Inferotemporal	97.9 (17.09)	88.1 (20.10)	-1.790	0.073
Inferonasal	110.4 (21.95)	100.9 (18.89)	-1.272	0.203

GCLIPL: ganglion cell layer inner plexiform layer; SD: standard deviation

thickness measured 106.3 µm in eyes with normal vision, with reduced thickness measuring 96.6 µm in eyes with visual impairment. The analysis showed that there was no significant difference in GCLIPL thickness with VA. Therefore, an association between GCLIPL thickness and visual impairment could not be established.

There was also a reduction in mean GCLIPL thickness in all anatomic sectors in subjects with abnormal vision compared to subjects with normal vision, but the reduction was not significant (Table 2). Table 3 shows the ocular characteristics of cerebral palsy patients with abnormal vision. All eyes in this cohort were diagnosed to have refractive error and they could not be fully corrected to Snellen VA better than 6/9. Refractive errors were classified as follows: low myopia < -3.00 D, -3.00 D < moderate myopia < -6.00 D, and high myopia > -6.00 D; low hypermetropia ≤ +2.00 D, +2.00 D < moderate hypermetropia < +5.00 D, and high hypermetropia > +5.00 D; 0.25 < low astigmatism < 1.5 D, 1.5 D < moderate astigmatism < 3 D, and high astigmatism > 3 D.

Of the 23 eyes with visual impairment, 12 eyes (52.2%) were hypermetropic (10 had low hyperopia and 2 had moderate hyperopia), 7 eyes (30.4%) were myopic (3 with low myopia, 3 with moderate myopia, and 1 with high myopia), and 4 eyes

(17.4%) were emmetropic. Nineteen out of 23 eyes (82.6%) had astigmatism: 11 eyes had low astigmatism, 5 eyes had medium astigmatism, and 3 eyes had high astigmatism. Only one subject in this cohort had strabismus. All subjects had otherwise normal dilated fundus examination.

The gross motor function of subjects was categorized using the Gross Motor Function Classification System (GMFCS). GMFCS is a five-level clinical classification system used to describe the gross motor function of people with cerebral palsy on the basis of self-initiated movement abilities. Lower GMFCS levels correspond to milder forms of cerebral palsy and vice versa.[16,17] All recruited subjects had good gross motor function with GMFCS level III and below as per the study's inclusion criteria, which required subjects able to cooperate and complete the ocular examination and SDOCT assessment. We observed that subjects with GMFCS level IV and V showed difficulty maintaining antigravity head/trunk postures and fixation and dyskinetic movement, which would have rendered ocular assessment and SDOCT capture challenging for this study.

Table 3. Ocular characteristics of eyes with abnormal vision

Patient	Eye	Sphere	Cylinder	BCVA (LogMAR)	Strabismus	Fundus examination
1	1	Emmetropia	Medium	0.30	No	Normal
	2	Emmetropia	Medium	0.30		
2	3	Low hyperopia	Medium	0.30	No	Normal
	4	Low hyperopia	Low	0.30		
3	5	Moderate hyperopia	Low	0.30	No	Normal
	6	Moderate hyperopia	Low	0.30		
4	7	Moderate myopia	Low	0.50	No	Normal
	8	High myopia	Medium	0.40		
5	9	Low hyperopia	Low	0.20	No	Normal
	10	Low hyperopia	No	0.20		
6	11	Low myopia	No	0.30	No	Normal
	12	Low hyperopia	Low	0.30		

Patient	Eye	Sphere	Cylinder	BCVA (LogMAR)	Strabismus	Fundus examination
7	13	Emmetropia	No	0.18	No	Normal
	14	Emmetropia	No	0.18		
8	15	Low hyperopia	Low	0.18	No	Normal
	16	Low hyperopia	Low	0.18		
9	17	Low hyperopia	Low	0.20	Yes	Normal
10	18	Low hyperopia	High	0.18	No	Normal
	19	Low hyperopia	Medium	0.18		
11	20	Moderate myopia	High	0.30	No	Normal
	21	Moderate myopia	High	0.30		
12	22	Low myopia	Low	0.30	No	Normal
	23	Low myopia	Low	0.30		

BCVA: best-corrected visual acuity

Discussion

A wide array of visual problems has been reported in children with cerebral palsy. Children with cerebral palsy often have comorbidities and associated deficits, such as cognitive defects and dyskinesia in athetoid cerebral palsy, which make the identification and evaluation of visual problems difficult. This is even more so in young and noncooperative cerebral palsy subjects. As a result, timely intervention and visual rehabilitation cannot be offered to children with cerebral palsy because of this diagnostic delay.

Accurate assessment of visual function and timely detection of visual problems among cerebral palsy patients will lead to improved patient care, thence quality of life. To date, the most appropriate ophthalmological tools which can be used to delineate ocular deficits of visual decline from cortical blindness in cerebral palsy patients are still unknown. Several studies have demonstrated OCT-verified thinning of GCLIPL in adult subjects with acquired CVI.[18-22] However, such studies are scarce in cerebral palsy subjects since they cannot undergo comprehensive

ocular assessment. A study conducted by Jacobson et. al. recruited a small number of cerebral palsy subjects and found convincing evidence of RTSD by establishing a topographical relationship between GCLIPL and visual field defects that corresponded to the location and extent of the primary brain lesion.[13,21] Therefore, we conducted this study with the aim to identify cerebral palsy patients with CVI by demonstrating a reduction in macular GCLIPL thickness.

Based on the analysis, our study has demonstrated a reduction in macular GCLIPL thickness among eyes with visual impairment compared to eyes with normal vision. We attribute the decrease in VA to CVI secondary to RTSD, as evidenced by the reduction of macular GCLIPL thickness. However, we could not establish a significant relationship between macular GCLIPL thickness and VA. Further analysis on eyes with visual impairment has shown that all eyes in this cohort were structurally normal and had refractive errors with reduced best-corrected Snellen VA of 6/9 or worse.

Several postulations have been made to explain the study outcome. First, we observed that the majority of eyes in visual impairment cohort were structurally normal and had refractive error with reduced best-corrected Snellen VA of ≤ 6/9 (Table 3). This could be attributed to amblyopia. Amblyopia is defined as reduction of BCVA to ≤ 6/9 in Snellen optotype that is not accounted for by other ocular pathologies as a result of abnormal visual stimulation which has occurred during the years of visual development. In our cohort, one subject had strabismus (Eye 17, Table 3), which might have caused amblyopia or a sequela of amblyopia. There were no other signs that could have predisposed our subjects to deprivational or anisometropic amblyopia. Moreover, additional tests such as streoacuity, binocular function, optokinetic nystagmus, visual evoked potential, etc., which can help to ascertain the diagnosis of amblyopia, were not performed in this study. Therefore, we faced a diagnostic dilemma as we were unable to discern CVI from amblyopia in our cohort with abnormal vision. This might explain the lack of significance with the use of macular GCLIPL thickness as a predictor of CVI in our study.

Moreover, we could not establish convincing solid evidence of RTSD in our study as our subjects did not undergo perimetry and neuroimaging with a special focus on the visual pathway, which can help relate GCLIPL topography to brain lesions. Thus, we could not confidently attribute the definite cause of vision impairment in our cohort to CVI and this helps to explain the insignificant reduction of macular GCLIPL thickness in our cohort. Thirdly, some children with cerebral palsy are able to perceive, but have difficulty understanding and organizing visual information. Cerebral palsy is commonly associated with 30% to 50% of intellectual disability and learning difficulties. Our subjects with visual impairment could be experiencing difficulty processing visual information rather than an inability to see. Our study could not have discerned between these two based on VA and refractive assessment alone. This could justify the insignificant reduction of GCLIPL complex in our subjects with visual impairment.

Most of the subjects recruited in our study had GMFCS level III and below. As a result, they were physically and intellectually able to complete our study's eye assessment. We postulate that subjects with low GMFCS levels correspond to milder cerebral insult, which results in minimal or no reduction in GCLIPL thickness as there is lesser degree of RTSD. Thus, the majority of the subjects in this study had comparatively well-preserved GCLIPL thickness. This sampling bias may have resulted in statistically insignificant association between GCLIPL thickness and visual impairment. Last but not least, the small sample size and lack of control group in this study have contributed to the insignificant study outcomes.

This is a pilot study. Our study had a number of other limitations, including its cross-sectional design, which restricts our ability to imply causality. Manual segmentation of the macula is not only time consuming, but also prone to operator error. Future studies may be improved by enrolling larger samples with control cohorts. Randomisation of subjects and recruitment of different subtypes of cerebral palsy will help to improve the generalizability of the study. Assessment of cerebral palsy subjects, especially in those with high GMFCS levels, pose immense challenges. Future studies will therefore be better conducted alongside an optometrist team specialising in CVI assessment for objective assessment of VA in cerebral palsy patients. The use of handheld SDOCT may also be considered to facilitate data collection.

Conclusion

Our study revealed a reduction of macular GCLIPL thickness in cerebral palsy patients with visual impairment but did not fully support the use of macular GCLIPL as a surrogate marker of CVI in cerebral palsy patients due to study limitations. Future longitudinal research with probability sampling could elicit convincing evidence of RTSD, thereby elucidating the topographical relationship between macular GCLIPL thickness and brain lesions in order to promote the use of macular GCLIPL as a potential indicator of CVI impairment in cerebral palsy patients.

Declarations

Ethics approval and consent to participate.
This work adheres to the guidelines and principles of the Declaration of Helsinki and is in accordance with the Malaysian Good Clinical Practice (MGCP) 4th edition 2018. Information sheets and consent forms regarding the screening programme was distributed to the parents/guardians of the students attending Johor Cerebral Palsy School's prior to the study and all subjects recruited in our study had informed consented from their parents/guardians to undergo eye examination. This research

is also registered with the National Medical Research Register (NMRR) and obtained publication/presentation approval granted by the Director General of Health Malaysia.

Competing interests
None to declare.

Funding
None to declare.

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References

1. Marret S, Vanhulle C, Laquerriere A. Pathophysiology of cerebral palsy. Handb Clin Neurol. 2013;111:169-76.
2. Vitrikas K, Dalton H, Breish D. Cerebral Palsy: An Overview. Am Fam Physician. 2020;101(4):213-20.
3. Striber N, Vulin K, Đaković I, et al. Visual impairment in children with cerebral palsy: Croatian population-based study for birth years 2003-2008. Croat Med J. 2019;60(5):414-20.
4. Schenk-Rootlieb AJ, van Nieuwenhuizen O, van der Graaf Y, Wittebol-Post D, Willemse J. The prevalence of cerebral visual disturbance in children with cerebral palsy. Dev Med Child Neurol. 1992;34(6):473-80.
5. Ego A, Lidzba K, Brovedani P, et al. Visual-perceptual impairment in children with cerebral palsy: a systematic review. Dev Med Child Neurol. 2015;57Suppl 2:46-51.
6. Galli J, Ambrosi C, Micheletti S, et al. White matter changes associated with cognitive visual dysfunctions in children with cerebral palsy: A diffusion tensor imaging study. J Neurosci Res. 2018;96(11):1766-74.
7. Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy: the European Cerebral Palsy Study. JAMA. 2006;296(13):1602-8.
8. de Vries-Knoppert WA, Baaijen JC, Petzold A. Patterns of retrograde axonal degeneration in the visual system. Brain. 2019;142(9):2775-86.
9. Schwartz SG, Monroig A, Flynn HW, Jr. Progression of Transsynaptic Retinal Degeneration with Spectral-Domain Optical Coherence Tomography. Am J Ophthalmol Case Rep. 2017;5:67-72.
10. Dinkin M. Trans-synaptic Retrograde Degeneration in the Human Visual System: Slow, Silent, and Real. Curr Neurol Neurosci Rep. 2017;17(2):16.

