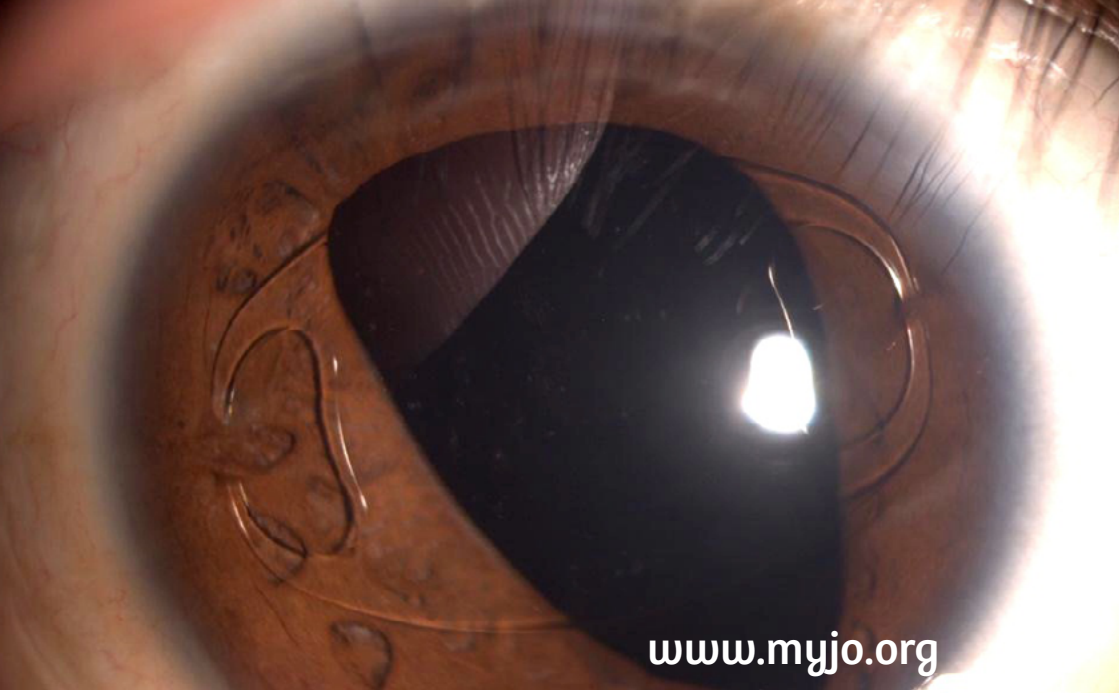

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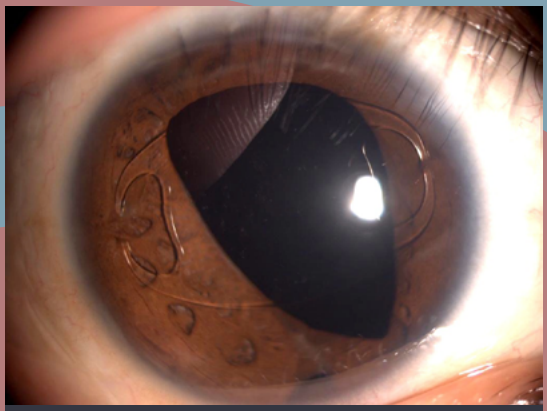

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Malaysian Journal of Ophthalmology

Editorial

Neonatal retinoblastoma: understanding the problem better

Michael Jones

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Retinoblastoma is a disease that does not discriminate between gender or race; however, it has long been reported there are marked differences in outcomes for patients around the world. Most affected children live in countries of low and middle income, where the mortality from retinoblastoma is about 70%, meaning that of the estimated 9,000 newly diagnosed patients every year, the majority will die.[1] Given that retinoblastoma is a rare disease, gathering more information to increase our understanding helps guide therapy for all children around the world and leads to better treatment outcomes. This is especially so in neonatal retinoblastoma, which is defined as affecting those aged less than 28 days or 44 weeks' gestation if born prematurely. In a 50-year review from Melbourne, Australia between 1939 and 1989, an audit of 17,417 necropsies failed to identify a single case of retinoblastoma in the series of 46 neonatal cancers.[2] In Toronto, Ontario, where there is a large retinoblastoma centre, 17 cases of neonatal retinoblastoma were reported in a total of 102 children with neonatal cancer.[3] Although small series of neonatal retinoblastoma in developing countries have been published,[4] many countries unfortunately do not report their retinoblastoma data. Efforts are being made to report and better understand the global picture of retinoblastoma[3]. Zohari and colleagues make a welcome contribution which again highlights the contrasting clinical picture in developing versus developed countries.

The disparity in retinoblastoma care between developed and developing countries is clearly evident when looking at those diagnosed in the neonatal period. In developed countries, from 7% to 10% of all retinoblastomas and 44% to 71% of familial retinoblastomas are diagnosed in the neonatal period, prompted by a positive family history leading to pre- or postnatal screening.[6] Family history has been reported elsewhere as the primary association reported regarding neonatal retinoblastoma in developed countries.[6] The importance of family history in the management of neonatal retinoblastoma was demonstrated in another study in the United States which showed that family history (67%) exceeded leukocoria (13%) as the most common reason for detection.[7] Altogether, review data shows that 72% in developed countries as opposed to 23% of familial retinoblastoma in developing countries were detected through screening.[6] Similarly, in the series published here,

the authors describe a difference in incidence due to a lack of screening in patients with a positive family history. Of the six patients identified with neonatal retinoblastoma, only two had a positive family history, both of which were siblings, and only one was screened for familial retinoblastoma.

This highlights the importance of patient education and counselling. It is safe to say that no country around the world has a perfect record in this regard. Given that retinoblastoma is a rare disease, we need continued efforts to better educate our colleagues in the medical profession as well as patients regarding the importance of family history and screening in retinoblastoma. This is more important than ever as the landscape continues to evolve with respect to genetic testing and treatment options.

A statement that we should all aspire to realise is that genome-level technologies could make genetic testing a reality for every family affected by retinoblastoma.[1] Our knowledge in this regard continues to grow. Initially, retinoblastoma was thought to be caused uniquely by loss of function of the RB1 tumour-suppressor gene, whereas more recently it has been shown that it can also be initiated by activation of the MYCN oncogene.[8] The vast majority of neonatal retinoblastoma is still however initiated by a germline mutation and therefore likely to result in bilateral disease. Patients with neonatal retinoblastoma pose a considerable challenge as most disease at presentation is advanced and rapidly evolving to involve the posterior pole and macula.[7] This was reported by Zohari and colleagues, as advanced disease was present with four patients (five eyes) having International Intraocular Classification of Retinoblastoma (IIRC) Group E eyes. Despite this, retinoblastoma remains intraocular and curable for 3–6 months after the first sign of leukocoria,[1] another common presentation of retinoblastoma and one identifiable with a simple red reflex check. Even with this in mind, early delivery and treatment remains controversial. Consideration for this is strengthened by the advanced stage of tumours often present at birth and therefore the desire for earlier intervention, when the tumours are less advanced and the burden of disease is less. In Canada, prenatal identification of an RB1 mutation means that obstetric care and premature delivery at 36 weeks' gestation is recommended.[1] Treatment in the neonatal period is a balance between the stage of disease and safety concerns in very young children. For example, systemic or intravenous chemotherapy is indicated in children under four months of age and not intra-arterial chemotherapy.[9] Limiting the morbidity of chemotherapy and concern regarding potential multi-drug resistance in neonates has led to consideration of treatments such as sub-Tenon chemotherapy for small volume tumours.[10]

Regardless of the challenges in diagnosing and treating neonatal retinoblastoma, the results of this study are encouraging. It should always be remembered that enucleation for advanced disease (IIRC Group E) can be a life-saving treatment and this was very appropriately practiced in this series, which reported no deaths and no metastatic disease. This is despite the expectation of germline disease in

neonatal retinoblastoma and bilateral disease developing later. All patients in the study presented here ended up with bilateral disease.

Advanced disease at presentation, rapid disease progression with high recurrence rate, and macular involvement are key factors in the consideration of neonatal retinoblastoma. Lack of awareness and education of surviving patients and also healthcare workers continue to pose challenges in both developed and developing countries alike. As the number of patients around the world with neonatal retinoblastoma inevitably increases, we can all work together to better understand the problem and its unique challenges and to hopefully offer our patients better outcomes in the future.

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Original article

Iris-claw intraocular lens, scleral-fixated intraocular lens, and angle-supported anterior chamber intraocular lens in Hospital Melaka: a four-year retrospective analysis

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Abstract

Introduction: Cataract surgery with insufficient capsular support has become an intense challenge to surgeons in intraocular lens (IOL) selection. Anterior chamber IOL (ACIOL), iris-claw (Artisan) IOL, and scleral-fixated IOL (SFIOL) are the three common types of IOL used. However, each type of IOL has its own characteristics and different clinical requirements. IOL selection is important in ensuring good visual outcome.
Purpose: The purpose of this study is to compare the duration or surgery, visual outcomes, and complications among ACIOL, Artisan IOL, and SFIOL.
Study design: Retrospective comparative analysis.
Material and methods: This is a four-year retrospective analysis of patients who underwent either ACIOL, Artisan IOL, or SFIOL implantation between January 2014 and January 2018. Patients were divided into ACIOL, Artisan, and SFIOL groups. Demographic data, duration of surgery, preoperative and postoperative visual acuity, and postoperative complications were identified and compared among different groups.
Results: Sixty-four eyes from 58 patients were analysed: twenty (31.3%) eyes with ACIOL, 28 (43.8%) eyes with Artisan, and 16 (25%) eyes with SFIOL. Mean surgery

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times for ACIOL, Artisan, and SFIOL were: 61 ± 27.8, 64 ± 26.9, and 104.1 ± 46.8, respectively. SFIOL showed significantly longer surgery time than the ACIOL and Artisan groups ($p < 0.05$). There was no significant difference in surgery time between the ACIOL and Artisan groups ($p > 0.05$). The Artisan group showed significantly better visual recovery at postoperative 1 week than both the ACIOL and SFIOL groups (Artisan *vs* ACIOL: 6/18 *vs* 6/24, $p < 0.05$; Artisan *vs* SFIOL: 6/18 *vs* 6/60, $p < 0.05$). However, final best-corrected visual acuity (BCVA) at two months was comparable among all three groups with a median BCVA of 6/9. Elevated intraocular pressure occurred in all IOL groups, retinal detachment developed in the Artisan and SFIOL groups, epiretinal membrane developed in the ACIOL and SFIOL groups, corneal decompensation developed in the ACIOL group only. Cystoid macular oedema and IOL tilt occurred in SFIOL only.
Conclusions: All three groups of IOL showed comparable good visual outcomes. The decision of IOL selection should be based on patients' clinical condition and availability of surgical skill and resources.

Keywords: anterior chamber intraocular lens, Artisan intraocular lens, capsular support, cataract surgery, scleral-fixated intraocular lens

Kanta intraokular cakar iris, kanta intraokular fiksasi scleral, dan kanta intraokular ruang anterior dengan sokongan sudut di Hospital Melaka: analisis retrospektif empat tahun

Abstrak

Pengenalan: Pemilihan lensa intraokular (IOL) bagi komplikasi pembedahan katarak tanpa sokongan kapsular yang mencukupi merupakan cabaran besar bagi pakar oftalmologi.. Lensa intraokular kamar anterior (ACIOL), IOL cakar-iris (Artisan) , dan IOL fiksasi scleral (SFIOL) adalah tiga jenis IOL yang biasa digunakan. Walau bagaimanapun, setiap jenis IOL mempunyai ciri yang tersendiri dan keperluan klinikal yang berbeza. Pemilihan IOL penting dalam memastikan hasil visual yang baik.
Tujuan: Tujuan kajian ini adalah untuk membandingkan jangka masa pembedahan, hasil ketajaman penglihatan, dan komplikasi di antara ACIOL, Artisan IOL, dan SFIOL.
Reka bentuk kajian: Analisis perbandingan retrospektif.
Bahan dan kaedah: Ini adalah analisis retrospektif selama empat tahun ke atas

pesakit yang menjalani implantasi ACIOL, Artisan IOL, atau SFIOL antara Januari 2014 dan Januari 2018. Pesakit dibahagikan kepada kumpulan ACIOL, Artisan, dan SFIOL. Data demografi, tempoh pembedahan, ketajaman penglihatan sebelum dan pasca pembedahan, dan komplikasi pasca pembedahan dikenal pasti dan dibandingkan di antara kumpulan yang berbeza.
Dapatan: Enam puluh empat mata dari 58 pesakit dianalisis: 20 (31.3%) mata dengan ACIOL, 28 (43.8%) mata dengan Artisan, dan 16 (25%) mata dengan SFIOL. Purata jangka masa pembedahan untuk ACIOL, Artisan, dan SFIOL adalah: 61 ± 27.8, 64 ± 26.9, dan 104.1 ± 46.8 minit. Implantasi SFIOL mengambil masa pembedahan yang jauh lebih lama daripada kumpulan ACIOL dan Artisan ($p < 0.05$). Tidak ada perbezaan yang signifikan dalam jangkamasa pembedahan antara kumpulan ACIOL dan Artisan ($p > 0.05$). Kumpulan Artisan menunjukkan pemulihan penglihatan yang lebih baik pada 1 minggu selepas pembedahan daripadakumpulan ACIOL dan SFIOL (Artisan vs ACIOL: 6/18 vs 6/24, $p <0.05$; Artisan vs SFIOL: 6/18 vs 6/60, $p < 0.05$). Wal au bagaimanapun, ketajaman penglihatan dengan pembetulan yang baik (BCVA) pada dua bulan selepas implantasi adalah setara di antara ketiga-tiga kumpulan dengan BCVA sekitar 6/9. Peningkatan tekanan intraokular (IOP) berlaku pada semua kumpulan IOL, lekang retina didapati dalam kumpulan Artisan dan SFIOL, pembentukan membran epiretinal terjadi dalam kumpulan ACIOL dan SFIOL, dekompensasi kornea pula berlaku dalam kumpulan ACIOL sahaja. Edema makular sistoid dan IOL kedudukan senget berlaku dengan SFIOL sahaja.
Kesimpulan: Ketiga-tiga kumpulan IOL menunjukkan hasil ketajaman penglihatan yang baik setelah implantasi. Keputusan pemilihan IOL harus berdasarkan keadaan klinikal pesakit, kemahiran pakar oftalmologi dan sumber yang ada.

Kata kunci: kanta intraokular Artisan, kanta intraokular ruang anterior, kanta intraokular fiksasi skleral, pembedahan katarak, sokongan kapsular

Introduction

Cataract is the leading cause of blindness in the world. According to World Health Organisation (WHO) Global Initiative for the Elimination of Avoidable Blindness, Vision 2020, global cataract prevalence is estimated to be 50 million and the estimated number of cataract surgeries performed worldwide is approximately 32.0 million, with a rate of 4000 cases per million population per year by year, 2020.[1,2] The 11th Report of the National Eye Database reported that in 2017, the total number of cataract surgeries performed at hospitals under the Malaysian Ministry of Health was 58,273.[3] As a result, cataract surgery is the most commonly performed surgery among ophthalmologists worldwide. Intraocular lens (IOL) are preferentially implanted into the capsular bag in uncomplicated cataract surgery.

However, in cases with insufficient capsular support due to congenital or secondary causes such as trauma, pseudoexfoliation, iatrogenic zonulolysis, or intraoperative posterior capsule rupture, surgeons are under intense challenge in terms of intraocular lens (IOL) selection. The modern treatment modalities for cataract surgery without capsular support have been evolving for the past decade. Several types of IOL were developed, include the angle-supported anterior chamber IOL (ACIOL), the scleral-fixated IOL (SFIOL), and the iris-claw IOL (IC-IOL).

ACIOL history began in 1952 with the Baron IOL. However, the closed-loop design of this IOL has a tarnished reputation of causing a variety of complications such as pseudophakic corneal decompensation, pigment dispersion, chronic iritis, cystoid macular oedema, and uveitis glaucoma hyphema (UGH) syndrome.[4,5] Subsequent generations of ACIOL in the 1990s with improved design in terms of reducing fixation point to three- or four-point, well-polished and haptic without holes have demonstrated good surgical outcomes and a reduction in the above mentioned complications.[6,7]

Sutured SFIOL is implanted by suturing through the *pars plana*. This technique was first described by Girard in 1981.[7] This method can be used in patients who are contraindicated for ACIOL implantation, such as glaucoma patients or patients with inadequate iris support. The IOL is placed in its anatomical location and reduces ACIOL-related complications. However, complications such as suture erosion and exposure, IOL decentration or tilting, cystoid macular oedema, retinal detachment, and endophthalmitis have been reported.[9-11] In addition, this method is limited by the availability of surgical skill and requires a steep learning curve.

IC-IOL was initially developed by Worst in the 1980s.[12,13] The lens is used in aphakic eyes with insufficient capsular support. The implantation is technically less demanding compared to sutured SFIOL. It can be anchored on the anterior iris surface or by means of retropupillary placement. Theoretically, the anterior chamber IC-IOL is located nearer to the corneal endothelium and causes relatively more endothelial cell loss compared to retropupillary fixation. However, studies did not find any evidence of corneal decompensation or significant difference in endothelial cell loss between these two methods of fixation.[14-16] Both methods showed comparable visual acuity outcomes.

The above three methods are the current treatment modalities for cases with no capsular support in Hospital Melaka and none of the above lenses is without drawbacks. Currently, there is a paucity of studies that compare these three types of IOLs. The aim of this study was to analyse the outcomes and complications of these three lenses during primary implantation, where the IOL was implanted immediately after removal of the crystalline lens in a single procedure, and secondary implantation, in which the removal of the crystalline lens and IOL implantation were performed as two separate procedures.

Material and methods

Institutional review board approval was not required for the present study. This was a retrospective analysis reviewing all patients that underwent either ACIOL, SFIOL, or IC-IOL (Artisan, Ophtec BV, Groningen, Netherlands) implantation at the Department of Ophthalmology, Hospital Melaka, Malaysia from January 2014 to January 2018. Patients were identified by reviewing the past operations list and patients' clinical record were reviewed. Both primary and secondary implantations were included in this study. Patients with pre-existing corneal scar, maculopathy, optic neuropathy, retinal detachment, and advanced glaucoma were excluded. All patients had a minimum follow-up of at least three months postoperatively. The patients were divided into ACIOL, Artisan, and SFIOL groups. Preoperative data included demographic data, Snellen visual acuity, and full ophthalmic examinations. Postoperative data included unaided visual acuity at one week and two months postoperative. Final best-corrected visual acuity was assessed at two months postoperative. Postoperative complications were also included.