11. Choi SH, Park SJ, Kim NR. Macular Ganglion Cell -Inner Plexiform Layer Thickness Is Associated with Clinical Progression in Mild Cognitive Impairment and Alzheimers Disease. PLoS One. 2016;11(9):e0162202.
12. Garcia-Martin E, Bambo MP, Marques ML, Satue M, Otin S, Larrosa JM, et al. Ganglion cell layer measurements correlate with disease severity in patients with Alzheimer's disease. Acta Ophthalmol. 2016;94(6):e454-9.
13. Jacobson L, Lennartsson F, Nilsson M. Ganglion Cell Topography Indicates Pre- or Postnatal Damage to the Retro-Geniculate Visual System, Predicts Visual Field Function and May Identify Cerebral Visual Impairment in Children - A Multiple Case Study. Neuro-ophthalmology (Aeolus Press). 2019;43(6):363-70.
14. Lennartsson F, Nilsson M, Flodmark O, Jacobson L, Larsson J. Injuries to the Immature Optic Radiation Show Correlated Thinning of the Macular Ganglion Cell Layer. Front Neurol. 2018;9:321.
15. Herro AM, Lam BL. Retrograde degeneration of retinal ganglion cells in homonymous hemianopsia. Clin Ophthalmol. 2015;9:1057-64.
16. Noble JJ, Gough M, Shortland AP. Selective motor control and gross motor function in bilateral spastic cerebral palsy. Dev Med Child Neurol. 2019;61(1):57-61.
17. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39(4):214-23.
18. Shao Y, Jiang H, Wei Y, et al. Visualization of Focal Thinning of the Ganglion Cell-Inner Plexiform Layer in Patients with Mild Cognitive Impairment and Alzheimer's Disease. J Alzheimers Dis. 2018;64(4):1261-73.
19. Živković M, Dayanir V, Stamenović J, et al. Retinal ganglion cell/inner plexiform layer thickness in patients with Parkinson's disease. Folia Neuropathol. 2017;55(2):168-73.
20. Schneider CL, Prentiss EK, Busza A, et al. Survival of retinal ganglion cells after damage to the occipital lobe in humans is activity dependent. Proc Biol Sci. 2019;286(1897):20182733.
21. Jacobson L, Lennartsson F, Nilsson M. Retinal ganglion cell topography predicts visual field function in spastic cerebral palsy. Dev Med Child Neurol. 2020;62(9):1100-6.
22. Gu S, Glaug N, Cnaan A, Packer RJ, Avery RA. Ganglion cell layer-inner plexiform layer thickness and vision loss in young children with optic pathway gliomas. Invest Ophthalmol Vis Sci. 2014;55(3):1402-8.

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Clinical evaluation of a new hydrophobic acrylic preloaded intraocular lens with a novel delivery system

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Abstract

Purpose: To evaluate clinical outcomes of patients implanted with the Clareon® monofocal intraocular lens (IOL) with AutonoMe™, an automated disposable preloaded delivery device.
Design: Retrospective review.
Methods: One hundred and eight eyes of 88 patients underwent uneventful phacoemulsification cataract surgery and implantation with the Clareon IOL. The primary endpoints were best-corrected distance acuity (BCDA), uncorrected distance acuity (UCDA), and proportion of patients achieving UCDA of logarithm of Minimal Angle of Resolution (logMAR) 0.18 or better at 1 month. Secondary endpoints included refractive stability and predictability, contrast sensitivity as well as wound stretch and surgically induced astigmatism (SIA).
Results: The mean BCDA and UCDA at 1 month were logMAR 0.06 ± 0.08 and 0.18 ± 0.17, respectively. 93.8% of eyes had BCDA of logMAR 0.18 or better, and all eyes had BCDA of logMAR 0.3 or better. 80.9% of eyes had UCDA of 0.18 or better, and 97.8% of eyes had UCDA of 0.3 or better. All eyes were within 0.75 D of refractive target, 90.9% were within 0.5 D, and 68.7% were within 0.25 D. The mean contrast values (logMAR) were 1.73 ± 0.18 at 3 cpd, 1.91 ± 0.24 at 6 cpd, 1.62 ± 0.25 at 12 cpd, and 1.09 ± 0.28 at 18 cpd. Mean wound stretch and centroid SIA for a 2.2 mm incision was 0.04 ± 0.05 mm and 0.10 D, respectively. There was no wound stretch for a 2.4 mm incision and centroid SIA was 0.23 D.

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Conclusion: The Clareon IOL provided excellent visual outcomes and good refractive predictability. The AutonoMe delivery system did not cause significant corneal wound stretch or astigmatism.

Keywords: Clareon AutonoMe, hydrophobic acrylic, Malaysia, preloaded intraocular lens

Abstrak

Pengajian klinikal kanta intraokular hidrofobik baru yang dimuatkan dengan sistem penghantaran novel

Tujuan: Untuk menilai keputusan klinikal pesakit yang menerima kanta Clareon® intraokular monofocal (IOL) dengan AutonoMe™, sistem penghantaran IOL yang automatik.
Jenis kajian: Retrospektif.
Kaedah: 108 mata daripada 88 pesakit menjalani pembedahan katarak phacoemulsification yang tiada komplikasi dan diimplantasi dengan Clareon® IOL. Titik akhir utama adalah ketajaman visual yang terbaik diperbetulkan (BCDA), ketajaman visual yang tidak dibetulkan (UCDA) dan perkadaran pesakit yang mencapai UCDA logaritma Sudut Minimum Resolusi (logMAR) 0.18 atau lebih baik pada 1 bulan. Titik akhir sekunder termasuk kestabilan dan ramalan refraktif, sensitiviti kontras serta regangan luka dan astigmatisme yang disebabkan pembedahan (SIA).
Keputusan: Purata BCDA dan UCDA pada 1 bulan masing-masing adalah logMAR 0.06 ± 0.08 dan 0.18 ± 0.17. 93.8% mata mempunyai BCDA logMAR 0.18 atau lebih baik, dan semua mata mempunyai BCDA logMAR 0.3 atau lebih baik. 80.9% mata mempunyai UCDA 0.18 atau lebih baik, dan 97.8% mata mempunyai UCDA 0.3 atau lebih baik. Semua mata berada dalam lingkungan 0.75D sasaran refraktif, 90.9% berada dalam lingkungan 0.5D dan 68.7% berada dalam lingkungan 0.25D. Purata sensitivity kontras (logMAR) adalah 1.73 ± 0.18 pada 3 cpd, 1.91 ± 0.24 pada 6 cpd, 1.62 ± 0.25 pada 12 cpd dan 1.09 ± 0.28 pada 18 cpd. Purata regangan luka dan centroid SIA untuk hirisan 2.2 mm adalah 0.04 ± 0.05 mm dan 0.10D, masing-masing. Tiada regangan luka untuk hirisan 2.4 mm dan centroid SIA adalah 0.23 D.
Kesimpulan: Clareon IOL memberikan hasil visual yang sangat baik dan ramalan refraktif yang baik.Sistem penyampaian AutonoMe tidak menyebabkan regangan luka kornea yang ketara atau astigmatisme.

Kata kunci: Clareon Autonome, hidrofobik akrilik, kanta intraokular pramuat, Malaysia

Introduction

The Clareon® intraocular lens (IOL) is a new, single-piece, hydrophobic acrylic IOL manufactured by Alcon Laboratories (Fort Worth, TX, USA) that became available for use in Malaysia in early 2019. This IOL is made from a new biomaterial, which is a hydrophilic copolymer (2-hydroxyethylmethacrylate)[1] with a water content of 1.5% (at 35°C), refractive index of 1.55, and glass transition temperature of 9.1°C.[2] Its overall design is based on the single-piece Acrysof IOL platform (water content of 0.4%), with the same 6.0 mm biconvex optic and 13.0 mm length. Clareon has an aspheric anterior surface with precision edge design for reducing edge glare and positive dysphotopsia, as well as a posterior square optic edge for reducing posterior capsular opacification. Clareon comes preloaded in an automated, disposable lens delivery system AutonoMe™ that is designed with a carbon dioxide-powered delivery mechanism. The tip of the injector has a depth guard, which prevents excessively deep insertion of the device into the incision and therefore, minimizes wound stretch.

This study presents our initial experience with the Clareon® CNA0T0 monofocal IOL and clinical outcomes in a routine cohort of cataract patients in Malaysia.

Methods

This study was a retrospective review of patients who underwent uneventful cataract surgery with implantation of the Clareon CNA0T0 monofocal IOL in three private ophthalmic surgical centres in Malaysia from March 2019 to March 2020. Ethics approval was not required as this study was an audit and patient identifiers were removed accordingly.

Patient selection

Eligible patients were those aged 18 years or older in good general and ocular health with significant cataract who underwent phacoemulsification and implantation of the Clareon CNA0T0 monofocal IOL. Eyes with previous refractive surgery and patients with pre-existing ocular diseases which may significantly impact visual acuity or in the opinion of the surgeon, compromise the stability of the IOL, were excluded. Eyes with greater than 1 D of corneal astigmatism as well as patients who had experienced intraoperative complications were also excluded.

Cataract surgery

The study authors, who were based in different ophthalmic centres, performed the surgeries on all the eyes assessed in this study. All eyes had sutureless phacoemulsification under topical anaesthesia through a 2.2 mm (MW Lee and KC Yeo) or a 2.4 mm corneal incision (FM Cheong) using the Centurion machine (Alcon Laboratories). All patients had optical biometry and the Barrett Universal II formula was used for IOL selection targeting emmetropia. If optical biometry was unsuccessful and immersion ultrasound was used instead, KC Yeo used the SRK-T formula to guide IOL selection. Patients were reviewed postoperatively on Day 1, Week 1, Month 1, and Month 3.

Study endpoints

The primary endpoints were uncorrected distance visual acuity (UCDA), best-corrected distance visual acuity (BCDA), and the proportion of patients achieving UCDA of logarithm of Minimal Angle of Resolution (logMAR) 0.18 or better at 1 month. Snellen visual acuities were converted to logMAR for analysis.

The secondary endpoints were refractive outcome and predictability (difference between postoperative spherical equivalent at 1 month and target spherical

Table 1. Demographics and preoperative characteristics of patients who received the Clareon IOL

Patients (*n*)	88
Age (years)	
Mean ± SD	65.15 **±** 7.14
Range	49 to 86
Eyes implanted with Clareon (*n*)	108
Right (*n*)	61
Left (*n*)	47
Axial length (mm)	
Mean ± SD	23.58 **±** 0.98
Range	21.49 to 26.15
Corneal astigmatism (mm)	
Mean ± SD	0.53 **±** 0.22
Range	0 to 0.93
BCDA (logMar)	
Mean ± SD	0.58 **±** 0.62
Range	0.18 to 1.78
UCDA (logMar)	
Mean ± SD	0.77 **±** 0.67
Range	0.1 to 2

BCDA: best-corrected distance acuity; IOL: intraocular lens; SD: standard deviation; UCDA; uncorrected distance acuity

equivalent), refractive stability (difference between postoperative spherical equivalent at 1 week and 1 month), contrast sensitivity measured under photopic conditions with the Vector Vision CSV-1000E contrast acuity chart (Greenville, USA) at 1 month, wound stretch (measured with the Memmen incision gauge [Terrebonne, Canada] before and immediately after IOL implantation), and surgically induced astigmatism (centroid SIA calculated with preoperative keratometry readings and postoperative keratometry measurements at 1 month using the http://sia-calculator.com/ website). Patients who had bilateral Clareon implants also underwent the Visual Function Index-14 (VF-14) Quality of Life questionnaire,[3] which was administered by telephone at 1 month. The VF-14 is often used to assess the outcomes of cataract surgery and consists of a series of 14 questions to assess the degree of difficulty faced by a patient when performing specific visual tasks.

Adverse events

All intraoperative or postoperative complications were also recorded. Eyes with intraoperative complications were excluded from analysis.

Data collection and analysis

Data was gathered on a Microsoft Excel database specifically designed for the study. Descriptive statistics which included mean, median, standard deviation (SD), and minimum and maximum values were used to analyse the data. Tests of statistically significant differences were performed using one-way ANOVA to compare postoperative manifest refraction (spherical equivalent) at 1 week, 1 month, and 3 months to assess the refractive stability of the Clareon IOL.

Results

A total of 125 eyes underwent phacoemulsification with implantation of Clareon monofocal IOL in the three centres from March 2019 to March 2020. Two eyes with posterior polar cataract had intraoperative capsular compromise and were therefore excluded from the study. Another 15 eyes did not complete the 1-month follow-up and were also excluded. Data from the remaining 108 eyes (from 88 patients) were available for analysis. The preoperative parameters of these patients are described in Table 1. Only data from 53 eyes were available for analysis at 3 months.

Visual outcomes

The mean logMAR UCDA improved from 0.77 ± 0.67 preoperatively to 0.18 ± 0.17 at 1 month postoperatively. The mean logMAR BCDA also improved from 0.58 ± 0.62 preoperatively to 0.06 ± 0.08 at 1 month postoperatively (Fig. 1). One hundred and five eyes (97.2%) had UCDA of logMAR 0.3 (Snellen 6/12) or better and 86 eyes

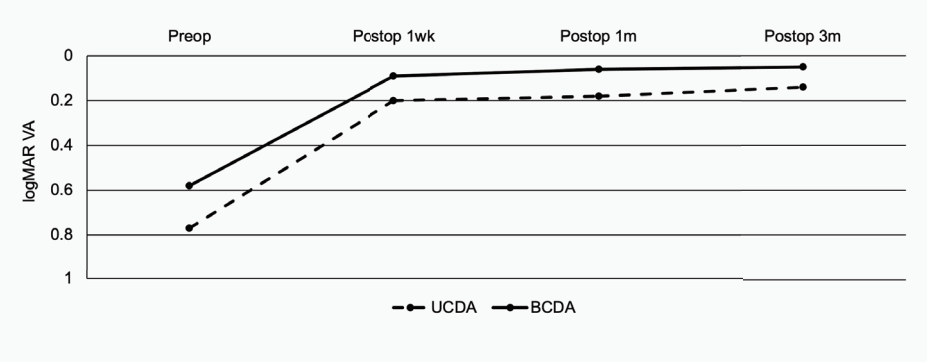

Fig. 1. Best corrected and uncorrected mean logMAR visual acuity of patients preoperatively at week 1, month 1, and month 3.

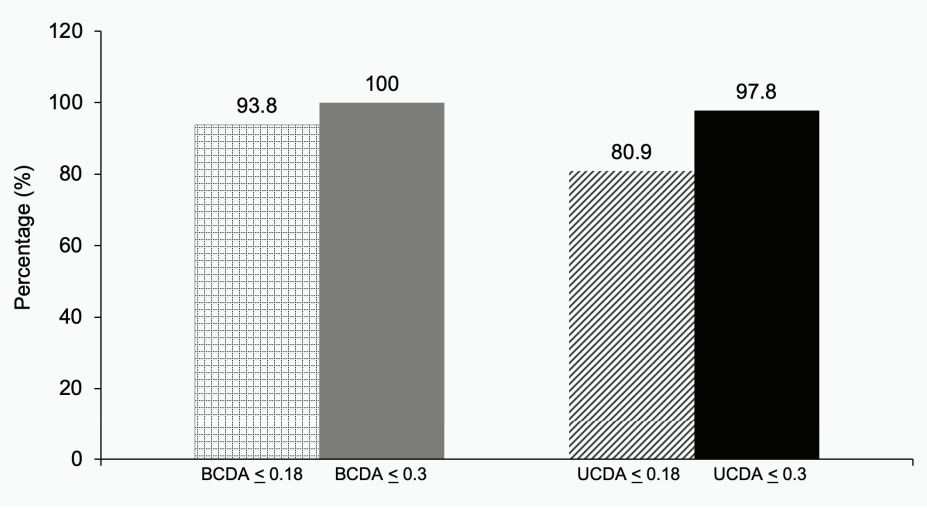

Fig. 2. Percentage of eyes with best corrected and uncorrected logMAR visual acuities of 0.3 or better and 0.18 or better.

(79.6%) had logMAR 0.18 (Snellen 6/9) or better. All eyes had BCDA of log MAR 0.3 or better and 101 eyes (93.5%) had logMAR 0.18 or better (Fig. 2).

The mean logMAR UCDA and BCDA at 3 months were 0.14 ± 0.11 and 0.05 ± 0.06, respectively. Fifty eyes (94.3%) had UCDA of logMAR 0.3 or better, 41 eyes (77.4%) had UCDA of logMAR 0.18 or better, and all eyes had BCDA of logMAR 0.18 or better.

Refractive outcomes

Postoperative spherical equivalent (SE) at 1 month was compared with preoperative target SE while refractive predictability was assessed by subtracting the pre-

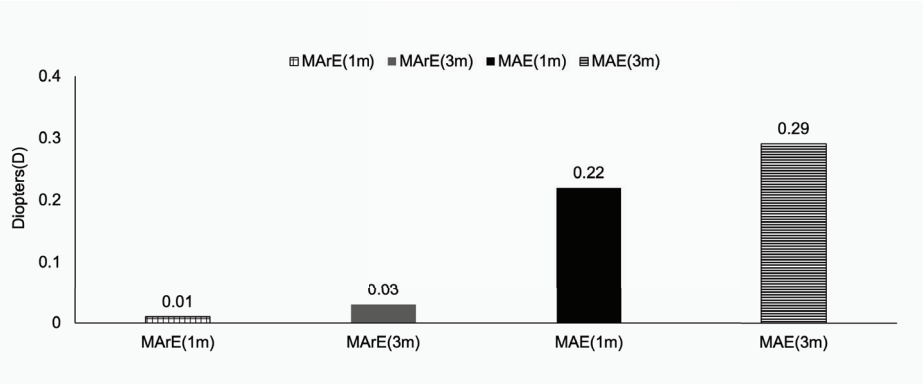

Fig. 3. Percentage of eyes with postoperative spherical equivalent within 0.25 D, 0.5 D, and 0.75 D of target.

operative SE from the postoperative SE and calculating the mean arithmetic error (MArE) as well as the mean absolute error (MAE). The MArE at 1 month was 0.01 ± 0.27 and the MAE was 0.22 ± 0.16. All eyes were within 0.75 D of target, 98 eyes (90.7%) were within 0.5 D, and 74 eyes (68.5%) were within 0.25D (Fig. 3). At Month 3, MArE was 0.03 ± 0.34, MAE was 0.29 ± 0.19 and 48 eyes (90.6%) of eyes were still within 0.5D of target SE.

Refractive stability was assessed by calculating the difference between the postoperative SE at 1 week and 1 month. Mean change in SE from 1 week to 1 month was -0.07 ± 0.31 and mean absolute change was 0.25 ± 0.20. All eyes had ≤ 1D change in SE from 1 week to 1 month. 100 eyes (92.6%) had ≤ 0.5D and 73 eyes

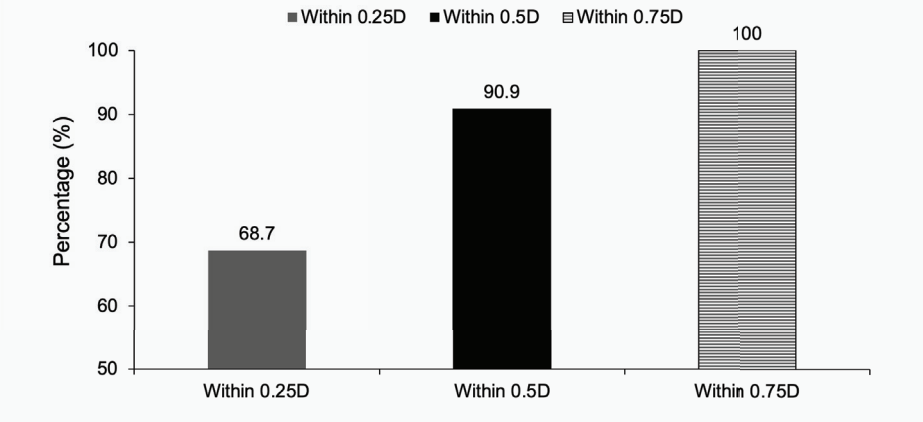

Fig. 4. Change in refraction (mean spherical equivalent) from 1 week to 3 months postoperatively.

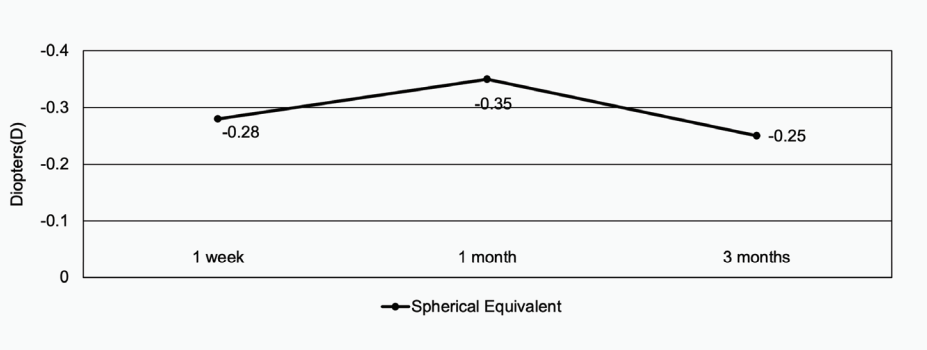

Fig. 5. Comparison of contrast sensitivity between aged-matched controls, Clareon, and other monofocal intraocular lenses.

(67.6%) had ≤ 0.25D change. Mean change in SE from 1 month to 3 months was -0.03 ± 0.32 and mean absolute change was 0.23 ± 0.22. All eyes at 3 months had ≤ 0.5D change in SE. The mean SE at 1 week, 1 month and 3 months were -0.28 ± 0.43, -0.35 ± 0.41 and -0.25 ± 0.32 respectively (Fig. 4). There was no statistically significant difference in SE at 1 week, 1 month or 3 months, postoperatively (P = .364).