Results

From January 2014 to January 2018, a total of 64 eyes in 58 patients were implanted with either ACIOL, IC-IOL (Artisan), or SFIOL due to lack of capsular support. Seven eyes were excluded due to pre-existing corneal, optic nerve, or retinal pathology as mentioned above. The models of ACIOL used were J&J AC51L (Johnson & Johnson, New Jersey, United States), FREEDOM PMS 603 (Freedom Ophthalmic Pvt Ltd, Tamil Nadu, India), Zeiss CT13A (Carl Zeiss Meditec AG, Jena, Germany) and AUROLAB AUROLENS A5520 (Aurolab, Tamil Nadu, India). The models of IC-IOL used were OPHTEC ARTISAN 205 (Ophtec B.V, Groningen, Netherlands); and types of SFIOL used were MORCHER 90L, 67G (Morcher GmbH, Stuttgart, Germany) and ALCON CZ70BD (Alcon, Geneva, Switzerland). All the surgeries were performed by 14 different surgeons. All patients received a minimum follow-up time of three months.

All the ACIOLs were implanted in a primary setting. Twenty-two cases involving Artisan lens were primary implantation and six cases were secondary implantation. Ten SFIOL implantations were primary implantations and six were secondary implantations. The demographic data and clinical information for each group of patients is summarized in Table 1. There was no significant difference in distribution of sex among different groups of IOLs. Patients who underwent Artisan IOL implantation were significantly younger than patients who received ACIOL or SFIOL ($p < 0.05$). However, there was no significant difference in mean age between the ACIOL and SFIOL groups ($p > 0.05$). The duration of SFIOL implantation was significantly longer than for the ACIOL and Artisan IOL groups ($p < 0.05$), whereas there

was no significant difference in duration of surgery between the ACIOL and Artisan groups ($p > 0.05$).

Overall, surgeons with at least five years of experience spent less time in surgery than younger surgeons, but the difference was not statistically significant (66.6 min [± 37.4] *vs* 72.9 min [± 27.3], $p = 0.260$).

Table 1. Demographic and preoperative characteristics

Parameter	ACIOL	Artisan	SFIOL	Total
n (%)	20 (31.3)	28 (43.8)	16 (25.0)	64
Mean age (SD)	68.6 (8.2)	38.5 (30.1)	61.5 (9.0)	
Sex (n)				
Male	12	21	13	46
Female	8	7	3	18
Indications of surgery				
Aphakia post lens removal	3	6	6	15
Subluxated lens	9	12	7	28
Dislocated IOL	0	8	3	11
Posterior capsule rupture	3	0	0	3
Posterior capsule rupture +				
Zonulodialysis	5	0	0	5
Congenital cataract	0	2	0	2
Mean duration of surgery (SD)	61.0 (27.8)	64.0 (26.9)	104.1 (46.8)	
Primary implantation	61.0 (27.8)	66.4 (26.7)	101.5 (68.7)	
Secondary implantation	-	55.3 (28.2)	64.3 (15.3)	

Preoperative and postoperative outcomes among all three different IOLs are summarized in Table 2. There was a significant difference in visual acuity at preoperative and one week postoperative. However, there was no significant difference in terms of visual acuity at two months postoperative. The results were compared separately using the Mann-Whitney U test with Bonferroni correction. There was a significant difference in preoperative visual acuity when comparing between the ACIOL and SFIOL groups. However, there was no difference when comparing the Artisan group with ACIOL and SFIOL. At one week postoperative, the Artisan group

showed significantly better visual acuity than both the ACIOL and SFIOL groups (Artisan *vs* ACIOL: 6/18 *vs* 6/24, $p < 0.05$; Artisan *vs* SFIOL: 6/18 *vs* 6/60, $p < 0.05$). There was no difference in visual acuity between the SFIOL and ACIOL groups at one week postoperative (SFIOL *vs* ACIOL: 6/60 *vs* 6/24, $p > 0.05$). Final best-corrected visual acuity (BCVA) at two months after surgery did not show any significant difference among the three types of IOL. Seventy-five percent (75%) of eyes which were implanted with ACIOL achieved final BCVA of 6/12 or better, whereas for the Artisan and SFIOL groups, the eyes with final BCVA of 6/12 or better were 89.3% and 81.3%, respectively.

Table 2. Comparison of visual acuity between Artisan, SFIOL, and ACIOL groups

Group	**Median**		
	Preoperative	**Postoperative 1 week**	**Postoperative 2 months**
Artisan group	6/24 (6/6 – CF)	6/18 (6/9 – 2/60)	6/9 (6/6 – 2/60)
SFIOL group	6/12 (6/6 – CF)	6/60 (6/12 – PL)	6/9 (6/6 – 6/60)
ACIOL group	3/60 (6/9 – PL)	6/24 (6/18 – PL)	6/9 (6/6 – CF)
X^2 (df	13.308 (2)	12.858 (2)	0.997 (2)
p- value	0.001	0.002	0.607

Kruskal-Wallis test

The postoperative complications that were observed in this study are summarized in Table 3. The overall complication rate for these three types of IOL was 21.9%. Elevated intraocular pressure (IOP) was the most common complication encountered, accounting for 7.8% of the cases. Elevated IOP developed in all three IOL groups and was detected between two and eight weeks postoperative. IOP elevation was transient, and only required temporary topical antiglaucoma treatment, except for two eyes. Both eyes with persistent high IOP developed after SFIOL implantation. A total of four (6.25%) eyes developed epiretinal membrane in the ACIOL and SFIOL groups. One eye with ACIOL developed corneal decompensation at 15 months postoperative. One case of retinal detachment developed in Artisan and SFIOL group. In the SFIOL group, there was one case of cystoid macular oedema (CMO). There were two eyes with tilted or decentred IOL in the SFIOL group.

Table 3. Complications by IOL type

Complications	ACIOL (n)	Artisan (n)	SFIOL (n)	Total (n)
Elevated IOP	1	3	1	5
Retinal detachment	0	1	1	2
CMO	0	0	1	1
Corneal decompensation	1	0	0	1
ERM	2	0	2	4
IOL tilt	0	0	2	2

CMO: cystoid macular oedema; ERM: epiretinal membrane ; IOP: intraocular pressure

Discussion

Insufficient capsular support can develop prior to or during cataract surgery. Choosing an appropriate IOL is crucial for surgical outcomes. Angle-supported ACIOL, IC-IOL (Artisan), and SFIOL are the three modalities used for cases with poor capsular support in Hospital Melaka. This study compared the surgical time based on surgeon experience, visual outcomes, and complications among these three types of IOLs. All three lenses showed comparable visual outcomes, with different surgical times and different postoperative complications.

SFIOL implantation demonstrated significantly longer surgical time than ACIOL and Artisan. The secondary implantation SFIOL group again showed longer duration than the Artisan group, but the difference was not statistically significant. In studies by Teng *et al.*, Mahajan *et al.*, and a meta-analysis comparing IC-IOL and SFIOL in aphakic eyes, the authors concluded that IC-IOL implantation is a more "time-saving" surgery than SFIOL implantation.[17-19] SFIOL implantation demands considerable surgical skill, which contributed to the longer surgical time compared to IC- IOL implantation, which is relatively easier and requires a shorter learning curve. The insignificant result for secondary implantation in our study may be attributed by different surgeons performing the surgery, which was not the case in the above prospective studies. In terms of surgeon experience and duration of surgery, surgeons who had at least five years of experience spent less time in surgery compared to those with less than five years of experience, but the results were statistically insignificant.

At one week after the surgery, the Artisan group achieved better visual acuity than the ACIOL and SFIOL groups. Visual recovery was significantly better in the Artisan group than in the other groups. However, the final BCVA at two months after surgery was comparable among all three groups of IOL with a median visual acuity of 6/9. There is a paucity of trials comparing these three types of IOL in cases

with impaired capsular support given that most trials compared only two out of the three groups. All the studies demonstrated insignificant differences in final visual outcome among different types of IOL.[17-19,20]Teng *et al.* conducted a prospective study in 45 eyes comparing visual outcomes between the Artisan IC-IOL and sutured posterior chamber intraocular lens (PCIOL) sulcus fixation. The results suggested that the Artisan IOL had significant BCVA at day one post-surgery, but subsequent review on corrected visual acuity at one month and three months after surgery did not find any significant difference among two groups of IOL.[17] This again suggests that the Artisan IOL provides better and faster visual recovery than SFIOL, but both IOLs ultimately achieved similar final visual acuity. A recent meta-analysis by Li *et al.* involving 14 studies and 845 eyes did not find any significant difference in postoperative BCVA between SFIOL and iris-fixated IOL.[20] Two retrospective studies comparing visual outcomes between ACIOL and SFIOL showed different results. Donaldson *et al.* did not find any significant difference in final BCVA in 181 eyes implanted with SFIOL or ACIOL.[6] However, a retrospective analysis of 36 eyes undergoing SFIOL or ACIOL implantation by Kwong *et al.* suggested that primary implantation of ACIOL achieved significantly better postoperative BCVA than SFIOL implantation.[21] The author suggested the possible cause of less favourable visual outcome in SFIOL was likely due to irreversible phototoxicity from the operating microscope, which had been proven by angiographic study, given the relatively longer operating time in SFIOL implantation or higher incidence of early pseudophakic cystoid macular oedema.[21,22] In addition, SFIOL implantation required relatively more intraocular manipulation intraoperatively, which ultimately resulted in more intense intraocular inflammation and higher risk of postoperative cystoid macular oedema.

Seventy-five percent (75%) of the eyes from the ACIOL group, 89.3% from the Artisan group, and 81.3% from the SFIOL group achieved a visual acuity of 6/12 or better. The results for ACIOL were similar to those reported in prospective and retrospective studies, which was between 68% and 79%.[23,24] For the SFIOL group, the percentage of eyes that had final BCVA of 6/12 or better was within the range for the outcomes of other studies, between 43% and 80.9%.[25-28] Lee *et al.* conducted a retrospective study that demonstrated that more eyes achieved BCVA of 6/12 or better in secondary implantation compared to primary implantation of SCIOL (58.6% *vs* 76.0%), but the result was statistically insignificant.[28]

The overall complication rate in our study was 21.9%. Elevated IOP was the most common complication, which was observed in all study groups, accounting for five (7.8%) of the overall cases. Three of the five cases required temporary antiglaucoma treatment. The remaining two eyes with persistent high IOP were from the SFIOL group. One developed prolonged postoperative inflammation requiring prolonged topical corticosteroid therapy and antiglaucoma therapy, another eye had to undergo glaucoma drainage device implantation to control IOP. The elevated IOP might be directly caused by prolonged inflammation or indirectly due to prolonged

corticosteroid use. The Laser Flare Cell Meter Study by Cellini *et al.*[29] compared the severity of intraocular inflammation among ACIOL, SFIOL, and iris-fixated IOL using a laser cell flare meter, which is a more objective and quantitative measurement. The results demonstrated that SFIOL had significantly more severe subclinical intraocular inflammation than the other two IOLs up to 90 days.[29] The eye that underwent glaucoma drainage device implantation was diagnosed preoperatively as primary angle-closure suspect. The narrowed anterior chamber angle might be further compromised in subclinical intraocular inflammation after surgery, causing persistent IOP elevation. One eye from each of the SFIOL and Artisan groups developed postoperative retinal detachment (RD). Our results for postoperative RD rates in the SFIOL group were less favourable compared to other studies which range between 3.7% to 4.8%.[21,24] This is due to our study having a relatively smaller sample size compared to other studies. Anterior vitrectomy was performed in both surgeries, which might contribute to development of retinal break and eventually RD. In addition, SFIOL implantation involves more intraocular manipulation, which may cause vitreous traction to retina which further increases the risk of retinal break and RD. Corneal decompensation developed in one eye (4.7%) with ACIOL 15 months after surgery. IOL was tilted or decentred in two eyes from the SFIOL group, but both IOLs were stable and patients had a BCVA of 6/12.

All three types of IOLs in this study were the common IOLs available for cataract surgery with impaired capsular support. At times, there is no consensus on which is the most suitable IOL to choose in cases without lens capsule in view of their comparable visual outcome. All three lenses have their own advantages and disadvantages. ACIOL and Artisan IOL implantations are technically less demanding and less sophisticated procedures, ultimately reducing the duration of surgery and postoperative inflammation. The Artisan IOL has faster postoperative visual recovery compared to the other two groups of IOL. This characteristic is especially important for patients that need faster postoperative visual recovery, such as paediatric patients, to minimize the risk of amblyopia. In addition, the Artisan IOL is relatively easier in terms of IOL exchange when necessary. ACIOL has been less commonly used due to its history of sight-threatening complications such as UGH and corneal decompensation, but with improved lens design that minimizes the risks of complications and satisfactory visual outcome, the role of ACIOL in cases with insufficient capsular support should not be overlooked. However, both lenses require adequate iris support and are contraindicated in eyes with shallow anterior chambers and glaucoma. SFIOL preserves the eye anatomy its placement in the posterior chamber. It is located further away from the corneal endothelium and ultimately reduces the risk of endothelial cell loss. It can be used in cases with inadequate iris support on top of the absence of capsular support. However, it requires a steep learning curve and is more technically demanding in terms of surgical skill. It is more time-consuming and manipulation of the vitreous increases the risk of posterior segment complications.

The limitations of this study are its retrospective nature, small sample size for each group, different age groups between the IOL groups, surgeries being performed by different surgeons, and wide range of follow-up duration. Documentation of the clinical findings was done by different individuals and data collection was not standardized. This may have led to bias and incomplete data collection. However, this is the first analysis of all three types of different IOLs in Malaysia that are commonly used in cases without capsular support.

Conclusions

All three types of IOL provide good visual outcomes in cataract surgeries with poor capsular support when the appropriate IOL is used. Decision on IOL selection should be based on the patient's clinical condition together with available surgical skills and resources.

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The authors have no conflicts of interest to declare. Institutional review board approval was not required for the present study.

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Original article

Evaluation of 18 artificial tears based on viscosity and pH

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Abstract

Introduction: Different polymers used in artificial tear formulations influence their physical properties, such as viscosity and pH, hence affecting their bioavailability. There is limited data available from manufacturers specifying the physical properties of artificial tears, even though these data can contribute to their efficacy and effectiveness.
Purpose: The aim of this study was to evaluate 18 artificial tears available in the Malaysian market based on their physical properties.
Methodology: Viscosity and pH of 18 artificial tears were evaluated using rheometer and compact pH-meter, respectively, at standard room temperature (25°C). The amount of fluid used for both tests of each artificial tear was standardised using micropipette. The Kruskal-Wallis test was employed to compare the viscosity median between the three groups (low, medium, and high viscosity) of artificial tears, while the independent t-test was used to compare the pH between preservative and non-preservative artificial tears. A p-value of 0.05 was set as the level of significance.
Results: The mean viscosity for all 18 artificial tears was 12.05 cP ± 10.21 within a range of 0.55 cP to 34.49 cP. There was a significant difference observed in viscosity between low- ($n = 7$), median- ($n = 8$), and high- ($n = 3$) viscosity groups, $\chi^2(2) = 14.474$, $p = 0.001$. The mean pH for all 18 artificial tears was 7.21 ± 0.43, with a range of 6.19 to 7.85. pH for preservative artificial tears was slightly alkaline compared to non-pre-

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servative artificial tears (7.26 ± 0.47 *vs* 7.14 ± 0.38, respectively).
Conclusion: Rheological findings indicated that different formulations of artificial tears have different viscosities, with most artificial tears falling within the recommended values. There was no difference in terms of pH between preservative and non-preservative artificial tears.

Keywords: artificial tears, pH, physical properties, viscosity

Penilaian terhadap 18 jenis air mata tiruan berdasarkan kelikatan dan pH

Abstrak

Pendahuluan: Polimer yang berlainan yang digunakan dalam formulasi air mata tiruan mempengaruhi sifat fizikalnya, seperti kelikatan dan pH, sehingga mempengaruhi ketersediaan bio mereka. Terdapat data terhad dari syarikat pengeluaran yang menyatakan sifat fizikal air mata tiruan, sedangkan data ini dapat menyumbang kepada keberkesanan dan keberkesanannya.
Tujuan: Bagimenilai 18 jenis air mata tiruan yang terdapat di pasaran Malaysia berdasarkan sifat fizikalnya.
Metodologi: Kelikatan dan pH 18 jenis air mata tiruan dinilai masing-masing menggunakan rheometer dan pH-meter padat, pada suhu bilik standard (25° C). Jumlah cecair yang digunakan untuk kedua-dua ujian setiap air mata tiruan itu diseragamkan menggunakan mikropipet. Ujian Kruskal-Wallis digunakan untuk membandingkan median kelikatan antara tiga kumpulan (kelikatan rendah, sederhana, dan tinggi) air mata buatan. Sementara ujian independent t digunakan untuk membandingkan pH antara air mata tiruan mengandungi pengawet dan tanpa pengawet. Nilai p 0.05 ditetapkan sebagai tahap perbezaan signifikan.
Hasil: Min kelikatan untuk kesemua 18 jenis air mata tiruan adalah 12.05 cP ± 10.21 dalam julat 0.55 cP hingga 34.49 cP. Terdapat perbezaan yang signifikan dalam kelikatan antara kumpulan kelikatan rendah (n = 7), median (n = 8), dan tinggi (n = 3), $\chi 2$ (2) = 14.474, p = 0.001. Min pH untuk semua 18 jenis air mata tiruan adalah 7.21 ± 0.43, dengan julat 6.19 hingga 7.85. pH untuk air mata tiruan mengandungi pengawet adalah sedikit alkali berbanding air mata tiruan tanpa pengawet (masing-masing 7.26 ± 0.47 *vs* 7.14 ± 0.38).
Kesimpulan: Penemuan reologi menunjukkan bahawa formulasi air mata tiruan yang berbeza mempunyai kelikatan yang berbeza, namun begitu kebanyakan air mata tiruan berada dalam nilai yang disyorkan. Tiada perbezaan dari segi pH antara air mata tiruan mengandungi pengawet dan tanpa pengawet.

Kata kunci: air mata tiruan, kelikatan, pH, sifat fizikal

Introduction

Artificial tears, also known as ocular lubricants, are commonly the first-line therapy among eye care providers in managing dry eye disease. Currently, artificial tears are the preferred choice for both patients and practitioners in managing ocular surface disorders due to their simplicity of use, minimal side effects, and affordability. Previous work[1-3] has suggested that long-term use of artificial tears was proven to revitalise ocular surface integrity; however, short-term effects remain debatable.[4-6] Commercially available artificial tear products are unique as their mechanism of action depends on the formulation used by the respective manufacturers. These formulations are not only limited to types of lubrication agents, demulcents, and emollients, but also the addition and selection of preservatives.[7,8]

It is an established fact that topical administration of artificial tears will increase the tear volume in the cul-de-sac, which in turn will drain through the *puncta*. The cul-de-sac has the anatomical limitation of being able to hold only approximately 30 µl under normal conditions when in upright position and unblinking state. Hence, overflow of tears from the cul-de-sac to the *puncta* occurs when this capacity is reached.[9,10] As a result, overflow leads to reduced bioavailability due to shorter ocular residence time between the ocular surface and the artificial tears. Artificial tears with higher viscosity are more effective due to prolonged residence time caused by slower drainage rate of tears from the ocular surface, while also increasing the adhesive capacity of macromolecules within the mucin layer.[11]

Despite increased residence time, high-viscosity artificial tears may cause other issues, such as ocular discomfort or irritation, and in the worst case, damage to the ocular epithelium due to an increased friction rate between the artificial tears and ocular surface during blinking.[12] Besides viscosity, another critical factor that can induce undesirable ocular symptoms is pH. It is crucial for manufacturers to ensure that artificial tear formulations fall within the normal ocular comfort range (pH range of 6.6 to 7.8).[13,14] Previous work[15] has commented that pH levels that lie outside the normal ocular comfort range could lead to epiphora as well as burning and stinging sensation, which can indirectly compromise patient compliance.

Hence, understanding the physical properties of artificial tears is crucial for eye care practitioners for better management of ocular surface-related diseases such as dry eye and pterygium. However, it is worth noting that information regarding these physical properties are not readily available on the leaflet packaging or pamphlets, thus leading to a lack of awareness among eye care practitioners. To the best of the authors' knowledge, there is no study or review that addresses the physical properties (viscosity and pH) of artificial tears in Malaysia. Thus, this study aimed

to determine the clinical physical properties, focusing on viscosity and pH, of 18 established artificial tears available in the Malaysian market.

Materials and methods

Eighteen commercially available artificial tears were selected at the International Islamic University Malaysia Eye Specialist Clinic (IESC) and International Islamic University Malaysia Optometry Clinic. The list was compiled based on the artificial tears available in the local market. The product profiles are listed in Table 1.

Viscosity was measured using Thermo Scientific Rheometer (Model HAAKE RheoWin, Version 3.61.0004, Thermo Fisher Scientific Inc, Massachusetts, USA) (Fig. 1). Viscosity was measured for each artificial tear. Each sample of artificial tear (1 ml) was collected using micropipette and applied on the lower measuring plate of the rheometer. The temperature of all samples was standardized to 25° C.[18] The measurement started as the upper plate of the rheometer started to move into rotation due to the torque applied, while the lower plate was fixed throughout the measurement.[18] The settings for torque and rotational speed were done manually, while shear stress was automatically set by the rheometer. The viscosity of each artificial tear was calculated by the built-in software,[18] based on the equation below:

$$\text{Viscosity } (\eta) = \frac{\text{Shearstress}(\tau)}{\text{Shearrate}\,(\gamma)}$$

Equation 1. Viscosity equation

For pH assessment, a compact pH-meter (LAQUAtwin pH-meter pH33, Horiba Advanced Techno Co., Ltd., Shiga, Japan) (Fig. 2) was used. Prior to measurement, two-point calibration was performed using a standard solution (pH 4.01 and pH 7.00).

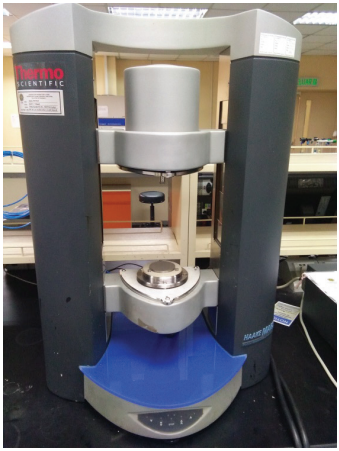

Fig. 1. Rheometer to measure the viscosity.

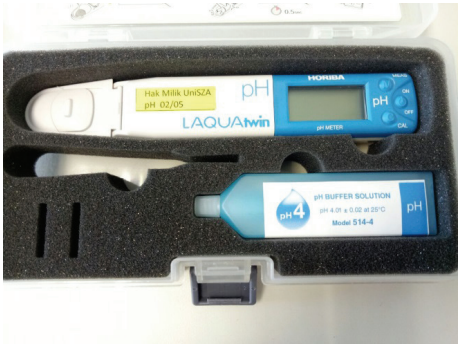

Fig. 2. Compact pH-meter for pH measurement.

A sample of each artificial tear (0.2 ml) obtained using micropipette was dropped on the flat sensor until it covered the entire flat sensor surface. The instrument then automatically measured the pH of the sample. The measurement was completed in approximately one minute. Three measurements were obtained for each sample and an average value was taken for analysis. Prior to the next artificial tear sample, the sensor was cleaned using distilled water to avoid sample cross-contamination.

IBM SPSS Statistics for Windows version 20 (IBM Corp., Armonk, N., USA) was used to execute the statistical calculations. The normality of the data was analysed using the Shapiro-Wilk normality test. The viscosity level was evaluated using the Kruskal-Wallis test[19] and grouped into low-, medium-, and high-viscosity, while the independent t-test was employed to compare the mean pH between preservative and non-preservative artificial tears.

Results

Viscosity

The viscosity of 18 artificial tears was evaluated at maximum shear rate (100 s^{-1}). Based on the findings, Vismed gel was found to have the highest viscosity (34.39 cP), while Cationorm had the lowest viscosity (0.55 cP). A graphic illustration of viscosity levels for all artificial tears tested is shown in Figure 3.

Based on single-sweep rheological analysis (Fig. 4), we found shear-thinning behaviour for all the artificial tears tested, meaning higher viscosity was observed at low shear stress and viscosity decreased under high shear stress. Thus, based on the findings, artificial tears can be further classified into three groups; low, medium and high viscosity. A previous study conducted by Meadows *et al.*[20] classified artificial tears with a viscosity of 2.7-7.7 cP as low viscosity, while Källmark and Pettersson[21] defined artificial tears in the range of 21-305 cP as high viscosity and artificial tears

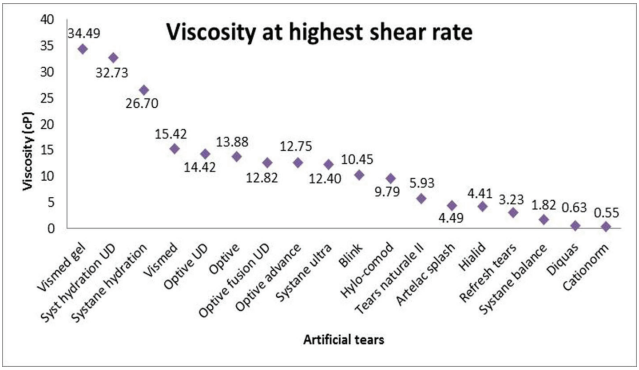

Fig. 3. Evaluation of different viscosity levels for 18 artificial tears tested in the study.

Table 1. Artificial tears profiles

Artificial tear brand	Manufacturer	Lubricant	Ingredients	Preservative	Discard after
Tears Naturale II	Alcon Laboratories Inc, Fort Worth, TX, USA	Dextran 0.1% Hypromellose 0.3%	Potassium chloride, purified water, sodium borate and sodium chloride. May contain hydrochloric acid and/or sodium hydroxide to adjust pH.	Polyquaternium 10.0011%	1 month
Systane Hydration unit dose (UD)	Alcon Laboratories Inc, Fort Worth, TX, USA	Sodium hyaluronate 0.1% Hydroxypropyl guar	Polyethylene glycol 400, propylene glycol, sorbitol, aminomethyl propanol, boric acid, sodium borate, potassium chloride and sodium chloride.	None	N/a
Systane Hydration	Alcon Laboratories Inc, Fort Worth, TX, USA	Sodium hyaluronate Hydroxypropyl guar	Polyethylene glycol 400, propylene glycol, sorbitol, aminomethyl propanol, boric acid, sodium borate, disodium EDTA, sodium citrate, potassium chloride, sodium chloride	Polyquaternium 10.0011%	3 months
Systane Balance	Alcon Laboratories Inc, Fort Worth, TX, USA	Propylene glycol 0.6%	Boric acid, dimyristoyl phosphatidylglycerol, edatate disodium, hydroxypropyl guar, mineral oil, polyoxyl 40 stearate, sorbitan tristearate, sorbitol, purified water, hydrochloric acid, sodium hydroxide	Polyquaternium 10.0011%	6 months

Artificial tear brand	Manufacturer	Lubricant	Ingredients	Preservative	Discard after
Systane Ultra	Alcon Laboratories Inc, Fort Worth, TX, USA	Polyethylene glycol 400 0.4% Propylene glycol 0.3%	Aminomethylpropanol, boric acid, hydroxypropyl guar, potassium chloride, purified water, sodium chloride, sorbitol, hydrochloric acid, sodium hydroxide	Polyquaternium 10.0011%	6 months
Hialid	Santen Pharmaceutical Co., Ltd., Japan	Sodium hyaluronate 0.1%	ε-aminocaproic acid, disodium edetate hydrate, propylene glycol, and benzalkonium chloride as additives	Benzalkonium chloride	1 month
Refresh Tears	Allergan Inc., Irvine, California, USA	Carboxymethylcellulose sodium 0.5%	Boric acid, calcium chloride, magnesium chloride, potassium chloride, purified water, sodium borate, sodium chloride. May contain hydrochloric acid and/or sodium hydroxide.	Purite	3 months
Optive Fusion unit dose (UD)	Allergan Inc., Irvine, California, USA	Sodium hyaluronic 0.1% Carboxymethylcellulose 0.5%	Boric acid, calcium chloride dehydrate, erythritol, levocarnitine, magnesium chloride hexahydrate, potassium chloride, purified water, sodium borate decahydrate, sodium citrate dihydrate	None	N/a
Optive Advanced	Allergan Inc., Irvine, California, USA	Carboximethylcellulose sodium 0.5% Glycerin 1% Polysorbate 80 0.5%	Boric acid, castor oil, erythritol, levocarnitine, carbomer copolymer type A, purified water, sodium hydroxide	Purite	6 months

Artificial tear brand	Manufacturer	Lubricant	Ingredients	Preservative	Discard after
Optive	Allergan Inc., Irvine, California, USA	Carboxymethylcellulose sodium 0.5% Glycerin 0.9%	Boric acid, calcium chloride dehydrate, erythritol, levocarnitine, magnesium chloride hexahydrate, potassium chloride, purified water, sodium borate decahydrate, sodium citrate dihydrate	Purite	6 months
Optive unit dose (UD)	Allergan Inc., Irvine, California, USA	Carboxymethylcellulose sodium 0.5% Glycerin 0.9%	Boric acid, calcium chloride dehydrate, erythritol, levocarnitine, magnesium chloride hexahydrate, potassium chloride, purified water, sodium borate decahydrate, sodium citrate dihydrate	None	N/a
Artelac Splash	Bausch & Lomb, Berlin, Germany	Sodium hyaluronate 0.2%	Potassium chloride, sodium chloride, disodium phosphate dodecahydrate, sodium dihydrophosphate dehydrate, purified water	None	N/a
Vismed Gel	TRB Chemedica, Germany	Sodium hyaluronate 0.3%	Sodium chloride, potassium chloride, disodium phosphate, sodium citrate, magnesium chloride, calcium chloride and water	None	N/a

Artificial tear brand	Manufacturer	Lubricant	Ingredients	Preservative	Discard after
Blink Intensive Tears	Abbott Medical Optics	Polyethylene glycol 400 0.25% Sodium hyaluronate 0.2%	Boric acid, sodium borate (decahydrate), sodium chloride, potassium chloride, calcium chloride (dihydrate), magnesium chloride, purified water	OcuPure	1 month
Cationorm Ophthalmic Emulsion	Santen Pharmaceutical Co., Ltd., Japan	Mineral oil	Cetalkonium chloride, tyloxapol, poloxamer 188, tris hydrochloride, tromethamine, mineral oils, glycerol, purified water	None	N/a
Hylo Comod	Ursapharm Arzneimittel GmbH, Germany	Sodium hyaluronate 0.1%	Citrate buffer, sorbitol, water	None	6 months
Vismed	TRB Chemedica, Germany	Sodium hyaluronate 0.18%	Sodium chloride, potassium chloride, disodium phosphate, sodium citrate, magnesium chloride, calcium chloride, and water for injections	None	N/a
Diquas*	Santen Pharmaceutical Co., Ltd., Japan	Diquafosol sodium 3%	Sodium phosphate hydrate, disodium edetate hydrate, sodium chloride, potassium chloride, dilute hydrochloric acid, sodium hydroxide	Chlorhexidine gluconate solution	1 month

*Diquas is a secretagogue agent that stimulates the secretion of tear fluid from conjunctival epithelial cells and mucin secretion from conjunctival goblet cells.[16,17]

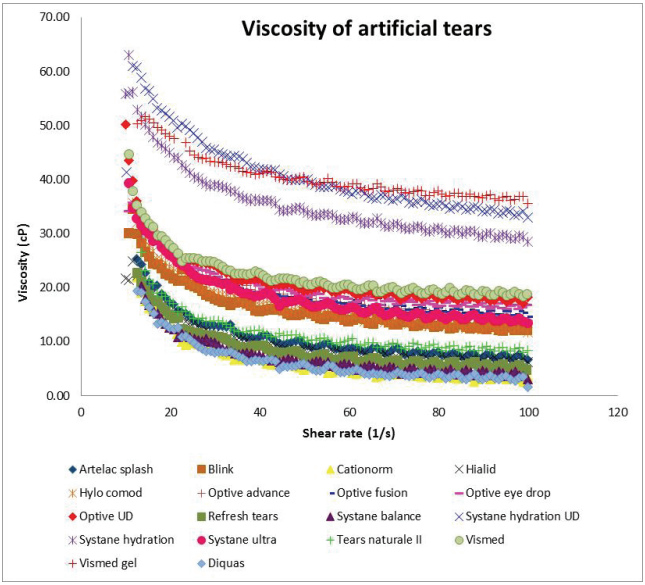

Fig. 4. Flow curves of dynamic viscosity as a function of shear rate.

in the range of 1.3-20 cP as low viscosity. However, neither study considered the range for medium-viscosity artificial tears. For this study, the viscosity groups of artificial tears were defined as follows: low viscosity, 0.55-7.7 cP; medium viscosity, 7.8-20 cP; and high viscosity, 21-305 cP.

The Kruskal-Wallis test was employed to compare the median between the three groups (low, medium, and high viscosity) of artificial tears. The result revealed that there was a significant difference in viscosity between the low ($n = 7$), median ($n = 8$), and high ($n = 3$) viscosity group, $\chi^2(2) = 14.474$, $p = 0.001$, with a mean rank viscosity of 4.00 for the low group, 11.50 for the medium group, and 17.00 for the high group, as summarised in Table 2.

pH

The majority (83.3%; 15 out of 18) of the selected artificial tears were weak bases, while the remaining four artificial tears were acidic (Fig. 5). Descriptive analysis revealed that mean pH for all artificial tears was slightly alkaline with a pH of 7.21 ± 0.43. A similar trend was noted between preservative and non-preservative artificial tears, in which mean pH was 7.26 ± 0.47 for preservative artificial tears and 7.14 ± 0.38 for non-preservative artificial tears. No significant difference ($p = 0.579$) in pH between these two groups was noted. The pH profiles for all selected artificial tears and comparison of pH between the preservative and non-preservative artificial tears are summarised in Figure 5 and Table 3, respectively.

Table 2. Comparison of variation in viscosity groups for 18 artificial tears

Artificial tear	Viscosity (cP)	Group	Viscosity mean rank	Chi-square (df)	*p*-value
Cationorm	0.55	Low-viscosity artificial tears (*n* = 7)	4.00	14.474 (2)	0.001
Diquas	0.63				
Systane Balance	1.82				
Refresh Tears	3.23				
Hialid	4.41				
Artelac splash	4.49				
Tears Naturale II	5.93				
Hylo Comod	9.79	Medium-viscosity artificial tears (*n* = 8)	11.40		
Blink	10.45				
Systane Ultra	12.40				
Optive Advance	12.75				
Optive Fusion UD	12.82				
Optive	13.88				
Optive UD	14.42				
Vismed	15.42				
Systane Hydration	26.70	High-viscosity artificial tears (*n* = 3)	17.00		
Systane Hydration UD	32.73				
Vismed Gel	34.49				

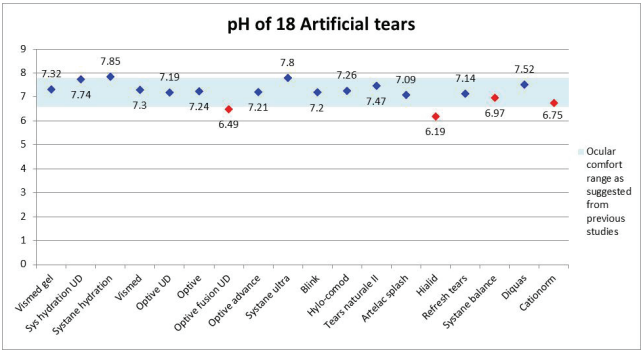

Fig. 5. pH of preservative and non-preservative artificial tears.

Table 3. Comparison of pH between preservative and non-preservative artificial tears

Artificial tears	Preservative artificial tears Mean (SD) (*n* = 10)	Non-preservative artificial tears Mean (SD) (*n* = 8)	*p*-value*
pH	7.26 (0.47)	7.14 (0.38)	0.579

*Based on independent t-test findings, with level of significance set at 0.05.

Discussion

Rheological analysis of artificial tears and its relation to ocular residence time

Rheology evaluates fluid flow and its deformation due to mechanical force, and one type of rheological analysis is evaluating viscosity under shear rate dynamics.[22] Related to artificial tears, rheological analysis can be used to characterise their behaviour on the ocular surface.[23] Previous studies have suggested that the cut-off viscosity of < 30 cP for artificial tears was crucial in order to avoid ocular discomfort, blurred vision, and ocular irritation that could indirectly lead to faster drainage of tears due to reflex tears and blinking.[24,25] However, the shear rate were not specified in these studies.[24,25] Therefore, the exact viscosity could be different depending on the shear rate applied by the rheometer. In this study, 16 out of 18 artificial tears (88.89%) had a viscosity < 30 cP (at shear rate of 100/s^{-1}), except for Vismed Gel (34.49 cP) and Systane Hydration UD (32.73 cP).

Generally, the rheology of natural tears can be categorised as that of a non-Newtonian fluid, as its viscosity is dependent on shear rate.[23,26] Specifically, the effects of viscosity on the ocular surface can be related to two phenomena, which are the blinking and inter-blinking state. A previous study estimated the shear rate in the open eye to be 10s^{-1}, rising to 10 000s^{-1} in the blinking eye, with zero shear rate in the closed eye.[27] Hence, it is important for manufacturers to ensure that the formulation of artificial tears has high viscosity at low shear rate (open eye) in order to increase ocular retention time, as maximises the bioavailability of artificial tears. Meanwhile, at high shear rate (blinking), low-viscosity formulations are able to provide comfort and prevent excessive stress to the ocular surface during blinking. With regards to this study, it was found that all selected artificial tears showed pseudo-plastic (shear-thinning) behaviour, whereby viscosity is inversely proportional to shear rate.