Contrast sensitivity

Contrast sensitivity for all eyes was performed at 1 month postoperatively with the Vector Vision CSV-1000E under photopic conditions at spatial frequencies of 3, 6, 12 and 18 cycles per degree (cpd). For purposes of analysis, linear values were converted to log units. The mean contrast values were 1.73 ± 0.18 at 3 cpd, 1.91 ± 0.24 at 6 cpd, 1.62 ± 0.25 at 12 cpd and 1.09 ± 0.28 at 18 cpd (Fig. 5).

Wound stretch and surgically induced astigmatism

Wound stretch was measured intraoperatively as previously described. The mean size (for the 2.2 mm incision) was 2.2 ± 0.02 mm pre-IOL implantation and 2.25 ± 0.06 mm post-implantation. There was no change in incision size for the 2.4 mm incision.

When assessed by individual surgeons, the centroid SIA for the right and left eyes were 0.10 D and 0.09 D, respectively (for MW Lee), 0.10D and 0.08D (for KC Yeo), and 0.23 D and 0.22 D (with FM Cheong).

VF-14 Questionnaire

Twenty patients had bilateral Clareon implants. The mean VF-14 score within this cohort was 95.2 ± 6.29 (range 80.56 to 100). Ten patients recorded a score of 100 (full marks).

Adverse events

Two eyes (in the same patient) with posterior polar cataract had intraoperative posterior capsular rupture with vitreous loss. In both eyes, reverse optic capture with the Clareon IOL was possible, with one eye requiring a return trip to the operating theatre for the removal of vitreous wick through the side-port incision. Both eyes achieved a final BDVA of Snellen 6/9 and 6/6, respectively but were excluded from analysis.

Three eyes had postoperative cystoid macular oedema, and all responded well to treatment with topical steroids and topical nonsteroidal anti-inflammatories. A final BCDA of logMAR 0 was achieved in two eyes and logMAR 0.3 in the remaining eye at 1 month.

One eye had raised intraocular pressure noted at 1 week which was attributed to a response to steroid treatment. The topical steroid was changed from prednisolone to loteprednol and intraocular pressure returned to normal with this eye achieving BCDA of logMAR 0 at 1 month.

Discussion

The Clareon IOL is made from a new biomaterial and previous *in vitro*[4-6] and *in vivo*[2] studies that evaluated the Clareon IOL have reported low levels of glistenings and surface haze compared with other commercially available IOLs. Initial clinical studies[7-10] have also shown this IOL to be safe and effective with good postoperative outcomes and minimal complications.[11,12] This retrospective study documents the initial clinical experiences using the Clareon IOL in Malaysian patients.

This study demonstrated that this IOL provided good visual and refractive outcomes in the early postoperative period with a high proportion of patients achieving UCDA of logMAR 0.3 or better and all eyes achieving BCDA of logMAR 0.3 or better. A previous study[1] evaluated the refractive stability of the Clareon IOL and showed little change in SE after 1 week and up to 3 months postoperatively. In this study, refractive stability was achieved early with no statistically significant change in SE from 1 week to 3 months postoperatively.

There was also very good refractive predictability with more than 90% of eyes within 0.5 D of target using the SRK-T or the Barrett Universal II formulae. This was achieved despite the lack of 'A' constant optimization. These good refractive outcomes could be attributable to the positional stability of this IOL. Previous publications on the three-piece version of the Clareon IOL[8] had reported excellent visual outcomes and a low rate of posterior capsular opacification.

The mechanical stability of this IOL was also evaluated in an experimental study[13] that compared Clareon IOL with other monofocal IOLs. Clareon IOL had very low levels of axial displacement. The corresponding simulated dioptric power shift likely offered better positional stability and optimized refractive outcomes for patients.

Stanojcic *et al.*[10] previously reported no difference in contrast sensitivity when comparing the Clareon IOL with the Tecnics PCB00 IOL (New Brunswick, USA). For practical purposes, contrast sensitivity in this study was tested under photopic conditions since most daily activities are conducted during daylight. The mean contrast sensitivity of all eyes under photopic conditions was found to be better than aged-matched normal controls as shown on the manufacturer's website (Population norms, Age group 50 to 75 years of age (http://www.vectorvision.com/csv1000-norms/). The mean contrast sensitivity was also comparable to other monofocal IOLs when the logMAR values were plotted together using data from an earlier study[14] comparing contrast sensitivity between three different aspheric IOLs. While comparisons across different studies were not recommended given the differing testing conditions, this provides an idea of how Clareon IOL compares with other monofocal IOLs.

The Clareon IOL comes preloaded in a disposable automated injector system (AutonoMe). In a previous study[15] assessing corneal tissue trauma, AutonoMe injector resulted in significantly less endothelial cell loss and misalignment as well as less tissue inflammation compared with the Monarch III injector.

In our study, implantation of the Clareon IOL through a 2.2 mm incision required a wound assisted approach with a second instrument to stabilize the eye as the injector tip did not fit through the incision. This approach resulted in minimal and likely insignificant wound stretch (average increase in wound size of less than 0.05 mm). For 2.4 mm incisions, the injector tip fit snugly into the incision up to the nozzle guard. No wound stretch was evident at all.

There was no significant surgically induced astigmatism as the postoperative centroid SIA values were comparable with each individual surgeon's previous calculated centroid SIA values (MW Lee, KC Yeo = 0.1 D and FM Cheong = 0.2 D).

Patients with bilateral implants (n = 20) were very satisfied with their visual function as evidenced from the high scores reported with the VF-14 questionnaire that evaluated the difficulty in performing visually dependent common daily tasks. In this study, 10 out of the 20 patients who had bilateral implants scored full marks. Three individuals scored below 90 and all had BCDA of ≥ logMAR 0.18 but reported moderate difficulty with near tasks (even with glasses). Further evaluation of their symptoms showed that they had significant dry eyes, which may have contributed to the difficulties they experienced.

The surgeons did not experience any adverse events with regards to the use of this novel injector system. Specific recommendations and training videos provided by the manufacturer flattened out the learning curve very quickly. Interestingly, in the two eyes with posterior capsular compromise, both Clareon IOLs remained well-centred and stable with a reverse optic capture technique. The surgeon (MW Lee) noted that Clareon IOLs were easier to manipulate compared with Acrysof and this could be related to its increased water content, which reduced stiffness.

The limitations of this study are related to its retrospective design and the inconsistent nature of data collection. Confounding factors were also introduced with the enrolment of patients under the care of different surgeons; variations in surgical practices could influence outcomes. Another limitation was the relatively short follow-up period, with only a small proportion of patients having at least 3 months of follow-up data. With the inclusion of a new biomaterial in the Clareon IOL, longer follow-up would be useful to identify the rates of posterior capsular opacification and more importantly, presence of surface scatter or sub-surface nanoglistenings which had been reported in other hydrophobic acrylic IOLs. Nevertheless, in this cohort of patients, no glistenings were found in the Clareon IOL up to 3 months of follow-up.

In summary, initial experience with the Clareon IOL in this cohort of Malaysian patients showed excellent visual outcomes, refractive stability and predictability, as well as safety with the use of the novel AutonoMe fully automated disposable injector system.

Declarations

Ethics approval and consent to participate
Ethics approval was not required as this study was an audit and patient identifiers were removed accordingly.

Competing interests
All three authors are paid speakers for Alcon Laboratories and all received grant support for the study.

Funding
This study was conducted with a grant from Alcon Laboratories (M) Sdn Bhd. The grant was used for the research assistants used by each centre for data collection and handling, presentations at meetings, and for the services of a medical writer to prepare the manuscript for submission.

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References

1. Negishi K, Masui S, Torii H, Nishi Y, Tsubota K. Refractive stability of a new single-piece hydrophobic acrylic intraocular lens and corneal wound repair after implantation using a new automated intraocular lens delivery system. PloS One. 2020;15:e0238366.
2. Werner L, Ellis N, Heczko JB, et al. In vivo evaluation of a new hydrophobic acrylic intraocular lens in the rabbit model. J Cataract Refract Surg. 2018;44:1497–1502.
3. Bilbao A, Quintana JM, Escobar A, Garcia S, Andradas E, Bare M, Elizalde B. Responsiveness and clinically important differences for the VF-14 index, SF-36, and visual acuity in patients undergoing cataract surgery; for the IRYSS-Cataract Group. Ophthalmology. 2009;116:418–424.e1.
4. Werner L, Thatthamla I, Ong M, et al. Evaluation of clarity characteristics in a new hydrophobic acrylic IOL in comparison with commercially available lenses. J Cataract Refract Surg. 2019;45:1490–1497.
5. Auffarth G, Schickhardt S, Wang Q, Fang H, Hengerer F. Optical purity evaluation and accelerated aging of the new Clareon biomaterial vs other hydrophobic acrylic material in a laboratory setup. Presented at the XXXV Congress of the European Society of Cataract and Refractive Surgeons (ESCRS), Lisbon, Portugal, October 2017.
6. Auffarth G, Schickhardt S, Wang Q, Fang H, Hengerer F. Laboratory evaluation of the new Clareon hydrophobic acrylic IOL material; biomaterial properties and capsular bag behaviour. Presented at the XXXV Congress of the European Society of Cataract and Refractive Surgeons (ESCRS), Lisbon, Portugal, October 2017.
7. Bauer NJC, Veldhuizen CA, Berendschot TTJM, Nuijts RMMA. The Clareon Intraocular Lens: First Clinical Experiences. Acta Ophthalmologica. 2018;96:34.
8. Maxwell A, Suryakumar R. Long term effectiveness of a 3-piece acrylic hydrophobic intraocular lens modified with hydroxyethyl-methacrylate: an open-label, 3-year follow-up study. Clin Ophthalmol. 2018;12:2031–2037.
9. Oshika T, Fujita Y, Inamura M, Miyata K. Mid-term and long-term clinical assessments of a new 1-piece hydrophobic acrylic IOL with hydroxymethyl methacrylate. J Cataract Refract Surg. 2020;46:682–687.
10. Stanojcic N, O'Brart D, Hull C, et al. Visual and refractive outcomes and glistenings occurrence after implantation of 2 hydrophobic acrylic aspheric monofocal IOLs. J Cataract Refract Surg. 2020;46:986–994.
11. Von Tress M, Marotta JS, Lane SS, Sarangapani R. A meta-analysis of Nd:YAG capsulotomy rates for two hydrophobic intraocular lens materials. Clin Ophthalmol. 2018;12:1125–1136.
12. Hillenmayer A, Wertheimer CM, Kassumeh S, et al. Evaluation of posterior capsular opacification of the Alcon Clareon IOL vs the Alcon Acrysof IOL using a human capsular bag model. BMC Ophthalmology. 2020;20:1-7.
13. Lane S, Collins S, Das KK, et al. Evaluation of intraocular lens mechanical stability. J Cataract Refract Surg. 2019;45:501–506.
14. Chin CYA, Gurusamy B, Keat A, Bastion MLC. Comparison of contrast sensitivity between 3 aspheric acrylic monofocal intraocular lenses: a prospective randomised trial. Malaysian Journal Ophthalmology. 2020;1:259–283.
15. Mastropasqua L, Toto L, D'Ugo E, et al. In vivo and in vitro results of an automated preloaded delivery system for IOL implantation in cataract surgery. Int Ophthalmol. 2020;40:125–134.