Previous literature has indicated that viscosity plays a significant role in increasing the residence time and enhancing the efficacy of artificial tears. A study by Paugh *et al.*[28] showed that higher-viscosity, pseudo-plastic artificial tears increased the precorneal residence time by more than two-fold compared to control solution (saline). The authors also commented that, apart from viscosity, the residence time of artificial tears could also be influenced by factors such as the degree of muco-

adhesion of viscous polymers, spreading of the drop upon instillation, and relative comfort after drop. A recent study[29] compared precorneal retention time between two different artificial tears (eye drops and eye gel) over 120 minutes, finding that the artificial tear with higher viscosity (eye gel) was retained on the ocular surface longer than the eye drop-based artificial tear. The eye gel-based artificial tear was found at maximum value after one minute of instillation and returned to baseline after 60 minutes of observation. This indicates that gel-based artificial tears with higher viscosity can prolong ocular residence time. However, they can also induce undesirable symptoms, such as blurred vision, due to its viscosity.

Effect of pH on ocular comfort

It has been previously reported that normal tear pH ranges from 6.5 to 8.0,[30-34] while a study conducted by Khurana *et al.*[35] indicated that the mean pH of tears among dry eye patients was 7.46 ± 0.24. Previous studies have suggested that the pH of artificial tears should be in the range of 6.6 to 7.8 pH in order to avoid any discomfort after instillation.[13,14,30,34] In our study, 14 artificial tears (77.78%) had a pH within the ocular comfort range of 6.19 to 7.85. It was found that Optive Fusion UD (6.49) and Hialid (6.19) had pH values < 6.6, while Systane Hydration had a pH beyond the maximum value of recommended ocular comfort rate (7.85) (Fig. 5).

In our study, comparison of pH between preservative and non-preservative artificial tears showed that preservative artificial tears were slightly alkaline (7.26 ± 0.47) compared to non-preservative artificial tears (7.14 ± 0.38). However, the difference between these two groups was insignificant (p = 0.579). This result suggested that preservatives added in artificial tears did not influence the pH. On the other hand, previous studies have suggested that the pH of artificial tears was closely related to buffering agents, as these agents act as pH stabilizers to ensure the formulations are soluble, active, and tolerable.[36] Common buffer agents used in artificial tears formulations are citrate, acetate, phosphate, borate, and Tris-HCl (tris hydroxymethyl aminomethane and hydrochloric acid); all of these agents are non-toxic to the eye.[36,37]

Generally, the results of this study showed that commercially available artificial tears have a wide range of pH levels. The pH levels of artificial tears that fall beyond the ocular comfort range can cause ocular irritation, stinging sensation, or ocular discomfort.[38,39] This not only compromises patient compliance, but also reduces bioavailability and efficacy due to excessive tearing, which results in rapid flushing of the instilled artificial tears.[40] Tong *et al.*[15] recommended patients to try several artificial tears in order to find the most comfortable formulation, with a suitable pH for their tear film. However, it is highly desirable that eye care practitioners themselves, *i.e.* the physicians who prescribe the artificial tears, guide patients in selecting the most suitable formulation on a case-by-case basis and along with the clinical evidence so that treatment is ultimately beneficial.

It is worth noting that, although this study evaluated 18 artificial tears, it only

covers two factors of the physical properties, namely, viscosity and pH. Thus, further improvements need to be done. We suggest that future studies should include more brands of artificial tears (both preservative and non-preservative artificial tears) available in Malaysia in order to provide more comprehensive data regarding their physical properties. Other physicochemical properties, such as osmolarity, surface tension, density, and molecular weight, should also be included in future analysie in order to provide inclusive data in determining the effectiveness of artificial tear formulations.[41] Our study had a significant technical limitation, as the rheometer we employed could only measure viscosity at a shear rate of $10s^{-1}$ to $100s^{-1}$. Given that the blinking process involves high shear rates (up to $10{,}000s^{-1}$),[27] we suggest that future studies use more advanced rheometers, as they are able to characterise the viscosity of artificial tears at this shear rate during blinking. Future studies could also determine whether basic or acidic artificial tear formulations offer better ocular sensation after instillation.

Conclusion

Viscosity and pH are important factors that determine patient compliance with treatment. Artificial tears with high viscosity and close to normal pH provide better tear distribution and ocular comfort, respectively. Our results suggested that certain properties vary significantly between the brands of artificial tears tested.

Acknowledgements

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Original article

The outcomes of selective laser trabeculoplasty at six months

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Abstract

Purpose: To study the intraocular pressure (IOP)-lowering effects of selective laser trabeculoplasty (SLT) at six months and to determine factors that can predict the success of SLT.
Study design: Prospective cohort study with convenience sampling.
Material and methods: The patients were seen at the Glaucoma Clinic, Selayang Hospital from October 2017 to September 2018. Patients with primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), and ocular hypertension (OHT) of mild to moderate severity that needed further IOP reduction were recruited. Baseline characteristics were documented followed by water drinking test (WDT) and SLT. Follow-up was scheduled at one week, six weeks, three months, and six months. WDT was repeated at six months.
Results: Eighteen eyes of 18 patients were recruited. IOP at baseline, 1 week, 6 weeks, 3 months, and 6 months was 19.3 ± 3.7,16.7 ± 3.8,16.5 ± 2.7,16.6 ± 3.2 and 15.3 ± 3.8 mmHg, respectively ($P < 0.05$). The reduction of baseline IOP, peak IOP, and IOP fluctuation were 20.7%, 26.7%, and 31.4%, respectively ($P < 0.05$). The cumulative success at six months was 44%. The significant success predictors were mean deviation on Humphrey visual field and IOP one week post-SLT.
Conclusions: SLT can be used to treat mild to moderate POAG, NTG, and OHT patients, either as first-line treatment or as an adjunct to medical therapy.

Keywords: intraocular pressure, glaucoma, selective laser trabeculoplasty, success predictor, water drinking test

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Dapatan kajian trabekuloplasti laser selektif pada enam bulan

Abstrak

Tujuan: Untuk mengkaji kesan tekanan intraokular (IOP) dari laser selektif trabekuloplasti (SLT) pada enam bulan dan untuk menentukan faktor-faktor yang dapat meramalkan kejayaan SLT.
Reka bentuk kajian: Kajian kohort prospektif dengan pensampelan mudah.
Bahan dan kaedah: Melibatkan pesakit yang dirawat di Klinik glaukoma, Hospital Selayang dari Oktober 2017 hingga September 2018. Pesakit dengan glaukoma sudut terbuka primer (POAG), glaukoma tekanan normal (NTG), dan hipertensi okular (OHT) peringkat ringan hingga sederhana teruk yang memerlukan pengurangan IOP telah direkrut. Ciri-ciri asas didokumentasikan diikuti dengan ujian minum air (WDT) dan SLT. Tindakan susulan dijadualkan pada satu minggu, enam minggu, tiga bulan, dan enam bulan. WDT diulang pada enam bulan.
Dapatan: Lapan belas mata dari 18 pesakit direkrut. IOP pada garis awal, 1 minggu, 6 minggu, 3 bulan, dan 6 bulan selepas SLT adalah 19.3 ± 3.7, 16.7 ± 3.8, 16.5 ± 2.7, 16.6 ± 3.2 dan 15.3 ± 3.8 mmHg ($p < 0.05$). Pengurangan IOP dari garis asas, puncak IOP, dan IOP fluktuasi masing-masing ialah 20.7%, 26.7%, dan 31.4% ($p < 0.05$). Kejayaan kumulatif pada enam bulan adalah 44%. Peramal kejayaan yang ketara adalah penyimpangan min pada medan visual Humphrey dan IOP satu minggu selepas SLT.
Kesimpulan: SLT boleh digunakan untuk merawat tahap awal dan sederhana pesakit POAG, NTG, dan OHT , sama ada sebagai rawatan peringkat pertama atau sebagai tambahan kepada terapi secara perubatan.

Kata kunci: glaukoma, laser selektif trabekuloplasti, peramal kejayaan, tekanan intraokular, ujian minum air

Introduction

Selective laser trabeculoplasty (SLT) was introduced by Latina and Park in 1995.[1] It works by selectively targeting the pigmented trabecular meshwork (TM) to increase aqueous outflow by mechanical[2] and cellular mechanisms.[3] The intraocular pressure (IOP)-lowering effect of SLT has been evaluated by numerous researchers with promising results. It was reported to be comparable to medical therapy[4,5] and has the potential to be the first-line treatment in the management of glaucoma. SLT avoids the issues of side effects, compliance, and cost related to medications, and it does not come with the risks associated with glaucoma surgery.

SLT success rates have been reported to vary from 40% to 84% in patient groups of different characteristics.[6-8] Much work has been done to identify the predicting factors for SLT success. Some researchers found high baseline IOP[9] and an absence of antiglaucoma medications[10-12] to be associated with success of SLT treatment, whereas factors such as age, sex, and diabetes mellitus were not consistent.

The role of IOP-lowering in delaying the progression of optic nerve damage is undebatable.[13-15] However, large diurnal fluctuations in IOP and IOP peaks that are not detected during office hours also contributes to the progression of glaucoma.[16] The water drinking test (WDT) has been proposed as a useful test to predict IOP peaks and fluctuations in the clinical setting.[16,17] IOP peaks detected during the WDT have a strong association with the severity of visual field defect and may be predictive of glaucoma progression.[16]

In this study, we aimed to study the IOP-lowering effect of SLT at six months and to determine factors that can predict its success. We also assessed the efficacy and sustainability of SLT in reducing IOP peaks and fluctuation using the WDT.

Materials and methods

This prospective cohort study recruited patients from the Glaucoma Clinic, Selayang Hospital from October 2017 to September 2018. The convenience sampling method was used. Approval from the Clinical Research Centre, Selayang Hospital, National Medical Research Registry (NMRR) and Medical Research Ethics Committee (MREC) were obtained and the study conformed to the tenets of the Declaration of Helsinki. Informed consent forms from all participants were signed before the study started.

Patients with ocular hypertension (OHT), normal-tension glaucoma (NTG), and primary open-angle glaucoma (POAG) of early or moderate disease with cup-disc ratio (CDR) 0.8 or less and mean deviation (MD) less than -12.0 dB, that required further reduction of IOP were included. Patients with IOP more than 30 mmHg, history of glaucoma surgery or laser trabeculoplasty, history of uveitis, patients with chronic kidney disease or cardiac failure, patients who were on diuretics or patients who were unable to consume the required volume of fluid within five minutes were excluded. For patients who had SLT in both eyes, the eye with higher baseline IOP was taken as the study eye.

On the first visit, baseline characteristics (age, gender, race, type of glaucoma, number of antiglaucoma medications, central corneal thickness [CCT], CDR, MD on Humphrey visual field [HVF], visual acuity) were taken. Baseline IOP was taken, followed by the WDT. SLT was performed after the WDT. IOP was measured again one-hour post-SLT. Follow-ups were scheduled at one week, six weeks, three months, and six months. WDT were repeated at six months.

SLT

SLT was performed by the author following WDT during first visit. It was performed using a Q-switched Nd:YAG laser (Ellex Solo, Ellex, Mawson Lakes, Australia) under topical anaesthesia using a Latina lens. Power was started at 0.5 mJ and titrated until bubble formation was just visible. One hundred contiguous, non-overlapping shots were placed onto 360° of the TM. All patients were treated with ketorolac eyedrops four times a day for one week post-SLT.

WDT

The WDT is an alternative measure that can be done during office hours to evaluate the aqueous outflow facility reserve and efficacy of the TM. In this study, patients were instructed not to ingest any fluid within two hours before the WDT. During the first visit, each patient was required to drink 10ml/kg of body weight of drinking water within five minutes after measuring baseline IOP. Then, IOP was measured four times at 15-minute intervals. The highest value was taken as the peak IOP. The difference between baseline IOP and peak IOP is noted as fluctuation. IOP measurements were done with a Goldmann applanation tonometer AT 900 (Haag-Streit, Koniz, Switzerland).

Statistical analysis

The primary outcome was successful IOP reduction at six months. Successful SLT was defined as IOP reduction $\geq$ 20% of baseline IOP. The secondary outcomes were possible predictors of success, which were compared between the success and non-success groups.

The sample size was calculated using PS Power and Sample Size Calculator version 3.1.2 (Department of Biostatistics and Vanderbilt University School of Medicine, USA). A total of 16 patients was required. In order to allow a dropout rate of 20%, 20 patients were recruited. Statistical analysis was performed using Statistical Package for Social Science (SPSS for MAC version 21.0, SPSS Inc., Chicago, USA). For numerical variables, the independent t-test and Mann-Whitney U test were used to detect statistical significance; for categorical variables, Fisher's exact test was used. Paired sample t-test was used for continuous data, *i.e.* to compare baseline IOP pre- and post-SLT, and IOP peak and fluctuation pre- and post-SLT. A P value < 0.05 was considered statistically significant. Univariate logistic regression analyses were performed for the possible predictors of success and any factors with p-value close to 0.05 were included in multivariate regression analysis.

Results

Twenty patients were recruited in total. One patient defaulted follow-up and another patient was prescribed new antiglaucoma drops, hence they were excluded

Table 1. Baseline characteristics and demographic data

Number of eyes	18
Age (years), median, IQR	62.5, 15
Gender, n (%) **- Female** **- Male**	 10 (55.6) 8 (44.4)
Race, n (%) **- Malay** **- Chinese** **- Indian**	 6 (33.3) 11 (61.1) 1 (5.6)
Diabetes mellitus, n (%) **- yes** **- no**	 10 (55.5) 8 (44.5)
Hypertension, n (%) **- yes** **- no**	 10 (55.5) 8 (44.5)
Glaucoma type, n (%) **- POAG** **- NTG** **- OHT**	 5 (27.8) 9 (50.0) 4 (22.2)
Antiglaucoma medications, n (%) **- 0** **- 1** **- 2** **- 3** **- 4**	 14 (77.8) 1 (5.6) 2 (11.1) 0 (0) 1 (5.6)
Baseline IOP, mmHg, mean ± SD	19.3 ± 3.7
CCT (mm), mean ± SD	548.3 ± 30.80
MD, mean ± SD	- 4.1 ± 2.96
CDR, median, IQR	0.7, 0.2

CDR: cup-disc ratio; CCT: central corneal thickness; IOP: intraocular pressure; MD: mean deviation; NTG: normal-tension glaucoma; OHT: ocular hypertension; POAG: primary open-angle glaucoma; SLT: selective laser trabeculoplasty

from the study. Eighteen eyes of 18 patients were included in the study analysis. The baseline characteristics and demographic data of the patients are shown in Table 1.

IOP lowering effects of SLT

The baseline IOP was 19.3 ± 3.7 mmHg. IOP increased to 23.4 ± 4.3 mmHg one hour post-SLT. However, IOP decreased below baseline level as soon as one week post-SLT and was maintained throughout the follow-up period (Table 2).

SLT significantly reduced the baseline IOP, peak IOP, and IOP fluctuations at six months post-treatment. There was a 20.7% drop in baseline IOP and a 26.7% drop in peak IOP. SLT also reduces IOP fluctuations from 5.1 mmHg to 3.5 mmHg, which is equivalent to a 31.4% reduction (Table 3).

Table 2. IOP pre- and post-SLT

Duration	IOP (mmHg), mean ± SD
Baseline	19.3 ± 3.7
1 hour post-SLT	23.4 ± 4.3
1 week post-SLT	16.7 ± 3.8
6 weeks post-SLT	16.5 ± 2.7
3 months post-SLT	16.6 ± 3.2
6 months post-SLT	15.3 ± 3.8

*$p < 0.05$ when baseline IOP was compared to all timepoints post-SLT treatment, except one hour post-SLT (general linear model, repeated measure)

Table 3. Comparison of baseline IOP, peak IOP, and IOP fluctuation between pre-SLT and six months post-SLT

	Pre-SLT (n = 18)		Post-SLT (n = 18)		% Mean IOP reduction	P-value
	Mean IOP (mmHg)	Standard deviation	Mean IOP (mmHg)	Standard deviation		
Baseline IOP	19.3	3.7	15.3	3.8	20.7	0.000
Peak IOP	24.3	4.4	18.8	3.5	26.7	0.000
IOP fluctuation	5.1	2.7	3.5	1.4	31.4	0.037

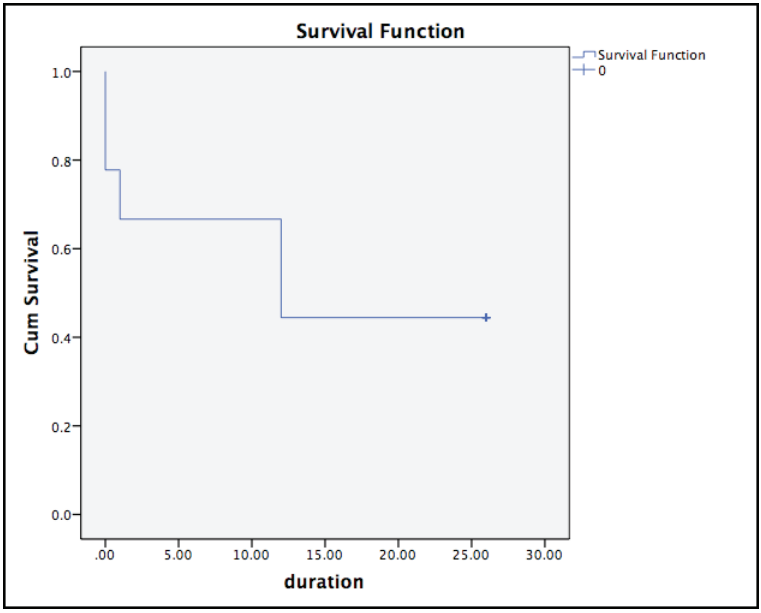

Fig. 1. Cumulative success rates.

Table 4. Baseline and post-SLT IOP in the success and non-success groups

Duration	Success*	Non-success	*P*-value
Baseline	20.1 ± 3.9	18.6 ± 3.6	0.402
1 hour	25.1 ± 4.3	22.1 ± 3.9	0.139
1 week	16.0 ± 4.7	17.3 ± 3.0	0.488
6 weeks	16.1 ± 3.1	16.8 ± 2.5	0.620
3 months	16.6 ± 3.5	16.6 ± 3.1	0.987
6 months	13.0 ± 2.1	17.1 ± 3.8	0.016

*$p < 0.05$ when baseline IOP was compared to all timepoints post-SLT treatment (general linear model, repeated measure)

The cumulative success at six months was 44% (Fig. 1).

IOP in the success group showed significant reduction as early as one week post-treatment and dropped further at six months. In the non-success group, there was no significant IOP reduction at any of the follow-up timepoints. IOP reduction at all timepoints post-treatment was statistically significant when compared to baseline IOP (Table 4).