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Case series
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Intravitreal Ozurdex® in non-intact posterior lens capsule: case series and dilemma

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Abstract

Background: Intravitreal Ozurdex® has been reported to be effective in treating macular oedema. It is more frequently used in resistant diabetic macular oedema cases that do not respond to anti vascular endothelial growth factor treatment. Despite the known risk of implant migration into the anterior chamber in non-intact posterior capsule eyes, the benefit of treatment occasionally outweighs the risk of complications, particularly in cases with good visual potential. The main potential vision-threatening complication involves permanent corneal decompensation.
Case presentation: We are reporting the follow-up and management of Ozurdex implantation in non-intact capsule eyes. The complication of anterior chamber migration if at all occurred, was managed accordingly.
Conclusion: Close follow-up is needed in patients with non-intact posterior lens capsules receiving intravitreal Ozurdex to monitor the risk of anterior chamber migration of the implant.

Keywords: anterior migration, non-intact posterior lens capsule, Ozurdex

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Intravitreal Ozurdex® dalam kapsul kanta posterior yang tidak utuh: siri kes dan dilema

Abstrak

Latar belakang: Intravitreal Ozurdex® telah dilaporkan berkesan dalam merawat edema makula. Ia lebih kerap digunakan dalam kes edema makula pada pesakit diabetes yang tidak bertindak balas terhadap rawatan *anti vascular endothelial growth factor*. Walaupun terdapat risiko penghijrahan implan ke dalam ruang anterior pada mata yang mempunyai kapsul posterior yang tidak utuh, faedah rawatan kadangkala mengatasi risiko komplikasi terutamanya dalam kes yang mempunyai potensi penglihatan yang baik. Komplikasi yang berpotensi mengancam penglihatan melibatkan dekompensasi kornea yang kekal.
Pembentangan kes: Kami melaporkan tindakan susulan dan pengurusan
Implantasi Ozurdex pada mata yang mempunyai kapsul yang tidak utuh. Komplikasi pemindahan ruang anterior jika berlaku, telah diuruskan dengan sewajarnya.
Kesimpulan: Susulan rapat diperlukan pada pesakit dengan kapsul kanta posterior yang tidak utuh yang menerima Ozurdex intravitreal untuk memantau risiko penghijrahan implan ke ruang anterior mata.

Kata kunci: anterior, kapsul posterior tidak utuh, Ozurdex, penghijrahan ke ruang

Introduction

Ozurdex® is a dexamethasone intravitreal implant that has been approved by the US Food and Drug Administration to treat macular oedema secondary to retinal vein occlusion and non-infectious uveitis affecting the posterior segment.[1] Due to its well-known potential side effects, the implant is not considered as first-line treatment in most cases. Ozurdex is relatively contraindicated in patients with non-intact posterior lens capsule.[2,3] However, in some challenging cases, the need for the implant arises when the disease has been recalcitrant to various other treatment options. We are reporting the management and follow-up of Ozurdex implantation in non-intact capsule eyes.

Case presentation

Case 1

A 60-year-old male with underlying diabetes mellitus presented with poor vision secondary to central involving diabetic macula oedema in the left eye. Despite repeated intravitreal ranibizumab injections, vision remained poor. Eventually the patient developed secondary epiretinal membrane (ERM) formation, for which he had combined surgery of phacoemulsification with intraocular lens (IOL) implantation, vitrectomy, and ERM peeling. The IOL was implanted in the sulcus as there was a small posterior capsule rent at the end of the surgery. Unfortunately, post-surgery, vision remained poor with persistent diabetic macular oedema. We decided to implant intravitreal Ozurdex in the left eye. The patient's visual acuity prior to intravitreal Ozurdex was 1/60. One month after implantation, the patient's visual acuity slightly improved to 6/60; however, the implant migrated into the anterior chamber. The sulcus IOL was found to be mildly subluxated, exposing a small portion of the opening in the capsule. This was likely the access for the implant to migrate anteriorly. Ozurdex was surgically removed from the anterior chamber. Postoperatively, the patient's visual acuity remained 6/60, most likely due to macular fibrosis.

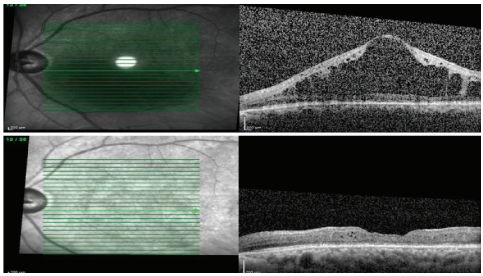

Fig. 1. Optical coherence tomography showing resolution of cystoid macular oedema 1 month after intravitreal Ozurdex in Case 2. Vision improved from 6/18 to 6/9.

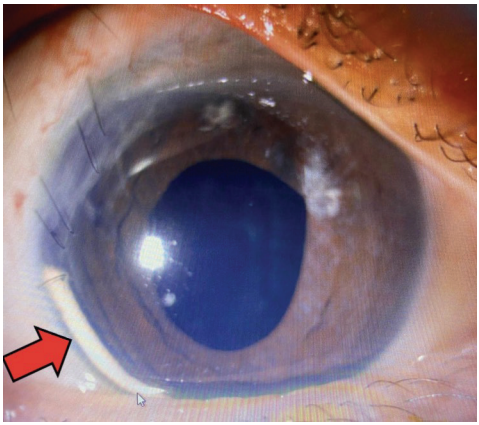

Fig. 2. The Ozurdex implant migrated into the anterior chamber at 4 weeks postoperative in Case 2. The patient had a scleral-fixated intraocular lens.

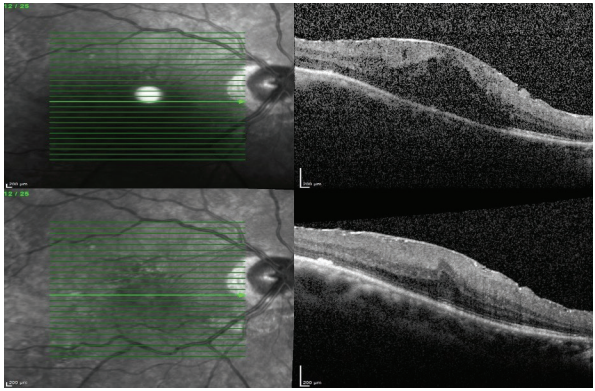

Fig. 3. Optical coherence tomography showing reduced central retinal thickness and resolution of macular oedema 1 month after intravitreal Ozurdex. The patient had received multiple intravitreal ranibizumab injections prior to Ozurdex implantation.

Case 2

A 64-year-old male who was pseudophakic for more than 20 years presented with bilateral dislocation of posterior chamber intraocular lens (PCIOL). Sequential vitrectomy was performed to remove the PCIOL and a sutureless scleral-fixated IOL was implanted. Postoperatively, vision in the right eye recovered to 6/9, while the fellow eye recovered to 6/12. At 5 months postoperative, the patient complained of blurred vision in the right eye. Upon examination, vision had dropped to 6/18 and cystoid changes at the macula were present. He did not respond well to a few months' treatment of topical non-steroidal anti-inflammatory drugs. Intravitreal Ozurdex was implanted. The cystoid macular oedema (CMO) resolved and vision improved to 6/9 (Fig. 1). However, the implant migrated into the anterior chamber at 4 weeks postoperative (Fig. 2). Implant removal was performed successfully. Vision improved to 6/9. The patient was followed up monthly and vision remained good at 6/9 up to 24 weeks postoperative. No recurrence of CMO was observed during follow-up sessions.

Case 3

A 63-year-old male underwent an uneventful bilateral cataract surgery in which an anterior chamber IOL (ACIOL) was implanted in the left eye. At 10 months, the patient complained of painless blurring of vision in the left eye. There was presence of CMO with subretinal fluid. Despite repeated intravitreal ranibizumab injections, the CMO persisted. We decided to implant intravitreal Ozurdex in the left eye. At the time of writing, the patient is still under monthly follow-up at our centre. Three months post-implant, no migration of the implant into the anterior chamber was observed. His visual acuity improved from 6/36 to 6/12. Optical coherence tomography at 3 months post-implant showed reduced central retinal thickness

and resolution of CMO (Fig. 3). Six months post-injection, best-corrected visual acuity was 6/12 with no signs of recurrence.

Discussion

Ozurdex is a sustained-released intraocular corticosteroid implant that delivers 0.7 mg of preservative-free dexamethasone in the vitreous cavity. It can be an effective alternative to antivascular endothelial growth factor (anti-VEGF) in treating persistent CMO.[2] A systematic review described excellent functional and anatomical improvements with Ozurdex injection.[4] In addition, Ozurdex was also described as an alternative in selected cases, such as pseudophakic and anti-VEGF-resistant eyes.[2] Although implanting Ozurdex in eyes with non-intact posterior capsules is fairly controversial, the clear benefit outweighs the potential risk in eyes that fail to respond to standard treatment and have a potentially good visual prognosis. Rock *et al.* reported intravitreal Ozurdex treatment in four patients with non-intact posterior lens capsule due to persistent macular oedema not responding to first-line treatments.[5] In our case series, Ozurdex was used after multiple attempts of standard treatment had failed. The presence of a non-intact posterior capsule was taken as a serious precaution and frequent follow-up was made compulsory in all cases.

Considering there is a risk for permanent visual loss in eyes with persistent CMO, intravitreal Ozurdex may be given in these patients. Although migration of Ozurdex into the anterior chamber is known as one of the rare complications, close follow-up is warranted in these cases. Ozcan *et al.* reported that four of six vitrectomized pseudophakic patients without intact posterior lens capsule receiving intravitreal Ozurdex had anterior migration within 2 to 6 weeks.[6] In our case reports, Case 1 and Case 2 were post-vitrectomized eyes. Both cases had anterior migration within 1 month and 2 weeks, respectively, post-intravitreal Ozurdex implantation. Migration did not occur in the third case, which had ACIOL implantation. This is likely due to the bulk of the vitreous remaining in the posterior cavity. The remaining gel probably can "hold" the implant compared to a post-vitrectomized eye.[7] Therefore, it is obvious that vitrectomized eyes are at a higher risk for anterior migration of Ozurdex compared to non-vitrectomized eyes.[7] Implant removal is mandatory in cases of anteriorly migrated Ozurdex. Corneal oedema with sequential decompensation is the most likely sequela of such migration.[1] Frequent close follow-up with timely removal of the implant is required, as demonstrated in these cases. All cases responded well to treatment. Improvement of vision as well as significant reduction of retinal thickening was achieved.

The surgical technique of removal largely depends on the size and age of the implant. During the first few weeks, the implant acts like a friable solid foreign body in the eye. Hence, simple aspiration will not be able to remove the implant

with ease. Most techniques described use viscoelastic as part of the manoeuvre.[8] Complete clearance of the implant is compulsory without leaving any residual piece in the anterior chamber. In both cases, viscoelastic assisted removal was done. A viscoelastic agent was used to orientate and direct the movement of the implant towards the limbal wound by creating a fluid wave that led to passive delivery of the implant.

Conclusion

Occasionally, anatomical and functional improvement with Ozurdex outweighs the risk of implant migration in eyes with non-intact posterior capsules. Close monitoring (less than a month) until complete resolution of the implant is necessary in patients with non-intact posterior lens capsules to look for anterior chamber migration of the implant. Post-vitrectomized eyes are at greater risk of migration.