Predictors of SLT success

The predictors of success of SLT under study were age, gender, race, diabetes mellitus, hypertension, type of glaucoma, number of glaucoma medications, baseline IOP, MD, CCT, CDR, visual acuity in logMAR, and IOP one week post-SLT (Table 5). Although the success group included older age, more antiglaucoma medications, higher baseline IOP, thinner CCT, and higher CDR, these factors were not statistically significant between the success and non-success groups. The significant predictors were MD and percentage of IOP reduction at one week post-treatment. The mean MD for the success group was -5.69 ± 3.59, whereas for the non-success it was -2.78 ±

Table 5. Comparison of the success and non-success groups

Variable	Success	Non-success	*P*-value
Age (years), median, IQR	67.0, 14	57.4, 14	0.083*
Gender (female/ male)	3/5	5/5	0.664^
Race, n - Malay - Chinese - Indian	 3 4 1	 3 7 0	0.472^
Diabetes mellitus, n (Y/N)	5/3	5/5	0.664^
Hypertension, n (Y/N)	4/4	6/4	1.000^
Glaucoma type, n - POAG - NTG - OHT	 3 4 1	 2 5 3	0.827^
Antiglaucoma medications, n - 0 - 1 - 2 - 3 - 4	 5 0 2 0 1	 9 0 0 0 0	0.127*
Baseline IOP, mmHg, mean ± SD	20.1 ± 3.9	18.6 ± 3.6	0.402**
CCT (mm), mean ± SD (range)	539.4 ± 30.9	555.5 ± 30.3	0.282**
MD, mean ± SD (range)	-5.69 ± 3.59	-2.78 ± 1.53	0.034**
CDR, median, IQR	0.80, 0.2	0.70, 0.2	0.194*
logMar, median, IQR	0.18, 0	0.18, 0	0.735*
1-week IOP reduction (%), mean ± SD	20.9 ± 15.0	6.0 ± 11.1	0.028**

*Mann Whitney U test; **independent t-test; ^Fisher's exact

CDR: cup-disc ratio; CCT: central corneal thickness; IOP: intraocular pressure; MD: mean deviation; NTG: normal-tension glaucoma; OHT: ocular hypertension; POAG: primary open-angle glaucoma; SLT: selective laser trabeculoplasty

Table 6. Univariate and multivariate regression analyses of the covariates affecting SLT success

	Univariate logistic regression		Multiple regression	
	***P*-value**	**Odds ratio**	***P*-value**	**Odds ratio**
Age	1.038	0.428		
Gender	0.597	1.667		
Race	1.000	0.000		
Diabetes mellitus	0.597	0.600		
Hypertension	0.672	1.500		
Glaucoma type	0.307	4.500		
Number of medications	0.163	3.440		
Baseline IOP	0.382	1.130		
CCT	0.272	0.980		
MD	0.068	0.630	0.114	0.177
CDR	0.563	5.610		
Visual acuity	0.873	0.520		
1-week IOP reduction (%)	0.068	0.900	0.094	0.777

CDR: cup-disc ratio; CCT: central corneal thickness; IOP: intraocular pressure; MD: mean deviation

1.53 ($p < 0.05$). The success group demonstrated 20.9% of IOP reduction at one week post-treatment compared to a 6% reduction in the non-success group.

Using univariate and multivariate analysis, none of the covariates were significantly associated with SLT success (Table 6).

Discussion

SLT is a relatively safe, easy-to-perform office procedure to lower IOP. In terms of SLT efficacy, our study demonstrated a 4.0 mmHg reduction of IOP and a cumulative success of 44% at six months post-SLT treatment. While the IOP reduction is comparable, our success rate is slightly lower than that published in a review showing a 3.8 to 8 mmHg reduction in IOP and a 55-82% success rate between 6 to 12 months.[18] In this review article, the pre-SLT IOP ranged from 23 mmHg to 26 mmHg, whereas our baseline IOP was 19.3 mmHg due to the majority of our patients

having NTG. Given that our study and the review used the same definition of success, the different success rates between our study and the review article is most likely accounted for by the difference in baseline IOP. This effect of lower percentage of IOP reduction due to lower baseline IOP was seen in a study on NTG by Lee *et al.*, where an IOP reduction of only 15% was reported with baseline IOP of 14.3 ± 3.4 mmHg.[19] Nevertheless, even 1 mmHg of IOP reduction can reduce the risk of visual field progression by 10%.[20] Positive results have also been reported in the LiGHT study. They demonstrated that SLT provided better IOP control over the course of three years, with more follow-up meeting target IOP compared to eyedrops, less intense drop treatment, lower rates of disease deterioration, and no further glaucoma surgeries needed.[21]

From the IOP trend in the success group, we can observe that IOP post-treatment decreased significantly as early as one week and a significant reduction was seen again at six months. This suggests that, in this group of patients with mild to moderate disease, it is worthwhile to wait for at least six months to observe the full effect of SLT before deciding the next steps of management, provided that the patient has responded at the early stage.

Besides baseline IOP, our study also showed that SLT significantly reduced peak IOP and IOP fluctuations. Higher mean IOP peak and IOP fluctuations during the WDT were reported to be associated with visual field progression.[17] Asrani *et al.* showed that large diurnal IOP fluctuations were an independent risk factor in glaucoma patients.[22] Our results are in line with a study by Lee *et al.* demonstrating significant reduction in mean, peak, and range of IOP during the nocturnal period, following additional SLT in medically treated glaucoma patients.[23]

Not all patients respond to SLT in the same manner. Our study attempted to identify the factors that might be able to predict likelihood of success, which can serve as a guideline in the management of glaucoma patients. In this study, SLT success was significantly predicted by MD on HVF and IOP one week post-treatment. Lower MD is indicative of greater disease severity. Gottanka *et al.* reported that increasing severity of POAG was accompanied by an increase in the amount of plaque material in the TM.[24] We postulate that SLT reduces TM resistance and improves the aqueous outflow, hence lowering IOP. This association has not been reported before in the literature. A study on Chinese patients looked at another HVF parameter, the visual field index (VFI), and reported no significant association.[25]

We found that lower IOP at one week can predict SLT success at six months. The significance of lower IOP in the earlier phase as a predictor of SLT success was also in line with other two studies by Lee *et al.* They found that lower one-day IOP post-treatment in POAG patients[26] and one-week IOP post-treatment in NTG patients[19] were both significant predictors for success. It was postulated that greater IOP reduction at an early phase may represent a higher level of metalloproteinase, cytokines, and macrophages, which have been proposed to be the biological agents responsible for IOP lowering.[27]

Many studies have reported that baseline IOP is a consistent and strong predictor of SLT success.[18,19,28] Our study failed to demonstrate this association significantly, although the success group did have a higher mean IOP compared to the non-success group. The reason for this might be due to lower baseline IOP in our study (as NTG made up of 50% of total cases) and small sample size. Similarly, Gracner *et al.* did not find a significant correlation between baseline IOP and success.[29] The baseline IOP in their study was 22.5 mmHg, which was lower compared to other similar studies. Lower baseline IOP has been associated with reduced pressure-lowering effect.[30]

The side effects of SLT are minor. A transient IOP spike is common. A short increase of more than 5 mmHg above baseline IOP was recorded in 4.5-27.0% of patients.[31-32] Our study documented a 4.2 ± 3.4 mmHg increase one hour post-SLT, which dropped below baseline IOP at one week. More severe side effects like corneal or macular oedema, peripheral anterior synechiae, hyphaema, severe uveitis, or persistent IOP rise were very rare and they were not seen in our study.

The main limitation of this study is its small sample size. Secondly, the patient population in this study included only mild and moderate disease. Therefore, the results of this study cannot be extrapolated to patients with severe and advanced disease. We selected this group of patients because it guaranteed that there would be no changes in treatment throughout the six-month study period. This may not be feasible in patients with severe and advanced disease. Thirdly, 50% of the patients in our study belonged to the NTG group, which provided a lower baseline IOP compared to other studies that mainly consist of POAG and OHT patients. Thus, the findings of this study might not reflect the true results of the POAG and OHT groups.

In conclusion, this study showed that SLT can be used to treat mild to moderate POAG, NTG, and OHT patients, whether as first-line treatment or as an adjunct to medical therapy before more invasive surgeries are considered. The success rate at six months was 44%. The significant predictors of success were MD on HVF and IOP one week post-treatment. In the future, further research is needed to demonstrate the repeatability of the procedure to maintain IOP under control.

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Brief report

Neonatal retinoblastoma: a brief report from the Malaysian Retinoblastoma Registry

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Abstract

Neonatal retinoblastoma is more widely reported in developed countries than in developing countries. We have conducted a retrospective case series to understand the nature of neonatal retinoblastoma in Malaysia due to lack of data from developing countries.

A retrospective record review of 295 patients was conducted from the Retinoblastoma Registry on the National Eye Database (NED) between January 2005 and December 2019. Six out of 295 patients (2.03%) were identified as neonatal retinoblastoma in Malaysia from 2005 until 2019 compared to developed countries, in which the detection rate were 3.5 to 10 times higher.

Lack of awareness among survivor parents about the risk of their newborns developing retinoblastoma in may be a contributing factor. Neonatal retinoblastoma is difficult to manage, thus close and continuous monitoring is needed in centres dedicated to retinoblastoma management.

Keywords: developing countries, familial retinoblastoma, leukocoria, neonatal retinoblastoma

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Retinoblastoma neonatal: laporan ringkas dari pengkalan data Pendaftaran Pesakit Retinoblastoma di Malaysia

Abstrak

Retinoblastoma neonatal lebih banyak dilaporkan di negara maju berbanding di negara yang sedang membangun. Kami telah menjalankan kajian siri kes retrospektif untuk memahami retinoblastoma neonatal di Malaysia kerana kekurangan data dari negara-negara membangun.

Kajian rekod retrospektif terhadap 295 pesakit dilakukan dari pengkalan data National Eye Database (NED) pada pendaftaran pesakit Retinoblastoma di antara Januari 2005 dan Disember 2019. Enam daripada 295 pesakit (2.03%) dikenal pasti sebagai retinoblastoma neonatal di Malaysia dari tahun 2005 hingga 2019 berbanding negara maju, di mana kadar pengesanannya adalah 3.5 hingga 10 kali lebih tinggi.

Di antara faktor penyumbang adalah kurangnya kesedaran di kalangan ibu bapa kanser survivor mengenai risiko bayi baru lahir mereka menghidap retinoblastoma. Retinoblastoma neonatal sukar dikendalikan, oleh itu pemantauan rapi dan berterusan diperlukan di pusat-pusat yang dikhaskan untuk merawatretinoblastoma.

Kata kunci: leukocoria, negara membangun, retinoblastoma keluarga, retinoblastoma neonatal

Introduction

Retinoblastoma is the most common intraocular malignancy that affects children, but it is rarely detected in neonates.[1,2] Neonatal retinoblastoma is diagnosed in infants younger than 28 days of life or in case of preterm birth, less than 44 weeks of gestational age.[1] Although previous studies in developed countries have demonstrated that neonatal retinoblastoma is a subgroup that behaves differently from a clinical standpoint, data from developing nations are lacking.[3,4] Therefore, the aim of this retrospective case series was to report Malaysia's perspective of neonatal retinoblastoma.

Materials and methods

Medical Research and Ethics Committee (MREC) of Ministry of Health, Malaysia approval was obtained. A retrospective record review of 295 patients was conducted from the Retinoblastoma Registry on the National Eye Database (NED) between January 2005 and December 2019. Six patients were identified as having neonatal retinoblastoma. Data obtained from the registry and hospital medical records include age at presentation, gender, ethnic group, family history, laterality, stage of ocular disease at presentation, mode of treatment, tumour recurrence, globe salvage, and patient death.

Results

Six patients (12 eyes) were identified as having neonatal retinoblastoma, comprising 2.03% of all the retinoblastoma found in the registry (Table 1).

Patient demographics

Five patients were born at term and one patient was a preterm infant. The mean age at diagnosis was 26 days for the full-term babies (range: 21-28 days), while the diagnosis of the preterm infant was made at 34 weeks corrected gestational age. Four were males and two were females. There were two Malays, three Chinese, and one Indian. Out of the six patients, two were siblings who had a positive family history of retinoblastoma. Four patients presented with leukocoria, while one patient was screened for familial retinoblastoma at 28 days of life. The premature neonate was diagnosed to have retinoblastoma during routine retinopathy of prematurity screening.

Tumour characteristics and staging

The eyes were classified according to the International Intraocular Classification of Retinoblastoma (IIRC) into Group A (n = 2), Group B (n = 5), Group C (n = 0), Group D (n = 0), and Group E (n = 5). Of the six children, two presented initially with unilateral disease but subsequently progressed to bilateral involvement. The first patient had a Group E tumour in the first involved eye and later developed a Group B tumour in the other eye eight months later. The second patient was diagnosed to have a Group B tumour in one eye before later developing a Group A tumour in the fellow eye nine weeks later. Only one child had advanced disease (Group E) in both eyes. Three other children had advanced disease (Group E) in one eye and less advanced disease (Group B) in the fellow eye. Two other patients had less advanced disease in both eyes. Eight eyes had macular involvement, with four patients having macular involvement in one eye and two patients having macular involvement in both eyes.

Table 1. Results of case reports based on patient demographics, tumour characteristics, staging, and mode of treatment

Patient	Age at presentation (days)	Term / preterm	Gender	Ethnicity	Family history	Tumour laterality	IIRC	Recurrence	Treatment	Globe salvage	Follow-up period (months)
1	28	Term	Female	Chinese	No	Bilateral	RE Group E	No	CRED + E	No	24
							LE Group E	No	CRED + E	No	
2	34 weeks CGA	Preterm	Male	Chinese	No	Unilateral to bilateral	RE Group A	No	CRED + LP	Yes	15
							LE Group B	Yes	CRED + LP + IAC	Yes	
3	28	Term	Male	Malay	Yes	Bilateral	RE Group B	Yes	CRED + LP	Yes	13
							LE Group A	Yes	CRED + LP + IAC	Yes	
4	27	Term	Males	Chinese	No	Bilateral	RE Group B	No	CRED + LP	Yes	6
							LE Group E	No	CRED + E	No	
5	21	Term	Female	Malay	Yes	Unilateral to bilateral	RE Group B	No	CRED + E	No	56
							LE Group E	No	CRED + LP	Yes	
6	28	Term	Male	Indian	No	Bilateral	RE Group B	Yes	CRED + LIO + C + SC	Yes	164
							LE Group E	No	CRED + E	No	

C: cryotherapy; CGA: corrected gestational age; CRED: chemoreduction; E: enucleation; IAC: intra-arterial chemotherapy; IIRC: International Intraocular Retinoblastoma Classification; LE: left eye; LP: laser photocoagulation; RE: right eye; SC: sub-Tenon chemotherapy

Mode of treatment
All the patients received systemic chemotherapy and locally directed therapies, such as laser photocoagulation and cryotherapy, to help manage the smaller tumours. Two of the patients required multiple intra-arterial chemotherapy (IAC) for new tumours that developed after systemic chemotherapy. One patient had multiple local injections of chemotherapeutic agents via the sub-Tenon route as an adjuvant to systemic chemotherapy.

Tumour recurrence
Tumour recurrence was seen in three patients (four eyes) in the form of new tumours after completion of systemic chemotherapy. All the patients developed solid tumour recurrence within the chorioretinal scars of treated retinoblastoma tumours (Fig 1). The mean duration for recurrence was 2.6 months after completion of systemic chemotherapy (range: 2-4 months). Three eyes developed recurrence within the macula.

Outcome
Of the 12 eyes with retinoblastoma, 5 eyes were enucleated as the eyes were staged to have Group E tumours. One patient had both eyes enucleated after three cycles of chemotherapy due to the advanced stage of Group E retinoblastoma.

Three patients with Group E retinoblastoma in one eye underwent enucleation before systemic chemotherapy were initiated. Histopathology findings confirmed the diagnosis of retinoblastoma with the presence of rosettes with no histopathological risk factors for extraocular extension. In the patient who underwent bilateral enucleation after chemotherapy, the histopathology findings showed shrunken orbit with intraocular necrotic tissue occupying almost the entire posterior segment up to the anterior chamber.

Ocular salvage was achieved in 7 eyes (58.3%) over a mean follow-up period of 42.3 months (median: 15 months; range: 6-164 months). No patients died during follow-up. No secondary malignancies or metastatic disease was seen until the last follow-up.

Discussion

Prior reports in developed countries showed that 7-10% of retinoblastoma is diagnosed in the neonatal period.[1] Our series demonstrated that 2.03% of retinoblastoma is diagnosed in neonates. According to a recent series from LV Prasad Eye Institute in India, a national referral centre for retinoblastoma in India, their results were similar to ours: < 1% of neonatal retinoblastoma was detected from 2006 to 2017.[5] These data indicate that detection of neonatal retinoblastoma is 3.5 to 10 times more frequent in developed countries. The reason for this disparity is mul-

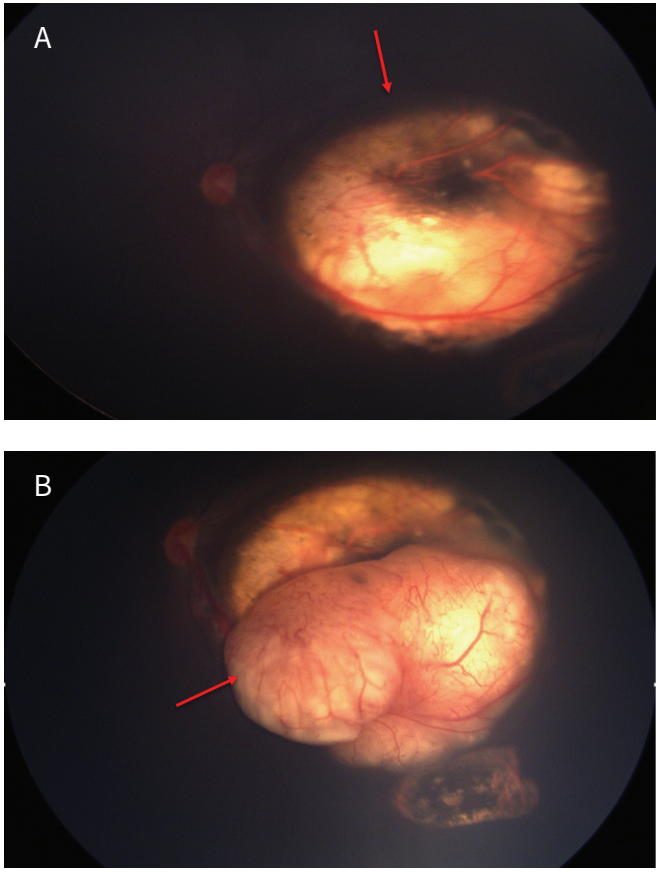

Fig. 1. (*A*) Left eye fundus photo taken with RetCam shows flat scar with calcification (red arrow) after completing systemic chemotherapy and laser photocoagulation treatment. (*B*) Left eye fundus shows recurrence within the chorioretinal scar (red arrow) of treated retinoblastoma tumour after ten weeks.

tifactorial, including delayed diagnosis of retinoblastoma in developing countries due to poor awareness by the public and healthcare services, especially the lack of awareness among survivor parents about hereditary malignancy.