Declarations

Consent for publication
The authors declare to have received informed, sufficient, and express consent from the patients to use their images and other clinical information in the article submitted.

Competing interests
None to declare.

Funding
None to declare.

Acknowledgements
None to declare.

References

1. Haller JA, Bandello F, Belfort R, et al. Ozurdex GENEVA Study Group. Dexamethasone intravitreal implant in patients with macular edema related to branch retinal vein occlusion: twelve-month study results. Ophthalmology. 2011;118(12):2453-60.
2. Khurana RN, Appa SN, McCannel CA, et al. Dexamethasone Implant Anterior Chamber Migration. Ophthalmology. 2014;121(1):67–71.

3. Ozurdex (dexamethasone intravitreal implant) [package insert]. Irvine, CA 92612, USA.: Allergan, Inc.; 2014.
4. Hu Q, Li H, Xu W, et al. Comparison between Ozurdex and intravitreal anti-vascular endothelial growth factor treatment for retinal vein occlusion-related macular edema: A systematic review and meta-analysis of randomized controlled trials. Indian J Ophthalmol. 2019;67(11):1800-1809.
5. Röck D, Bartz-Schmidt KU, Röck T. Risk factors for and management of anterior chamber intravitreal dexamethasone implant migration. BMC Ophthalmol. 2019;19(1):120. Published 2019 May 28.
6. Kayıkcıoğlu Ö, Doğruya S, Sarıgül C, et al. Anterior Chamber Migration of Ozurdex Implants. Turk J Ophthalmol. 2020;50(2):115-122.
7. Stepanov A, Codenotti M, Ramoni A, et al. Anterior chamber migration of dexamethasone intravitreal implant (Ozurdex®) through basal iridectomy (Ando) in a pseudophakic patient. Eur Joul Ophthalmol. 2016;26(3):e52–e54.
8. Pitcher, JD, III. 2014. A no-touch technique for removal of a dexamethasone implant 3rd edition. Retina Today, USA. 2014;36-8.

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Double rosette cataract: a case report

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Abstract

Cataract is commonly seen in the elderly population and is a major cause of blindness in Malaysia. The most common morphological types of cataracts associated with the elderly are cortical, nuclear, and posterior subcapsular cataract. Rosette cataracts are commonly associated with blunt trauma. We report a case of a patient who presented with unilateral, non-traumatic, double rosette cataract. He successfully underwent cataract extraction with posterior chamber intraocular lens implantation and the final visual outcome was good.

Keywords: double rosette cataract, non-traumatic cataract

Katarak roset berganda: laporan kes

Abstrak

Katarak biasa dijumpai di kalangan populasi warga emas dan merupakan faktor penyebab utama kebutaan di Malaysia. Jenis morfologi katarak yang biasa terdapat di kalangan warga emas termasuk katarak kortikal,katarak nuklear dan katarak posterior subkapsular. Katarak roset selalunya dikaitkan dengan trauma tumpul. Kami melaporkan suatu kes di mana pesakit mengidap katarak roset berganda di sebelah mata sahaja yang tidak dapat dikaitkan dengan sebarang trauma. Pesakit berjaya melalui pembedahan katarak dengan implantasi kanta intraokular posterior dengan pemulihan penglihatan yang baik selepas pembedahan.

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Kata kunci: katarak roset berganda, katarak tidak berkaitan dengan trauma

Introduction

Cataract is the major cause of bilateral blindness in many countries, including Malaysia according to the Malaysian National Eye Survey (NES II) of 2018.[1] Using the Rapid Assessment of Avoidable Blindness (RAAB) method, NES II reported untreated cataract as the leading cause of blindness in Malaysia.[1] Numerous reports have been published in the past regarding cataract and the pathophysiology underlying its development.[2] Based on a literature search in PubMed, we found limited data available for rosette cataract. Shah *et al.* classified all traumatic cataract according to morphology and reported 8% of rosette cataract.[3] We describe a case of a patient who presented with unilateral, non-traumatic, double rosette cataract.

Case presentation

A 56-year-old Malay man with underlying hypertension and ischaemic heart disease presented with painless, progressive, generalized blurring of vision for 2 years. He had no history of floaters or flashes of light. He denied any history of previous trauma and was currently a pensioner.

His best-corrected visual acuity was 1/60 in the right eye and 6/24 in the left eye. The slit lamp examination showed a stellate pattern cataract in the right eye (Figs. 1–3). Examination of the left eye showed nuclear sclerosis and posterior subcapsular cataract. Other anterior segment findings were unremarkable. The intraocular pressure was 17 mmHg for both eyes. Bilateral posterior segment examination was normal. There was no significant family history of similar cataract to suggest familial or hereditary traits. The patient had no history of metabolic diseases or diabetes mellitus as evidenced by the pre-clerking random blood sugar of 5.6 mmol/L, which was within normal limits. He subsequently underwent a successful cataract extraction with intraocular lens implantation in the right eye. Six weeks postoperatively, his best-corrected visual acuity was 6/7.5.

Discussion

Petaloid or double rosette cataract is classically seen in patients with blunt trauma to the eye following direct lens trauma or concussion to the lens.[4] The lens opacity may appear immediately after the trauma or with a delay of up to a few months and may progress to become more severe over time. There is limited literature available

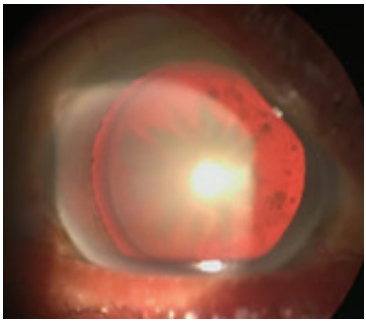

Fig. 1. Retroillumination view of double rosette cataract in the right eye.

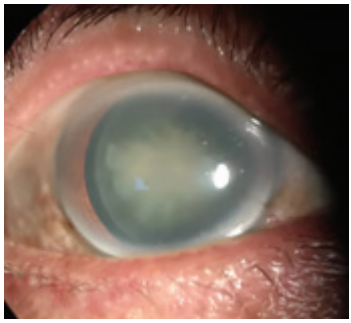

Fig. 2. Diffuse illumination of double rosette cataract in the right eye.

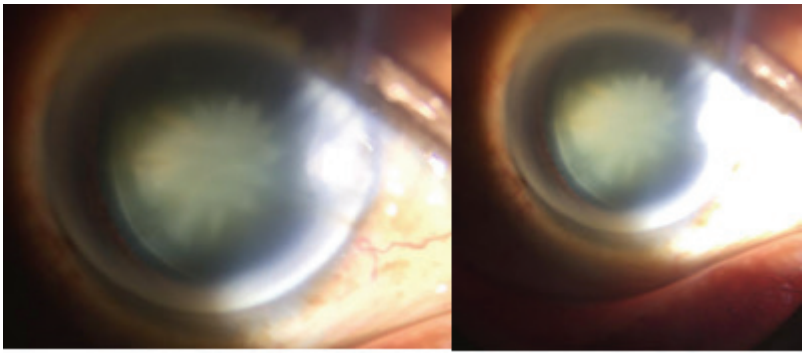

Fig. 3. Slit lamp view of double rosette cataract in the right eye.

describing non-traumatic double rosette cataract. The few reported incidences of non-traumatic rosette cataract include cases following an acute hyperglycaemic state in a diabetic patient as well as following electrical injury and lightning injury.[5-7] However, our patient denied association with any of the conditions mentioned above; the identification of this type of cataract was an accidental finding during ophthalmology examination for typical cataract symptoms in an aging patient., In the absence of other signs of trauma to other ocular structures, a history of unnoticed trivial injury is unlikely in this patient. The incidence of this type of non-traumatic cataract remains unknown. In 2019, Sethi *et al.* reported the most recent data on double rosette cataract in a patient without significant history of trauma or systemic illnesses.[4] To date, this is the only article published that we came across after extensive navigation via several search engines. Thus, limited knowledge is available regarding its pathogenesis and possible associated risk factors.

Conclusion

Non-traumatic double rosette type of cataract has never been reported in Southeast Asia. We report a case of double rosette cataract found incidentally in our clinic.

Declarations

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

Competing interests
None to declare

Funding
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References

1. Chew FLM, Salowi MA, Mustari Z, et al. Estimates of visual impairment and its causes from the National Eye Survey in Malaysia (NESII). PLoS One. 2018;13(6): e0198799.
2. Nartey A. The Pathophysiology of Cataract and Major Interventions to Retarding Its Progression: A Mini Review. Adv Ophthalmol Vis Syst. 2017;6(3):00178.
3. Shah MA, Shah SM, Shah SB, et al. Morphology of traumatic cataract: does it play a role in final visual outcome? BMJ Open. 2011;1:e000060.
4. Sethi A, Ramasubramanian S. Double rosette cataract: A striking image! Indian J Ophthalmol. 2019;67:124-5.
5. Rathi M, Bhatt N, Dhull CS, Sachdeva S, Phogat J. Electric cataract: a report of two cases and a review of the literature. Egypt J Cataract Refract Surg. 2016;22:54-5.
6. Venkateswaran, N, Galor A. Rosette-shaped cataract due to lightning injury. JAMA Ophthalmol. 2018;136(1).
7. Ramkumar H, Basti S. Reversal of bilateral rosette cataracts with glycemic control. ScientificWorld-Journal. 2008;8:1150-1.

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Case report
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Remarkable ophthalmic improvement following early diagnosis and treatment of paediatric prolactinoma-compressing optic chiasm: a case report

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Abstract

Background: Prolactinomas frequently manifest as visual field defects and are often undetected due to their slow gradual progression. Chronic optic nerve compression will result in irreversible diffuse nerve atrophy and is associated with permanent severe vision and field loss.
Case report: A 12-year-old boy presented with acute visual loss, right eye ptosis, and decreased visual acuity (VA). Band atrophy at the optic disc and bitemporal hemianopia were found. MRI revealed a homogenic solid lesion in the intrasellar to suprasellar region, suggesting pituitary macroadenoma. Laboratory results showed increased prolactin hormone (33.6 ng/ml), decreased thyroid hormones (FT4 0.68 mg/dL and TSH 0.07 mg/dL), and decreased testosterone (< 0.025 ng/mL). Subfrontal craniotomy, hormonal therapy, and photon radiotherapy were done. On follow-up, VA was 6/6 and band atrophy and bitemporal hemianopia had disappeared.

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Conclusion: Early diagnosis and treatment of prolactinomas might give a good clinical outcome for the patient.