As seen in our series, leukocoria exceeded positive family history as the most common reason for detection of neonatal retinoblastoma. On the other hand, a series performed in developed countries showed screening prompted by positive family history as the main factor for detection (44% to 71%).[1,3] This can be explained by the fact that there are many more cases of familial retinoblastoma in developed countries compared to developing countries, where medical resources are limited and survivors with familial retinoblastoma are more rarely seen.[2] Leukocoria is also

quite common as a presenting feature in neonatal retinoblastoma, especially in those with no positive family history, which is suggestive of sporadic occurrence of retinoblastoma.[1,3] Interestingly a premature baby was diagnosed to have neonatal retinoblastoma during routine retinopathy of prematurity screening. A recent meta-analysis performed to evaluate the impact of prematurity on retinoblastoma showed that data was insufficient to conclude whether premature birth has an impact on the development of retinoblastoma.[6] A common characteristic of neonatal retinoblastoma is that unilateral disease at the time of diagnosis is common, but it has a very high rate of becoming bilateral.[1,3,7] In a study of 46 children with neonatal retinoblastoma, 26 (57%) had unilateral involvement, of which 22 (85%) eventually developed bilateral disease.[3] Our results showed that two of the patients presented with unilateral disease at diagnosis, but eventually developed bilateral involvement less than a year later, while the remaining four patients presented with bilateral disease. This is essential for advising and guiding parents about the importance of regular fundus screening for early and accurate detection of tumours in the otherwise normal eye for timely treatment and better outcomes. Although only two of the patients had a history of familial retinoblastoma in the parent, germline mutation is suggestive for the rest, as they also had bilateral disease.

Multiple studies conducted in developed countries have established that screening for retinoblastoma in babies with positive family history of retinoblastoma usually has less advanced grouping of retinoblastoma with the presenting eye usually having a Group B tumour while the fellow eye will typically have a Group A tumour because of short screening intervals after diagnosis of the first eye.[1] This can be clearly seen in two of the patients in our series that were diagnosed to have neonatal retinoblastoma from fundus screening. Interestingly, the patients in our series that presented with leukocoria has more advanced disease. All but one patient presented with one eye having Group E tumours while one patient presented with both eyes having Group E tumours.

As patients with neonatal retinoblastoma present at such a young age, the chances of macular involvement are high.[1] This is because tumour location in relation to retinal topography varies with age of diagnosis. This relationship follows a central-to-peripheral distribution, with macular tumours presenting earliest and anterior tumours presenting last.[3] These findings are supported by our study. All the patients in our series presented with at least one eye with macular involvement under the assumption that patients with large tumours filling most of the globe (Group E) have macular involvement. Of the six patients in our series, two patients had bilateral macular involvement, and four patients had unilateral macular involvement with the contralateral eye having extramacular tumours.

In retinoblastoma, treatment is dependent on the laterality and symmetry of disease. In our series, all the patients required systemic three-agent chemotherapy consisting of carboplatin, vincristine, and etoposide, except for two relatively younger patients who were administered two-agent chemotherapy, consisting of

carboplatin and vincristine alone, due to the leukogenic concerns of etoposide.[4] Despite undergoing systemic chemotherapy and locally directed therapies when the need arose, 33.3% of eyes in our series developed recurrence after completion of systemic chemotherapy. In another study, tumour relapse was noted to be 44% of eyes.[5] The tendency for local relapse is a commonality of neonatal retinoblastoma, which quite often develops new tumours after or during systemic chemotherapy. The reasons speculated for the failure of systemic chemotherapy and locally directed therapies are the lack of vascular supply in smaller tumours and also the lack of pigments in the neonatal retina.[1] All these potential pitfalls make neonatal retinoblastoma a challenge to manage in spite of early diagnosis and earlier-than-average tumour stage.

Globe salvage rates in neonatal retinoblastoma vary from 72% to 92%.[1,3] In our series, we were able to salvage 58.3% (7 eyes). This is because five of the eyes presented at stage Group E, requiring enucleation. This shows that early age of diagnosis does not guarantee an early stage of intraocular disease. In our series, there was no evidence of secondary non-ocular malignancies, metastatic disease, or death.

Conclusion

The management of neonatal retinoblastoma is highly complex, requiring a multidisciplinary approach and specialized centres dedicated to retinoblastoma management. We need to increase parental awareness by effectively conveying genetic information for parents of children with neonatal retinoblastoma to take advantage of prenatal or postnatal genetic testing, when available, and proper postnatal screening of familial retinoblastoma.

Acknowledgements

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Case report/Case series

Devastating sight and life-threatening laser blepharoplasty complications

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Abstract

A 53-year-old woman was referred to our centre by a private aesthetic clinic. She presented with bilateral severe periorbital swelling and reduced visual acuity in her left eye for three days prior to presentation. She had undergone CO_2 laser blepharoplasty one week prior to assessment. Ophthalmic examination revealed periorbital swelling in both eyes with pouring pus discharge from the lower lid as well as underlying erythematous and ulcerative skin. There was limitation of extraocular muscle movement and conjunctival chemosis. Right-eye vision was 6/9, left-eye vision was counting fingers secondary to anterior segment inflammation. No sign of optic nerve involvement was noted. Computed tomography findings showed rim-enhancing preseptal collections with air pockets bilaterally involving the lower eyelids and measuring 2.6 x 4.3 x 2.7 cm on the left and 2.3 x 4.2 x 2.8 cm on the right with an extension of the collection into the lateral extra-conal region. She was treated as bilateral orbital cellulitis secondary to postsurgical infection. The patient underwent incision and drainage and started with systemic antibiotics promptly. She showed significant improvement after treatment. This is an unusual complication from cosmetic surgery in which delayed treatment can lead to sight- and life-threatening complications.

Keywords: bilateral orbital cellulitis, CO_2 laser blepharoplasty, eyelid, postsurgical infection

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Komplikasi teruk laser blefaroplasti yang mampu mengancam penglihatan dan nyawa

Abstrak

Seorang wanita berusia 53 tahun dirujuk ke pusat kami oleh klinik estetik swasta. Dia mengalami pembengkakan periorbital kedua-dua belah mata yang teruk dan pengurangan ketajaman penglihatan di mata kirinya selama tiga hari sebelum ini. Dia telah menjalani laser karbon dioksida blefaroplasti seminggu sebelum itu. Pemeriksaan oftalmik menunjukkan pembengkakan periorbital di kedua-dua mata dengan lelehan nanah dari kelopak mata bawah serta terdapat radang dan ulseratif pada kulit. Pergerakan otot ektraokular adalah terhad dan terdapat kemosis pada konjunktiva . Penglihatan mata kanan adalah 6/9, dan mata kiri cuma kiraan jari akibat keradangan segmen anterior. Tidak ada tanda-tanda penglibatan saraf optik. Imbasan CT menunjukkan terdapak koleksi pada preseptal rim dengan poket udara pada kedua mata melibatkan kelopak mata bawah, berukuran 2,6 x 4,3 x 2,7 cm di sebelah kiri dan 2,3 x 4,2 x 2,8 cm di sebelah kanan dengan koleksi merebak ke kawasan ekstrakonal. Dia dirawat sebagai selulitis orbital pada kedua mata akibat komplikasi jangkitan pasca pembedahan. Pesakit menjalani pembedahan segera dan menerima antibiotik sistemik. Dia menunjukkan tindakbalas yang baik selepas rawatan. Komplikasi sebegini jarang berlaku ekoran dari pembedahan kosmetik di mana jika tidak mendapat rawatan awal ia boleh menyebabkan komplikasi penglihatan dan mengancam nyawa.

Kata kunci: jangkitan pasca pembedahan, kelopak mata, laser blefaroplasti karbon dioksida, selulitis orbital

Introduction

Lower lid laser blepharoplasty is a surgical procedure performed with carbon dioxide laser (CO_2) in which excessive skin or fat tissue is removed. Postoperative infections after blepharoplasty are a rare complication. Approximately 0.2% of infections post blepharoplasty have been reported.[1,2] This is the first reported case of bilateral periorbital abscess secondary to laser blepharoplasty in Malaysia.

Materials and methods

Case report.

Case report

A 53-year-old Chinese woman with no underlying medical comorbidities was referred to us by a private aesthetic clinic with bilateral severe periorbital swelling and reduced visual acuity in her left eye for three days. She had undergone lower eyelid laser blepharoplasty with UltraPulse CO_2 laser (Coherent, Dieburg, Germany) at the referring clinic one week prior to presentation. Ophthalmic examination revealed periorbital swelling in both eyes with pouring pus discharge from the lower lid as well as underlying erythematous and ulcerative skin (Fig. 1). Extraocular muscle movement was limited due to generalized severe conjunctival chemosis. Visual acuity in the right eye was 6/9 and counting fingers in the left eye. Intraocular pressure for both eyes were normal. Anterior segment findings in the right eye were normal, but the left eye showed significant inflammation with cornea oedema. The relative afferent pupillary defect was negative and there was no sign of optic nerve compression.

A computed tomography (CT) scan of the orbit showed rim-enhancing preseptal collections with air pockets involving the lower eyelids with an extension of the collection into the lateral extra-conal region bilaterally (Fig. 2). The patient was treated as periorbital and preseptal abscess complicated with orbital cellulitis secondary to postsurgical infection.

The patient underwent incision and drainage of both lower lids abscesses and started systemically on intravenous ceftriaxone 1 gm daily. Topically she was given gutt ciprofloxacin QID in both eyes and hypertonic saline 3% every four hours in the

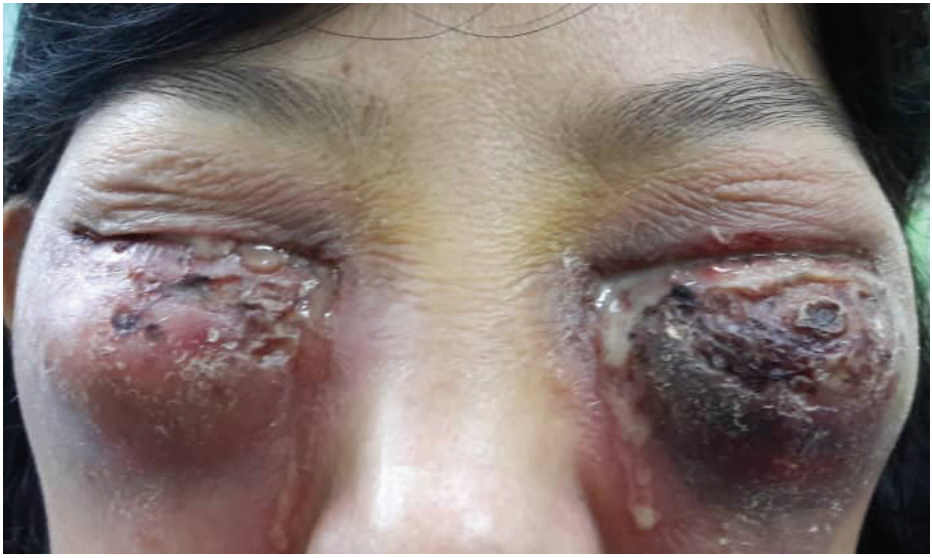

Fig 1. Periorbital lid swelling in both eyes with pus discharge.

left eye. Gutt Pred Forte (Allergan, Dublin, Ireland) was started for the left eye on the third day of admission. She showed significant improvement with treatment, with resolved minimal periorbital skin discolouration and final vision of 6/9 in both eyes (Fig. 3).

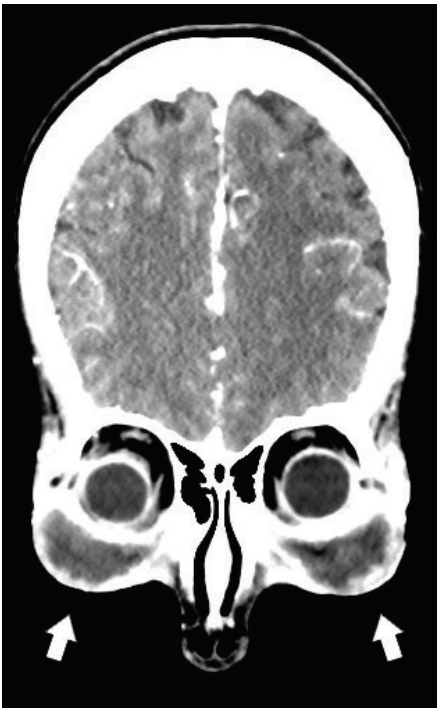

Fig 2. Arrows show bilateral periorbital pus collection in CT scan.

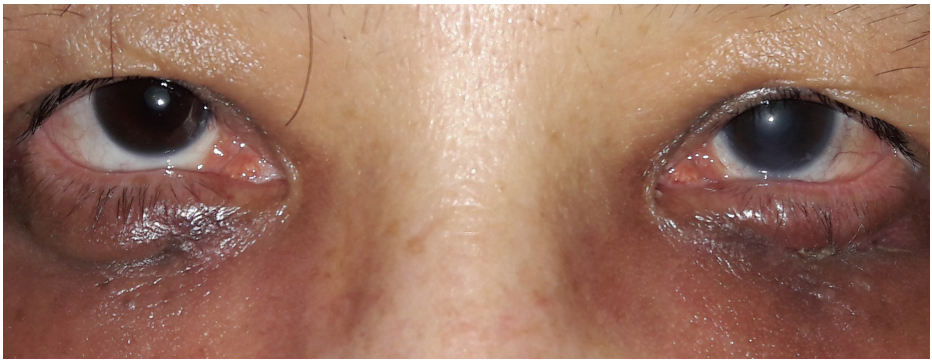

Fig 3. Hyperpigmented lesion with periorbital scarring post-treatment.

Discussion

Lower lid blepharoplasty is performed by excising skin and excessive subcutaneous fat in the lower eyelids in order to restore and improve anatomical appearance. The surgery can be performed by a transconjunctival or infracilliary approach.[3] There are two widely applied methods for performing this procedure: the traditional method, which uses blades to perform the incision and excision, and the new advanced method, which uses the CO_2 laser technique.

Postoperative infection in blepharoplasty is a rare occurrence. Based on a study performed at the Phillips Eye Institute in Minneapolis (MN, USA), of a total of 2,227 patients who underwent blepharoplasty from January 1999 to December 2004, there was only one case (0.04%) of postoperative infection reported.[2]

Preseptal cellulitis is an infection that involves the periorbital fat tissues which are localized anterior to the orbital septum.[4] Delayed treatment may lead to a periorbital abscess, the spreading of which may in turn lead to involvement of the orbit, brain, and even organs at a systemic level.[4]

Factors that contribute to postoperative infection or surgical site infection include the patient's background health status, method and type of surgery performed, and clinical interventions provided to patients throughout medical care.[5]

In our case report, the patient underwent laser blepharoplasty in an aesthetic private clinic and the procedure was conducted by a general practitioner. The procedure was performed as an office-based surgery. She was not prescribed antibiotics postoperatively as a prophylaxis measure. In a study carried out in North Texas Ophthalmic Plastic Surgery Hospital (Fort Worth, TX, USA), only 0.26% of post-blepharoplasty patients who were prescribed with Bacitracin ointment recorded infections, while 6.3% patients that were not prescribed antibiotics developed infections.[6] These results support the idea of using antibiotics to prevent postoperative infections.

In Malaysia, this procedure is being performed widely by general doctors in aesthetic clinics with no background ophthalmological knowledge or experience. The current situation has caused a surge of patients being referred to ophthalmology centres once complications occurred. This practice has to be re-evaluated and strict rules need to be implemented to assure that effective interventions are in place for all patients that are planned for lid blepharoplasty. Proper surveillance may help reduce complications from this procedure.

Conclusion

Periorbital abscess and orbital cellulitis are rare complications of simple cosmetic laser blepharoplasty surgery, but delayed treatment can lead to sight- and life-threatening complications.

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The authors wish to thank the Ophthalmology Department, University Malaya Medical Centre (Kuala Lumpur, Malaysia).

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Case report/Case series

Charlie ant insect bite-associated preseptal cellulitis

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Abstract

Preseptal cellulitis is a worrying condition in children. One of the commonest causes is from insect bite. The Charlie ant or *Paederus fuscipes* has been reported as a dermatitis-causing agent due to its toxin, pederin. The aim is to report a case of preseptal cellulitis secondary to Charlie ant insect bite. A two-year-old girl presented with bilateral eyelid swelling, redness, and pain for two days. The Charlie ant was at the nasal bridge before the presentation. There was presence of generalised bilateral eyelid swelling, redness with multiple pustules, excoriated skin, and eye discharge. She was admitted and started on antibiotics. The pustules ruptured, left the skin exposed, and her condition improved. Preseptal cellulitis is a contiguous spread of infection. An attack by Charlie ant has become a public health concern. There is no specific treatment for this condition. Early detection may prevent complications.

Keywords: Charlie ant, eyelid swelling, insect bite, *Paederus fuscipes*, preseptal cellulitis

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Selulitis preseptal akibat gigitan serangga semut Charlie

Abstrak

Selulitis preseptal adalah keadaan yang membimbangkan pada kanak-kanak. Salah satu penyebab yang paling biasa adalah dari gigitan serangga. Semut Charlie atau *Paederus fuscipes* telah dilaporkan sebagai agen penyebab dermatitis melalui kesan toksinnya, pederin. Tujuan laporan kes ini adalah untuk melaporkan kes selulitis preseptal akibat gigitan semut Charlie. Seorang gadis berusia dua tahun mengalami pembengkakan kelopak mata, kemerahan, dan kesakitan pada kedua-dua mata selama dua hari. Semut Charlie dilihat berada di atas batang hidung sebelum dia mengalami gejalapembengkakan kelopak mata pada kedua-dua belah, kemerahan dengan banyak pustula, kulit yang menggelupas, dan lelehan cecair dari mata. Dia dimasukkan ke wad dan dirawat dengan antibiotik. Rawatan yang diberikan menyebabkan pustula pecah danmeninggalkan kulit terdedah seterusnya keadaan bertambah baik. Selulitis preseptal boleh berlaku akibat penyebaran jangkitan berdekatan. Serangan oleh semut Charlie telah menjadi perhatian kesihatan awam. Tidak ada rawatan khusus untuk keadaan ini. Pengesanan awal dapat mengelakkan komplikasi.

Kata kunci: bengkak kelopak mata, gigitan serangga, Paederus fuscipes, selulitis preseptal, semut Charlie

Introduction

Preseptal cellulitis is an infection of the soft tissue of eyelids and periocular region anterior to the orbital *septum*. It is a worrying condition in infants and children younger than five years due to association with bacteraemia, septicaemia, and meningitis.1 Several studies reported a mortality rate ranging from 5% to 25% of periorbital or orbital cellulitis with intracranial complication.[2] *Staphylococcus aureus* is the most common bacterial pathogen in this situation.[1] The pathogenesis can occur by three possible mechanisms: spread of infection from the upper respiratory tract, direct inoculation from trauma or insect bite, and spread of infection from the skin and adjacent structures.[3]

The Charlie ant, also known as rove beetle, is one of the most feared insects in Malaysia. It has been reported as a dermatitis-causing agent for the outbreak cases in Terengganu, Kelantan, and Penang.[4] Since the 1990s, the Charlie ant has become a public health concern due to many outbreaks reported worldwide.[4] This insect belongs to the family of Staphylinidae and its species is recognised

as *Paederus fuscipes*.[4] It features a dark orange body with black head and abdominal end (Fig. 1). When the insect is in contact with human skin, it releases a coelomic fluid that contains a toxin called pederin.[4] It has been reported that the production of pederin depends on the activities of a pathogenic bacteria from the *Pseudomonas* sp. within the insect's body.[4] The effects of this toxin on human skin cause peculiar dermatitis, also known as linear dermatitis, characterised by erythematous and bullous lesions.[5]

Fig. 1. Paederus fuscipes, commonly known as Charlie ant.

Case report

A two-year-old Malay girl with no known comorbidities presented to the emergency department of Hospital Universiti Sains Malaysia with bilateral eyelid swelling, redness, and pain for two days. Before this presentation, the patient's mother noted an insect called Charlie ant crawling on the patient's nasal bridge. There was no fever and no upper respiratory symptoms. However, her symptoms worsened, which led the patient to seek medical attention. She had no history of drug or food allergies.

On examination, visual acuity assessment was unreliable as the patient was uncooperative. However, she was able to fixate and follow near objects. On inspection, there was presence of generalised bilateral eyelid swelling, redness with multiple pustules, excoriated skin, and eye discharge (Fig. 2), which appeared worse on the left eyelid. There was no relative afferent pupillary defect, proptosis, or chemosis. Her bilateral extraocular movement was normal. The anterior and posterior segments revealed normal findings with normal intraocular pressure.

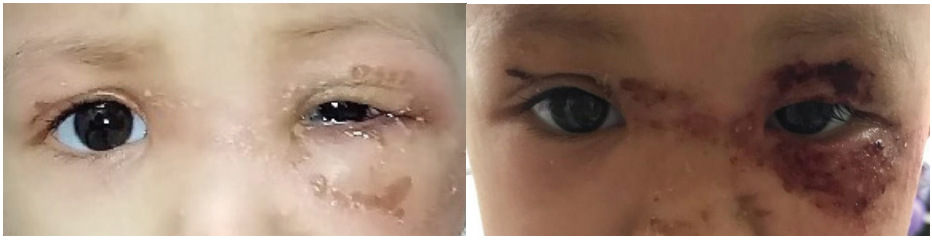

Fig. 2. (*Left*) Swelling, redness, and multiple pustules in both eyes. (*Right*) Swelling, redness, and multiple pustules in both eyes with more slough and excoriated skin with eye discharge noted on the second day of admission.

Full blood count showed raised total white blood cell count. The left eyelid was swabbed for culture and sensitivity but obtained no growth. She was admitted and treated with intravenous augmentin and topical moxifloxacin for one week. During her admission, the pustules ruptured and she underwent daily normal saline dressing over her periorbital wound. Excoriated skin and slough were removed, leaving the periorbital skin exposed (Fig. 3). Chloramphenicol ointment was applied daily. The exposed area dried and healed quickly (Fig. 4). The patient was discharged and seen at the ophthalmology clinic two weeks later, at which point the condition had improved considerably (Fig. 5).

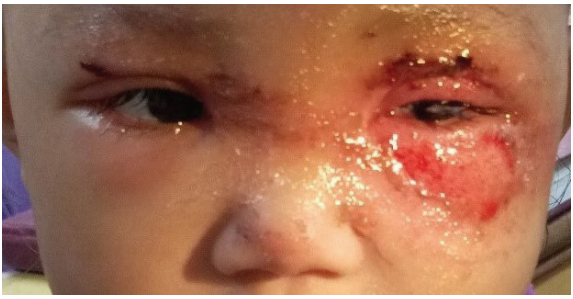

Fig. 3. After daily dressing with removal of slough and excoriated skin. Chloramphenicol ointment was applied.

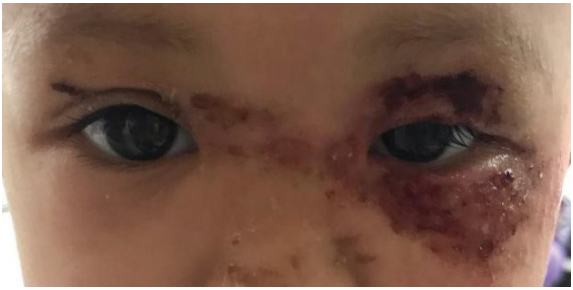

Fig. 4. The exposed skin dried and healing quickly.

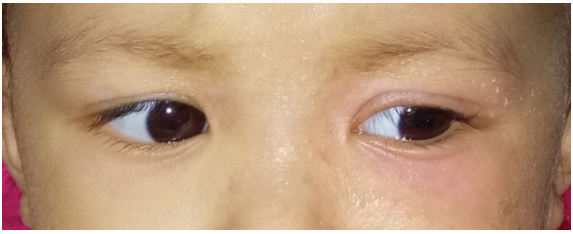

Fig. 5. Two weeks after being discharged from the ward, the wound was healing well with no apparent scar.

Discussion

In this case report, the patient developed preseptal cellulitis secondary to a Charlie ant insect bite. Preseptal cellulitis is a contiguous spread of infection commonly caused by an insect bite. Ordinarily, skin reactions secondary to Charlie ant bite do not require admission. However, patients in this age group with signs of eyelid infection should be admitted for close observation.

History-taking and clinical examination played an important role in this patient. In the age group under six years of age, orbital cellulitis needs to be ruled out given that the orbital septum is not fully developed and consequently, the infection may spread posteriorly, causing severe complications. Investigations act as a guide for treatment. The raised total white blood cell count indicates an infection and the eye swab for culture and sensitivity was done to identify the responsible pathogen. Computed tomography is done only when complications are suspected or on difficult examination.[3] This may help clinicians treat accordingly.

Usually, the effect of the Charlie ant causes the infected skin areas to be erythematous, itchy, and edematous after 24 to 48 hours from first contact.[4] Several days later, the infected area may have visible scars which take a few weeks or months to disappear.[4] Secondary infections often occur upon scratching, leading to extensive exfoliation and ulcerating dermatitis, which requires hospitalisation.[4] The treatment is usually empirical. A patient who presents with preseptal cellulitis is treated with broad-spectrum topical and intravenous antibiotics. The complications that arise due to preseptal cellulitis may occur as the infection spreads posteriorly. The Charlie ant insect bite may also cause other ocular manifestations, such as conjunctivitis and keratoconjunctivitis.[6]

Several steps were taken by the district health office, such as fogging, termite medicine, and some environmental adjustments, to reduce the infestation of Charlie ants. However, this issue is something that needs to be further studied to determine definitive prevention methods to control outbreaks.

Conclusion

Preseptal cellulitis is a contiguous spread of infection commonly caused by an insect bite. Charlie ant bites have become a public health concern as they have been reported in many Malaysian states, especially in Kelantan. Unfortunately, there is no specific treatment for this condition. Early detection and close observation may prevent unexpected complications.

Declaration of patient consent

The authors certify they have obtained consent from the patient's parents for the child's images and other clinical information to be reported in this journal.

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Case report/Case series

Discharging sinus from the eyelid following accidental impaction of wood fragment

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Abstract

Injury to the eyelid is one of the most common emergencies at eye hospitals. Injuries to the eye and its surrounding tissues may result from several types of foreign bodies. The injured eye must be carefully and gently examined to prevent missed injuries and to avoid putting pressure on the globe, which might cause prolapse of intraocular contents.

We report an unsightly upper eyelid discharging sinus with wood fragment impaction that was incompletely removed by the first attending physician for a period of eleven months. The wood fragments were carefully and completely removed under local anaesthesia, and debridement and dressing of the wound were done by an ophthalmic plastic surgeon when the patient was eventually referred to the tertiary institution. The need to include basic eye care courses in continued medical education for all general practitioners is advocated to reduce resultant ocular morbidity from such ocular injuries. This will aid this group of physicians in decision-making while providing care to patients with eye injuries.

Keywords: discharging sinus, eyelid, impaction, injury

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Sinus bernanah dari kelopak mata akibat serpihan kayu terbenam berikutan kemalangan yang tidak disengajakan

Abstrak

Kecederaan pada kelopak mata adalah salah satu kes kecemasan sering dirawat di hospital mata. Kecederaan pada mata dan tisu di sekitarnya mungkin disebabkan oleh beberapa jenis badan asing. Mata yang cedera mesti diperiksa dengan cermat dan berhati-hati untuk mengelakkan kecederaan yang terlepas dari pengesanan dan mengelakkan dari memberi tekanan pada bola mata, yang mungkin menyebabkan berlakunya prolaps kandungan intraokular.

Kami melaporkan kes kecederaan pada kelopak mata atas yang membentuk sinus akibat serpihan kayu yang tidak dikeluarkan sepenuhnya oleh doktor yang merawat buat pertama kali setelah sebelas bulan berlalu. Pesakit dirujuk ke hospital tertiari dimana serpihan kayu dikeluarkan dengan hati-hati dan sepenuhnya di bawah bius setempat, dan dibersihkan sepenuhnya serta dibalut oleh pakar bedah plastik oftalmik. Adalah penting untuk kursus penjagaan mata asas menjadi sebahagian dari pendidikan perubatan yang berterusan untuk semua pengamal perubatan am bagi mengurangkan morbiditi okular akibat kecederaan mata seperti ini. Ini akan membantu pengamal perubatan am dalam membuat keputusan dalam merawat pesakit yang mengalami kecederaan mata dengan lebih baik.

Kata kunci: kecederaan, kelopak mata, pengecutan, sinus bernanah

Introduction

The eye is the third most common organ affected by injuries after the hands and feet.[1] However, injury to the eyelid is one of the most common emergencies at eye hospitals.[2] Injuries to the eye and its surrounding tissues may result from several types of foreign bodies, which will determine the clinical presentation of the patient.[3] The need to carefully examine the injured eye is germane since some penetrating eye injuries can easily be missed; some injuries may be self-sealing and signs of abnormality are subtle.[2] A visual acuity of 6/6 in a penetrating eye injury does not necessarily exclude serious problems apart from the resultant ocular deformity. Therefore, specific signs must be closely investigated, otherwise they may be easily missed.[2] The deformity can have a negative psychosocial impact as well as lowered self-worth and health-related quality of life for the injured patient.[4]

Inability to recognize the complete removal of organic foreign body from the eyelid by the managing non-ophthalmic doctor and failure to appropriately refer to a specialist can result in secondary infection with aesthetically unacceptable complications.

We report a cosmetically unsightly upper eyelid discharging sinus due to incomplete removal of impacted wood fragment by the non-specialist physician that provided care for the injured patient, who presented to our hospital eleven months after the event.

Case report

A 45-year-old male passenger on motorcycle accidentally hit his right eye on a plank and some fragments of wood got impacted on the eyelid eleven months before presenting to our facility. There was bleeding from the site of injury and he developed pain in the eye but there was no loss of consciousness. He was taken to a general hospital, where some wood fragments were removed. The non-specialist physician who provided emergency care to the patient thought the impacted wood fragments had been completely removed. He subsequently dressed the wound and prescribed systemic antibiotics and oral analgesic. He was placed on daily dressing in the general hospital facility.

Eleven months after the accident, the patient noticed copious discharge and a protruding foreign body from the wound site, which had not healed. This prompted the patient to visit a private eye clinic, where antifungal and antibiotic eye medications were prescribed. He was then referred to our tertiary facility. He was not a known diabetic and had no history suggestive of diabetes mellitus. On examination, a very apprehensive patient was seen with stable vital signs. Ocular examination revealed

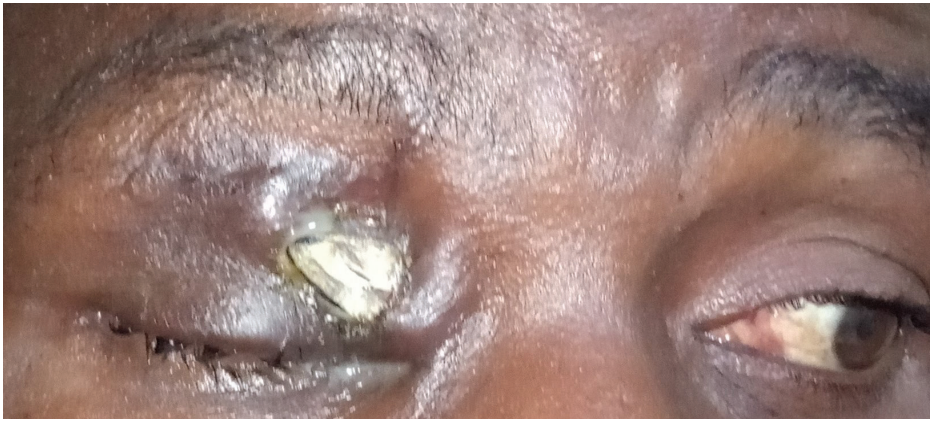

Fig. 1. The patient with foreign body impaction of the upper eyelid.

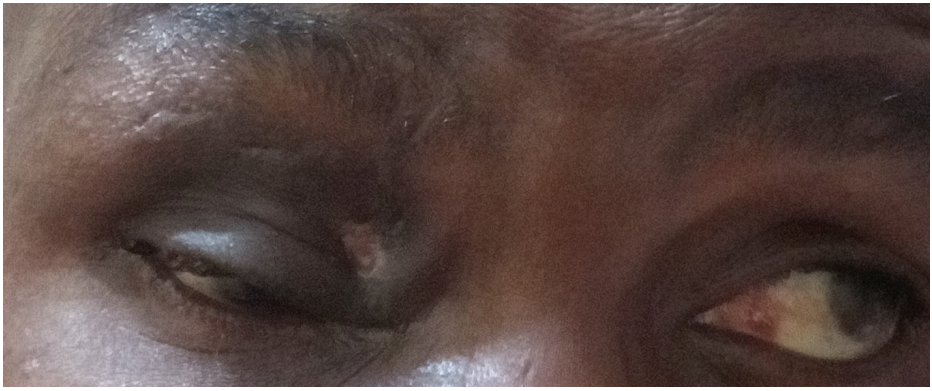

Fig. 2. Postoperative state with healed scar and upper eyelid *ptosis*.

a visual acuity of 6/36 in the right eye and 6/5 in the left eye. There was complete mechanical *ptosis* in the right eye and fumigating, foul-smelling, copious discharge on the right upper eyelid (Fig. 1). A discharging sinus involving the medial third of the right upper eyelid with a protruding whitish foreign body on the eyelid was observed. There were no other ocular findings in both the anterior and posterior segments. The working diagnosis of right upper eyelid discharging sinus with impacted wood fragment secondary to road traffic accident was made. The patient was taken to the procedure room, where the eye was cleaned with 10% povidone iodine and draped, topical tetracaine applied, and 2% xylocaine with adrenaline was infiltrated around the wound site. The fragments of the wound were carefully removed using micro-artery forceps. Haemostasis was secured. Debridement was performed, the wound was dressed, and the patient was prescribed oral cefuroxime 500 mg bd, metronidazole 500 mg tds, analgesic, and topical antibiotics. The removed fragments were sent for microscopic culture and sensitivity. Daily dressing was done for one week and the wound healed with scarring and residual *ptosis* (Fig. 2).

Discussion

Management of eye injuries has been documented to pose difficult dilemmas.[5] However, the standard practice is to undertake primary surgical repair to restore structural integrity of the globe and the *adnexa* after a careful examination of the eye.[5] This will reduce the possibility of any resultant ocular deformity that can cause negative psychosocial effects on the patient. It has been reported that when there is penetrating eyelid injury, objects may easily penetrate the orbit and even the cranial cavity through the orbit.[2] Therefore, examination should be very gentle to avoid putting pressure on the globe, which might cause prolapse of intraocular contents.[2]

The case that presented in this tertiary facility was a young man in an economically productive age group, the breadwinner of the family who was doing legitimate daily activities, and who was at risk of eye trauma.[6] Unfortunately, the patient was not seen by an ophthalmic specialist because there were none in the health facility. Moreover, he was not referred timely and appropriately. This caused the patient to experience undue pain and unnecessary loss of time and revenue, which could have been reduced by appropriate referral. This emphasizes the need for a good referral network between the primary eye care level and tertiary eye care level — where these ophthalmic specialists are available —to be established in Nigeria. Moreover, continued medical education for all general practitioners should include basic eye care courses to aid them in decision-making while providing care to patients such as the one this case. Although delayed presentation is common in many eye injuries,[7] this patient presented within 24 hours of injury. Unfortunately, his emergency was not managed adequately by the attending physician due to the lack of prerequisite knowledge of management of ocular injuries, which resulted in avoidable ocular morbidity in this patient.

Conclusion

A cosmetically unsightly discharging sinus arising from accidental, prolonged impacted wood fragment in the upper eyelid was properly managed. The need to include basic eye care courses in continued medical education for all general practitioners is advocated. This will aid this group of physicians in decision-making while providing care to patients with eye injuries.

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Case report/Case series

Leptospira, the ocular predator

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Abstract

Neuroretinitis is an inflammatory optic neuropathy with a classic funduscopic appearance of optic disc swelling and hard exudates on the macula in a star formation. It can be a manifestation of systemic, infectious or autoimmune disease. Here, we report three patients who presented with sudden onset of painless blurring of vision. Ophthalmic evaluation revealed a characteristic picture of neuroretinitis. Detailed study of the cases revealed leptospirosis being the aetiology of the neuroretinitis. Leptospirosis is a zoonotic infection caused by spirochetes *Leptospira*, which presents with both ocular and systemic manifestations. Neuroretinitis has been reported in the few cases of leptospirosis. We present three cases of leptospirosis with bilateral and unilateral neuroretinitis presenting with sudden loss of vision, optic disc oedema, and macular star. Leptospirosis was confirmed by serological test and the disease responded optimally to specific therapy. Although funduscopic examination showed marked inflammatory changes in the retina and optic nerve head, the recovery following medical treatment was remarkable.

Keywords: leptospirosis, macular star, neuroretinitis

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Leptospira, pemangsa okular

Abstrak

Neuroretinitis adalah neuropati optik radang dengan penampilan klasikal menunjukkan pembengkakan cakera optik dan eksudat keras pada makula dalam pembentukan umpama bintang pada fundus. Ia boleh menjadi sebahagian dari manifestasi penyakit sistemik, jangkitan kuman atau penyakit autoimun. Kami melaporkan tiga pesakit yang mengalami penglihatan kabur secara tiba-tiba tanpa rasa sakit . Penilaian oftalmik menunjukkan gambaran ciri neuroretinitis. Penyiasatan yang terperinci seterusnya menunjukkan leptospirosis menjadi etiologi bagi neuroretinitis dalam kesemua kes. Leptospirosis adalah jangkitan zoonosis yang disebabkan oleh spirochetes Leptospira, yang muncul dengan manifestasi okular dan sistemik. Neuroretinitis telah dilaporkan dalam beberapa kes leptospirosis. Kami mengemukakan tiga kes leptospirosis dengan neuroretinitis pada kedua belah mata dan satu kes yang mengalami kehilangan penglihatan secara tiba-tiba, edema cakera optik, dan pembentukan seperti bintang pada makula. Leptospirosis disahkan oleh ujian serologi dan penyakit ini bertindak balas secara optimum terhadap terapi spesifik yang diberikan. Walaupun pemeriksaan funduscopic menunjukkan perubahan keradangan pada retina dan kepala saraf optik, pemulihan setelah rawatan perubatan berlaku dengan baik sekali.