Keywords: craniotomy, pituitary macroadenoma, neuro-ophthalmology, prolactinoma, visual field loss

Diagnosa dan rawatan awal untuk prolaktinoma yang melibatkan chiasm optik telah memberi pemulihan oftalmik yang ketara dalam pesakit kanak-kanak: laporan kes

Abstrak

Pengenalan: Prolaktinoma kerap menjelma sebagai kecacatan medan penglihatan dan selalunya tidak dapat dikesan kerana perkembangannya yang perlahan. Mampatan saraf optik kronik akan mengakibatkan atrofi saraf optik yang kekal dan dikaitkan dengan penglihatan teruk yang kekal serta.
Ilustrasi kes: Ini ialah laporan kes seorang budak lelaki berumur 12 tahun dengan kehilangan penglihatan akut, ptosis mata kanan, penurunan ketajaman penglihatan (VA). Atrofi jalur pada saraf optik dan kehilangan medan penglihatan bitemporal ditemui. MRI menunjukkan satu ketumbuhan sekata yang pejal dari kawasan intrasellar ke suprasellar konsisten dengan makroadenoma pituitari. Pemeriksaan makmal menunjukkan peningkatan hormon prolaktin (33.6 ng/ml) dan penurunan kedua-dua hormon tiroid (FT4 0.68 mg/dL dan TSH 0.07 mg/dL) dan testosteron (< 0.025 ng/mL). Kraniotomi subfrontal, terapi hormon, dan radioterapi photon telah dilakukan. Pada susulan di September 2020, VA ialah 6/6 dan atrofi jalur serta hemianopia bitemporal telah hilang.
Kesimpulan: Diagnosis awal dan rawatan prolaktinoma mungkin memberikan hasil klinikal yang baik untuk pesakit.

Kata kekunci: kehilangan medan penglihatan, kraniotomi, makroadenoma pituitari, neuro-oftalmologi, prolaktinoma

Introduction

Prolactinomas are benign tumours of the pituitary gland that are grouped into pituitary adenomas. There are two main types of tumours that occupy the

pituitary fossa: craniopharyngiomas and pituitary adenomas. Craniopharyngiomas account for up to 90% of paediatric tumours arising in the pituitary region and are the most common paediatric neoplasm associated with hypopituitarism in children. Pituitary adenomas, on the other hand, comprise only 2.7% of supratentorial tumours in children, are usually benign, and are classified according to size, functional status, primary cell origin, and secreted hormone. Prolactinomas are the most common pituitary adenomas in adults and children, with 53% of paediatric pituitary adenomas identified as prolactinomas.[1] Presenting symptoms of prolactinoma include galactorrhoea, headache, visual field defects, menstrual disorders, amenorrhea, blurred vision, and growth retardation.[2] Therefore, male paediatric patients with growth retardation should undergo ophthalmic examinations such as visual acuity (VA) and visual field tests.

Case presentation

A 12-year-old boy was referred to our hospital for acute visual loss. Two weeks before hospitalization he suffered orbital discomfort and visual loss associated with frontal headache. The headache had been felt for 6 months. On admission in June 2020, ophthalmological examination revealed ptosis in the right eye (severe ptosis

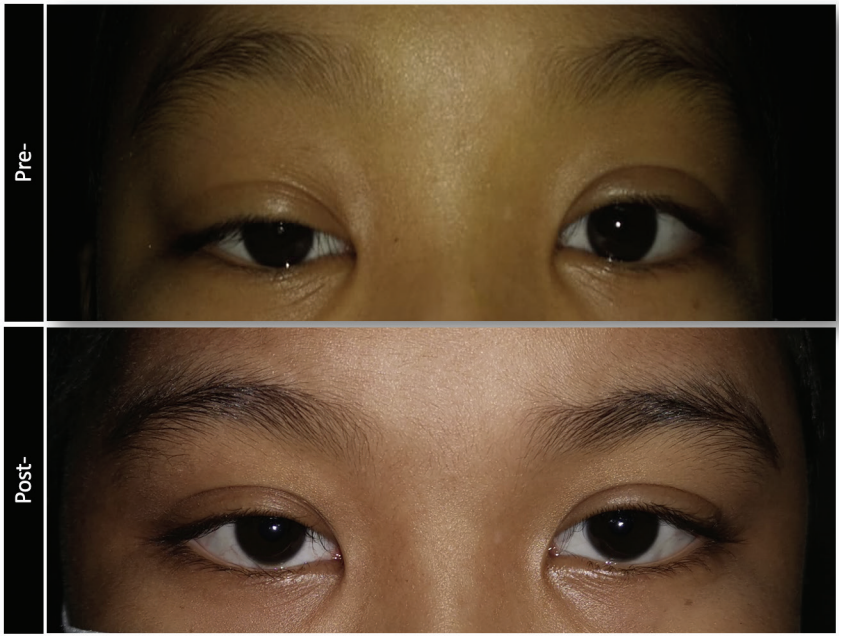

Fig. 1. (*Top*) Preoperatively, the patient had ptosis in the right eye (note the use of the frontal muscle). (*Bottom*) Improvement after treatment protocols.

with marginal reflex distance 1 = 0 mm, levator function test = 2 mm, (Fig. 1 top), decreased bilateral pupillary reflex with VA 6/15 in both eyes, decreased contrast sensitivity, and dyschromatopsia. Nine gaze eye movement examination showed a right oculomotor nerve palsy (Fig. 2). The patient was suspected with growth retardation as his height was 135 cm (below the 5th percentile). Band atrophy was found at the optic discs (Fig. 3). Contrast-enhanced magnetic resonance imaging of the brain showed a homogenic solid lesion located in the intrasellar to suprasellar region, lobulated in shape with size 5.2 cm x 2.4 cm x 3.3 cm, which the radiologist assessed as pituitary macroadenoma (Fig. 4). Bitemporal hemianopia appeared on the Humphrey Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany) (Fig. 5). Laboratory examination showed increased prolactin hormone (33.6 [0.9–12.9] ng/ml), decreased thyroid hormones (FT4 0.68 [0.98–1.63] mg/dL and TSH 0.07 [0.51-4.30] mg/dL), and decreased testosterone (< 0.025 [0.03–0.68] ng/mL).

The patient underwent a treatment protocol consisting of bromocriptine tab 2.5 mg b.i.d, levothyroxine tab 0.025 mg once daily, hydrocortisone tab 20 mg t.i.d, and desmopressin tab 0.05 mg b.i.d for 1 month. The patient underwent subfrontal craniotomy tumour removal to remove the lesion due to undergoing compressive optic neuropathy by tumour mass. The result was pituitary macroadenoma prolactinoma suspect, with negative immunohistochemical findings of oestrogen receptor, epithelial membrane antigen, and glial fibrillary acidic protein. Tele radiotherapy with 3D photons (conformal photon radiotherapy/3DCRT) was done to clear the residual tumour. Upon follow-up in September 2020, VA had improved to OU 6/6, contrast sensitivity improved to 1.35, ptosis improved to mild ptosis (marginal reflex distance 1 = 2 mm, symmetric between right and left eye, see Fig. 1 bottom), and bitemporal hemianopia had disappeared.

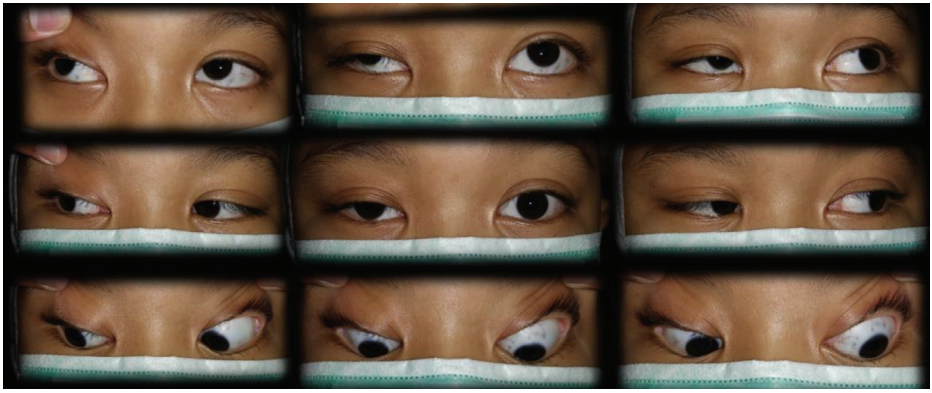

Fig. 2. Nine gaze eye movement examination showed a right oculomotor nerve palsy in the right eye.

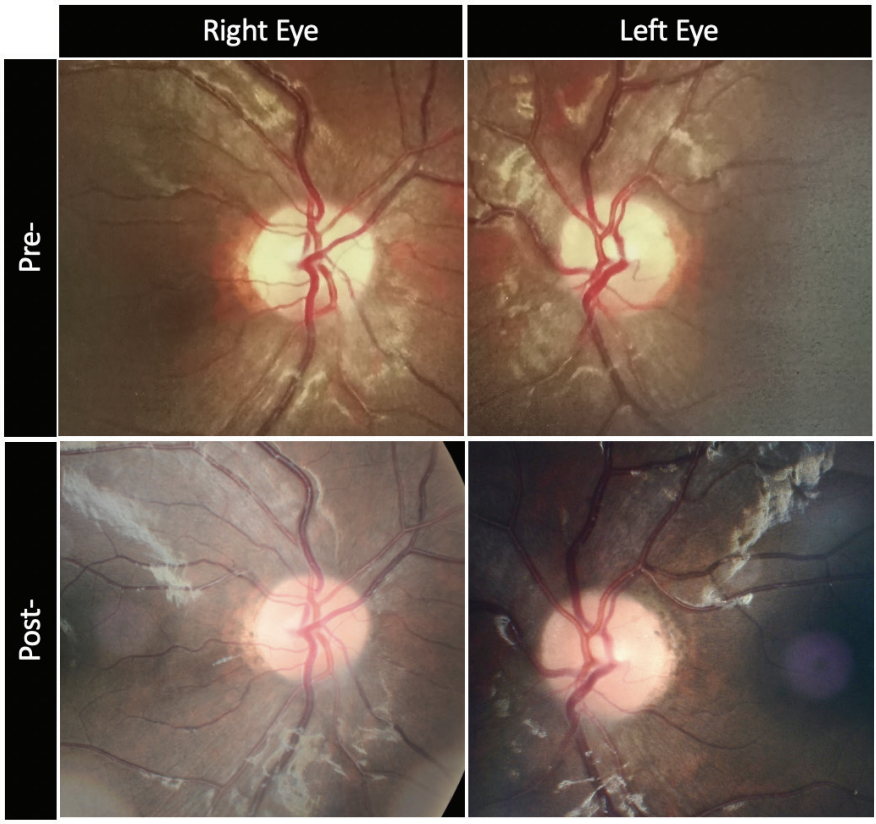

Fig. 3. (*Top*) Before treatment, the patient had band atrophy due to chiasmal compression. (*Bottom*) Improvement after treatment protocol (note: no colour reproduction was made).

Discussion

We report a case of prolactinoma in a 12-year-old boy with compressing optic chiasm resulting in decreased VA, ptosis, and bitemporal hemianopia. In the present study, hyperprolactinemia is under control using hormonal therapy only. Furthermore, compressive optic neuropathy symptoms were improved significantly after surgery and radiotherapy. Chronic nerve compression by a pituitary mass results in diffuse, irreversible atrophy of the optic nerve which is typically associated with permanent severe vision and field loss.[1] If it is not immediately diagnosed, macroprolactinomas have a tendency to grow over time, thus requiring more aggressive treatment.

Treatment goals in this patient included the early release of chiasm compression surgically and hormonally to attain normal gonadal function as well as to ensure

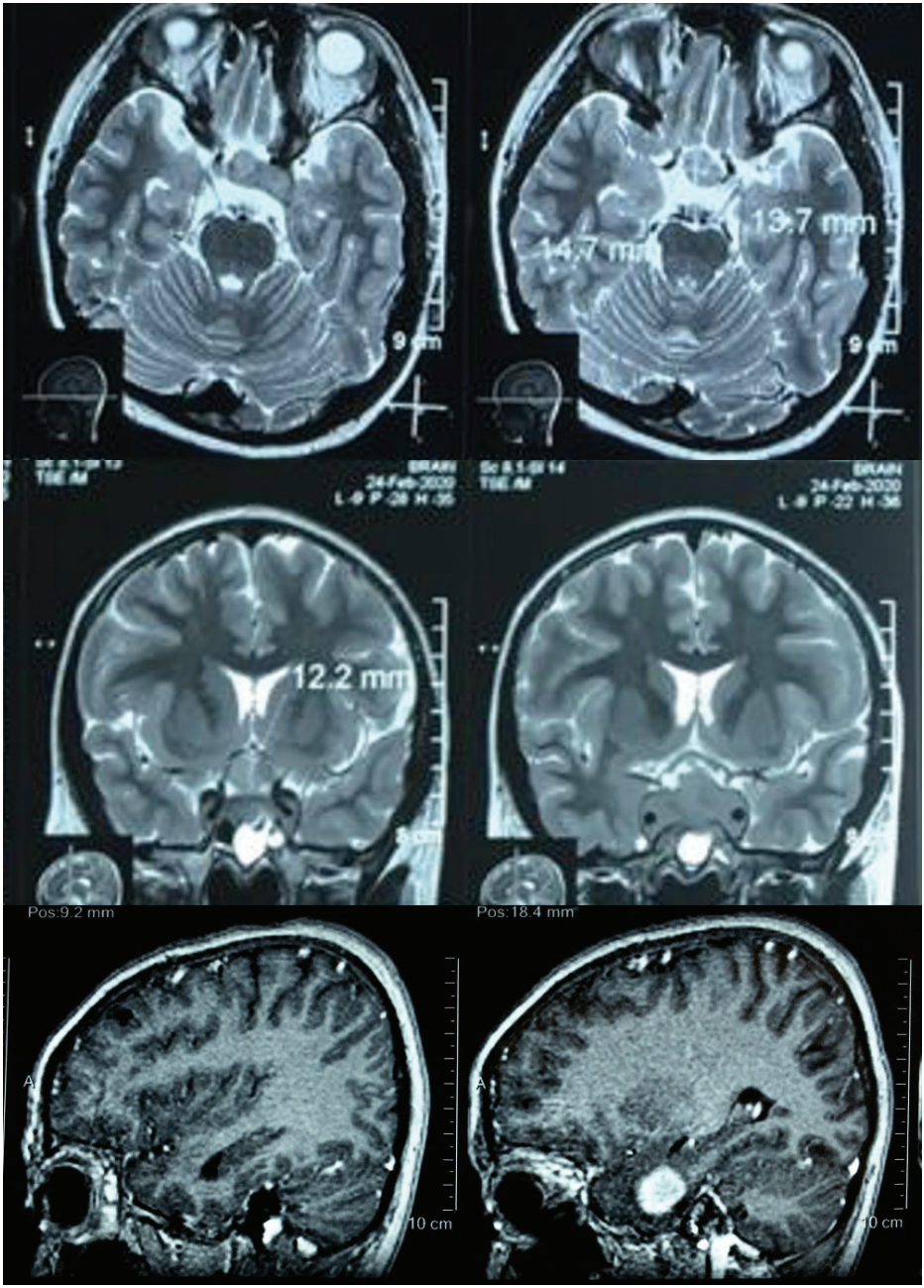

Fig. 4. Magnetic resonance imaging showing a tumour mass in the sellar region compressing the optic chiasm.

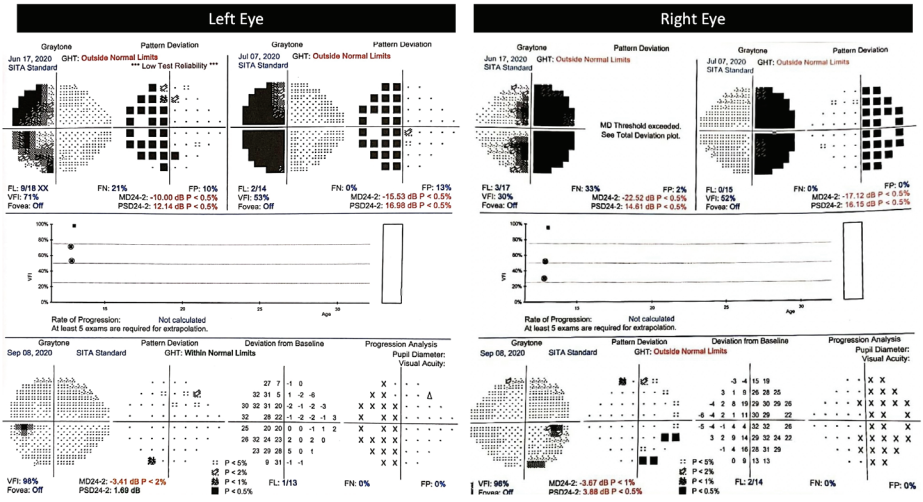

Fig. 5. Improvement of visual field defect after treatment protocols with no sign of bitemporal hemianopia.

future fertility. A systematic review and meta-analysis study showed that disease remission after surgery without dopamine agonist treatment was lower than dopamine agonist treatment alone.[3] Therefore, in this patient, dopamine agonist treatment was administered prior to and after surgery. Dopaminergic agonists are the initial therapy of choice in children, adolescents, and adults due to their effectiveness and tolerance.[4,5] In macroprolactinoma, surgery should be reserved for medically intractable tumours or neurosurgical emergencies.[6] Irradiation might have side effects such as neurological sequelae, hypopituitarism, and increased risk for second malignancies.[7] In this patient, radiation therapy was administered to prevent tumour growth and resolve tumour hypersecretion.[8] After 3 months, prolactin levels and ophthalmic findings were normal.

Conclusion

Early diagnosis and treatment of prolactinomas might give a good prognosis for the patient. The aim of surgical therapy was to reduce the tumour mass and acquire tissue samples to establish the correct diagnosis. Hormonal therapy can control the disease effectively, with the hopes of restoring prolactin levels to normal and achieving gonadotropic restoration. Radiotherapy was important to reduce the tumour mass since surgical therapy did not remove the tumour tissue completely.

Declarations

Consent for publication
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient's parent.

Competing interests
None to declare.

Funding
None to declare.

Acknowledgements
None to declare.

References

1. Kamboj A, Lause M, Kumar P. Ophthalmic manifestations of endocrine disorders-endocrinology and the eye. Transl Pediatr. 2017;6(4):286–299.
2. Liu Y, Yao Y, Xing B, et al. Prolactinomas in children under 14. Clinical presentation and long-term follow-up. Childs Nerv Syst. 2015 Jun;31(6):909-16.
3. Zamanipoor Najafabadi AH, Zandbergen IM, de Vries F, et al. Surgery as a Viable Alternative First-Line Treatment for Prolactinoma Patients. A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2020;105(3):e32–41.
4. Fideleff HL, Boquete HR, Suárez MG, Azaretzky M. Prolactinoma in Children and Adolescents. Horm Res. 2009;72(4):197–205.
5. Breil T, Lorz C, Choukair D, et al. Clinical Features and Response to Treatment of Prolactinomas in Children and Adolescents: A Retrospective Single- Centre Analysis and Review of the Literature. Horm Res Paediatr. 2018;89(3):157–165.
6. Barker FG 2nd, Klibanski A, Swearingen B. Transsphenoidal surgery for pituitary tumors in the United States, 1996-2000: mortality, morbidity, and the effects of hospital and surgeon volume. J Clin Endocrinol Metab. 2003;88(10):4709-19.
7. Brada M, Ajithkumar TV, Minniti G. Radiosurgery for pituitary adenomas. Clin Endocrinol. 2004;61(5):531-43.
8. Royce TJ, Loeffler JS, Shih HA. Transsphenoidal Surgery: Complication Avoidance and Management Techniques. USA: Springer, Cham; 2017. Radiation therapy for pituitary tumors. P. 559-579.

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Eye-quiz
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Successful treatment of scleral perforation in a patient with surgically induced necrotizing scleritis

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Clinical context

A 59-year-old man presented with pain in the left eye and worsening vision for 1 day. He had underlying bilateral, surgically induced necrotizing scleritis following pterygium surgeries on immunosuppressive therapy, steroid-induced glaucoma, and central retinal vein occlusion. His visual acuity declined from hand movement to light perception in the left eye.

Question 1

Describe the findings in Figure 1a.

Question 2

What are the treatments given in Figure 1b?

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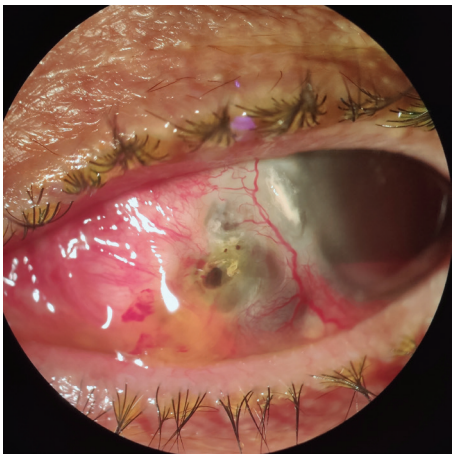

Fig. 1a.

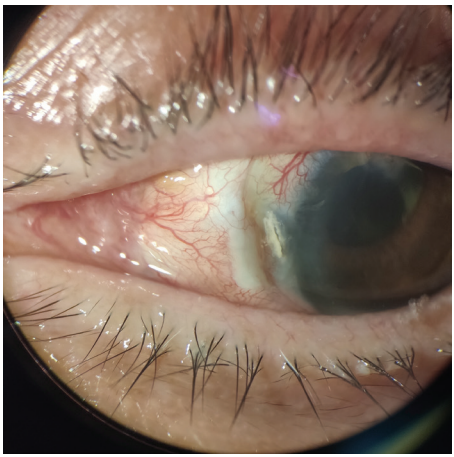

Fig. 1b.

Answer 1

Slit-lamp photograph of the left eye demonstrating three nasal scleral perforations, with the biggest perforation measuring 1 mm horizontally and 1 mm vertically at 8 o'clock and another two pinpoint scleral perforations above it at 9 o'clock. There was presence of vitreous loss and underlying scleral thinning.

Answer 2

Vitrectomy, scleral patch grafting, and amniotic membrane transplantation were performed. Globe integrity was restored and his pain resolved. The patient was treated with intravenous methylprednisolone 250 mg qid for 3 days, followed by oral prednisolone 1 mg/kg and tapered slowly. Immunosuppressive agents, which included azathioprine 50 mg bd and cyclosporine 150 mg od, were given. At the 8-month postoperative follow-up, visual acuity was no worse than preoperative visual acuity, with no recurrence or scleral patch rejection. Scleral grafting in conjunction with systemic immunosuppressive therapy halted the progression of the destructive process.[1,2]

References

1. Nguyen QD, Foster CS. Scleral patch graft in the management of necrotizing scleritis. Int Ophthalmol Clin. 1999;39(1):109-131.
2. Sainz de la Maza M, Tauber J, Foster CS. Scleral grafting for necrotizing scleritis. Ophthalmology. 1989;96(3):306-310.

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