Kata kunci: bintang makula, leptospirosis, neuroretinitis

Introduction

Leptospirosis is a zoonotic infection caused by spirochetes of genus *Leptospira*.[1] The disease has high incidence and prevalence in both developed and developing countries. Systemic features are common in the acute bacteraemic phase of the disease, whereas ocular features are common in the immunological phase.[2] Thus, systemic features usually precede the ophthalmic complaints. There are only a few reported articles in the literature on *Leptospira* neuroretinitis. Here, we present three rare cases of neuroretinitis caused by leptospirosis.

Materials and methods

Case series.

Case presentation

Case 1

A 13-year-old male with a ten-day history of painless blurring of vision in the right eye and mild fever was diagnosed with neuroretinitis. He had a history of swimming in a waterfall one month back. Ocular examination showed the best-corrected visual acuity (BCVA) was 6/60 in both eyes. Anterior segment examination was normal and bilateral fundoscopy revealed oedematous optic disc with macular star (Fig. 1). Optical coherence tomography (OCT) of the macula showed bilateral

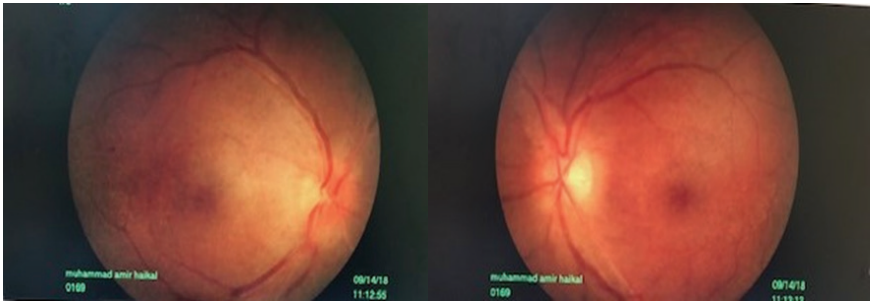

Fig. 1. Fundus examination showed bilateral swollen optic discs.

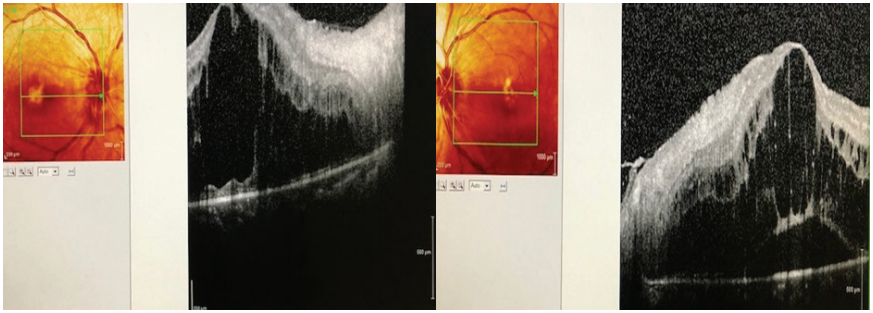

Fig. 2. Macular OCT showing bilateral macular oedema.

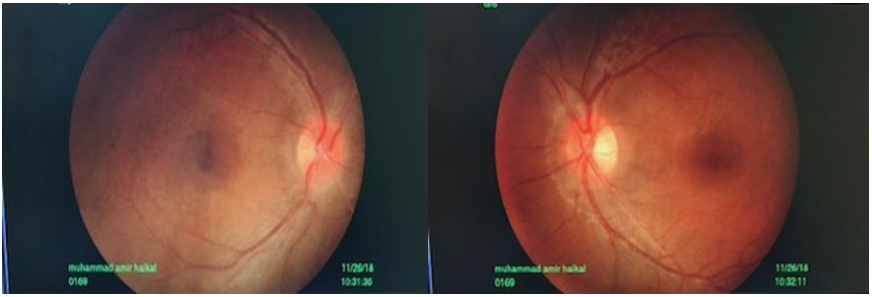

Fig. 3. Fundoscopy at 12 weeks of follow-up showing persistent bilateral disc oedema.

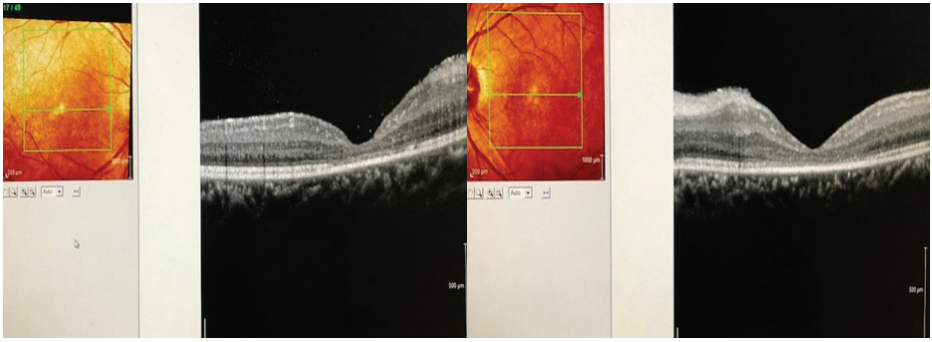

Fig. 4. Macular OCT at 12 weeks of follow-up showing resolution of macular oedema.

macular oedema (Fig. 2). Haematological investigations revealed mild leucocytosis. Microscopic agglutination test (MAT) for *Leptospira* serology was positive. He was treated with oral doxycycline 100 mg twice a day for six weeks. After four weeks of follow-up, BCVA improved to 6/24 and 6/36 on the right and left eye, respectively. Bilateral fundoscopy revealed mild resolution of disc oedema and macular oedema. On follow-up after 12 weeks, bilateral BCVA improved to 6/18. There was almost total resolution of macular oedema (Fig. 3). However, the disc oedema persisted in both eyes (Fig. 4).

Case 2

This case involved a 20-year-old male who presented with bilateral painless blurring of vision and redness for three days with a history of jungle trekking two weeks prior to presentation. On examination, BCVA of hand movement (HM) in the left eye and 6/18 in the right eye were noted with impaired colour vision. There was presence of keratic precipitates with cells of 3+ in both anterior chambers. Bilateral fundus examination revealed swollen, hyperaemic optic discs and star-shaped hard exudates on the macula (Fig. 5). Bilateral macular OCT showed subretinal and intraretinal fluid (Fig. 6). The clinical findings of anterior segment inflammation and optic disc oedema coupled with macular star were consistent with a diagnosis of panuveitis with neuroretinitis. Blood investigation revealed mild leucocytosis with neutrophilia, high erythrocyte sedimentation rate (ESR), and a positive *Leptospira* serology. The patient received oral doxycycline 100 mg twice a day for six weeks, intravenous ceftazidime 1 g twice a day for two weeks, and oral prednisolone 30 mg (0.5 mg/kg/day) once daily, which was tapered to 5 mg weekly. Guttae dexamethasone 0.1% and guttae atropine 1% were started for both eyes. The anterior segment inflammatory signs resolved within a few days and vision improved to 6/9 in both eyes after a period of two weeks. On the sixth week of follow-up, bilateral BCVA was 6/6 with almost complete resolution of macular oedema (Fig. 7). However, the disc oedema still persisted in both eyes (Fig. 8).

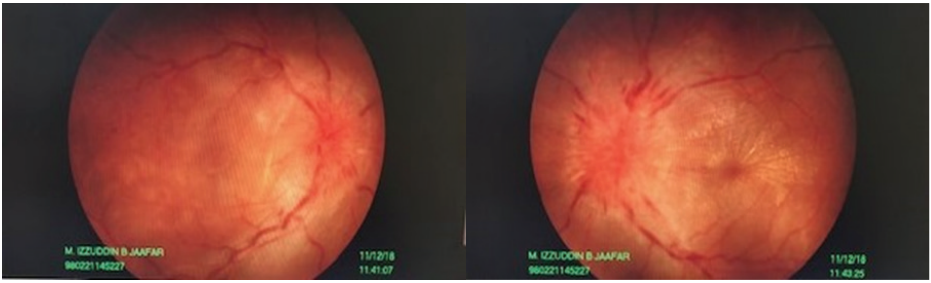

Fig. 5. Fundus photograph showing bilateral optic disc oedema with macular star.

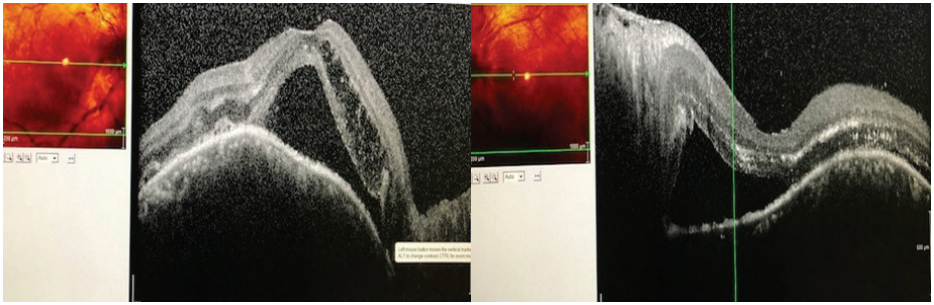

Fig. 6. Macular OCT showing macular oedema with subretinal fluid of both eyes.

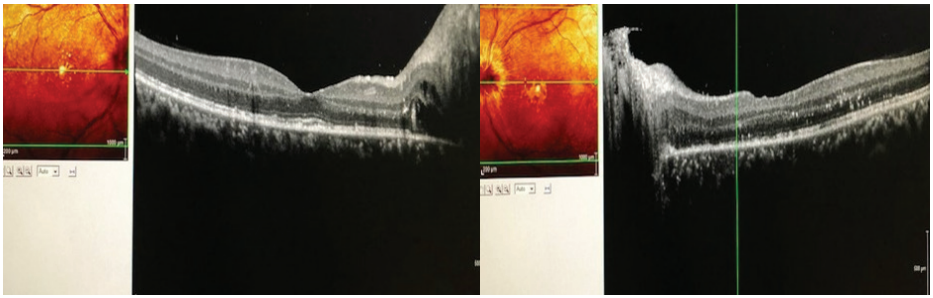

Fig. 7. Macular OCT at six weeks showing resolution of macular oedema.

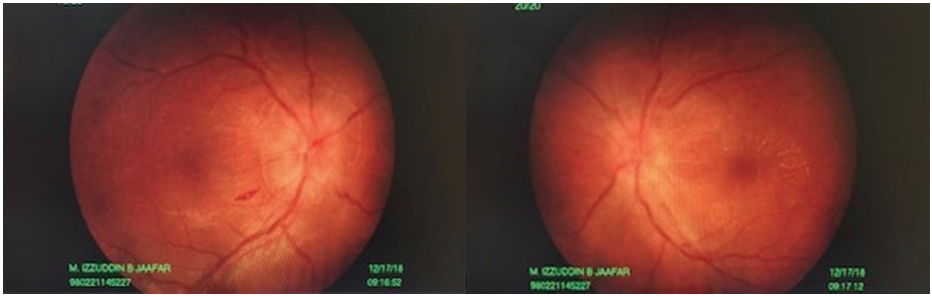

Fig. 8. Bilateral fundoscopy showing persistent optic disc swelling.

Case 3

A 46-year-old female presented with a progressive decrease in vision in the left eye for three weeks. On examination, BCVA was 6/6 in the right eye and 1/60 in the left eye. The left optic disc was hyperaemic, with blurred margins and presence of a macular oedema (Figs. 9 and 10). The patient developed stellate maculopathy two weeks later. Colour vision was severely impaired in the left eye. Visual fields of this patient revealed a centrocaecal scotoma in the left eye. The other eye was unre-

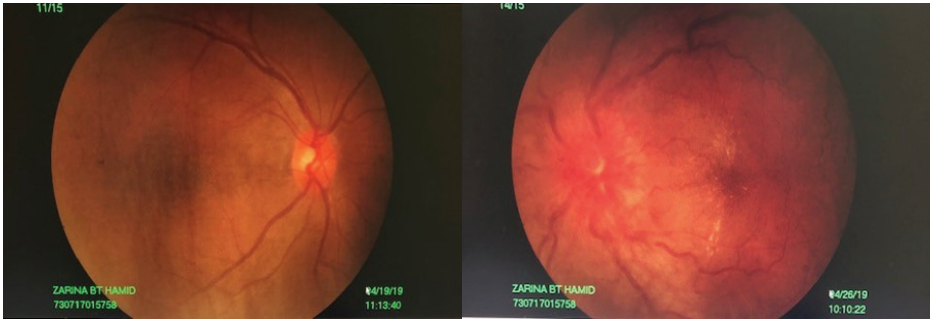

Fig. 9. Fundus photograph showing left optic disc oedema with macular star.

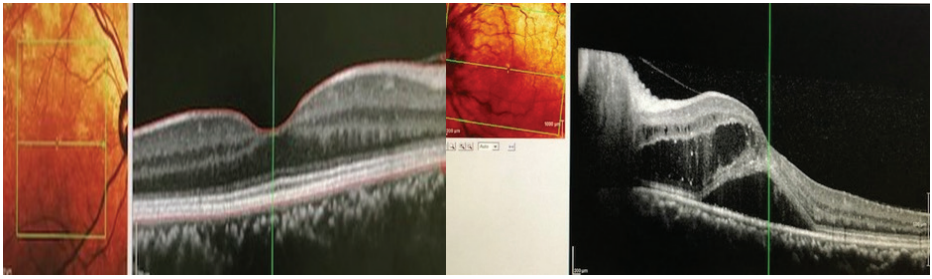

Fig. 10. Macular OCT of the left eye showing macular oedema with subretinal fluid.

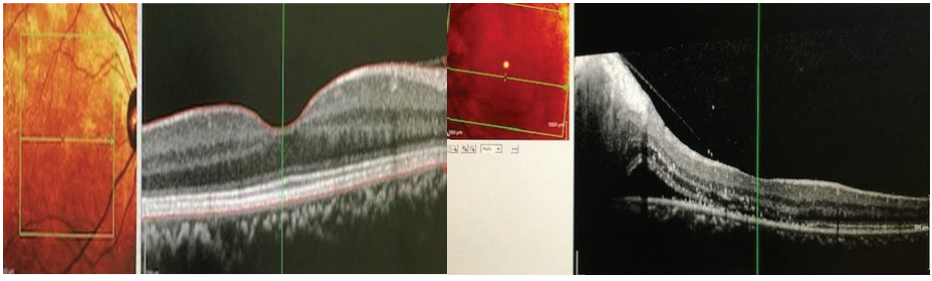

Fig. 11. Macular OCT macula at six weeks showing resolution of macular oedema in the left eye.

markable in all aspects. Computed tomography of the brain and orbit was within normal limits. MAT for *Leptospira* serology was positive. Neuroretinitis secondary to leptospirosis was diagnosed. The patient was started on oral doxycycline 100 mg twice a day for six weeks, along with tapering oral prednisolone. Six weeks after onset, the optic nerve swelling persisted, but the macular oedema had resolved (Fig. 11). The left-eye vision returned to 6/9.

Discussion

Neuroretinitis is a type of optic neuropathy characterised by an acute visual loss in the setting of optic disc swelling accompanied by star-shaped hard exudates around the fovea. The pathogenesis of neuroretinitis is associated with the direct involvement of the optic nerve fibres by the infectious process or the inflammation, leading to oedema and fluid exudation from the inflamed cellular area of the peripapillary retina.

Infections like syphilis, tuberculosis, cat-scratch disease, Lyme disease, hepatitis B, mumps, measles, toxoplasmosis, leptospirosis, and cysticercosis may cause neuroretinitis.[3] Leptospirosis presents with both systemic and ocular manifestations. Neuroretinitis is an uncommon manifestation of the disease. Dreyer *et al.* first reported a case of neuroretinitis in leptospirosis.[4] Later, Ray *et al.*[3] and Rathinam *et al.*[2] described similar cases.

The pathogenesis of leptospirosis is not well understood and is classified into two distinct phases: the direct effect of the organism during the bacteraemic phase and the host's response to an infection in the immunological phase. After entering the body, the organism invades the blood stream, resulting in a bacteraemia, disseminating into various organs such as the kidney, liver, lungs, heart, and central nervous system.[2]

The onset of systemic leptospirosis is characteristically abrupt, with severe headache, myalgia, chills, and rapidly rising temperature. Abdominal pain, retrobulbar pain, skin rash, and arthralgia are also seen. Ocular involvement in leptospirosis may occur during both the systemic bacteraemic and immunological phases. Ocular manifestations in an acute phase include conjunctival congestion without discharge, chemosis, or subconjunctival haemorrhage.[5] Uveitis is an important complication of the late immunological phase, and hypopyon may occur when inflammation is severe. Other ocular immunological manifestations include interstitial keratitis, hyperaemic disc, membranous vitreous opacities, perivasculitis without vascular occlusion, retinal haemorrhage, and neuroretinitis.[5] OCT has documented the evolving phases in neuroretinitis beginning with disc swelling, macular thickening, and subretinal fluid collection. This is followed 1-2 weeks later by spontaneous decrease in macular thickening and resorption of subretinal fluid.

MAT is currently considered the gold-standard test. Laboratory testing should be tailored for every individual depending on the history and physical examination findings. Minimum laboratory work-up should include tests for tuberculosis, syphilis, and *Bartonella* species. Other tests that may be requested include serologies against viruses, bacteria, or protozoa (such as human immunodeficiency virus [HIV], toxoplasmosis, and Lyme disease), ESR, urinalysis, autoimmune panel, and blood cultures. In selected cases, neuroimaging and lumbar tap with cerebrospinal fluid analysis may be warranted.

Treatment of neuroretinitis is directed to the specific underlying cause. Appropriate antibiotic therapy is required for infectious aetiologies (secondary type) while idiopathic (primary type) neuroretinitis exhibits good spontaneous visual recovery and does not require any treatment. The role of steroids in treatment remains unclear in both the primary and secondary types. Management for *Leptospira* neuroretinitis in the past varied from observation to medical therapy with antibiotics alone or in combination with steroids. The antibiotics used were mainly a combination of quinolone (for its excellent intraocular penetration) and cyclines (to eliminate possible intracellular location of the organism) for a period of three weeks. Steroids have been used for *Leptospira*-associated neuroretinitis in the belief that it may hasten recovery of vision.[6] However, there is no good evidence that it affects visual outcome. There are reports which show the administration of steroids in the acute phase or when the optic disc is involved.[7]

Our cases concern neuroretinitis with elevated *Leptospira* IgM. Route of entry was probably contaminated water during the trip to the waterfall and jungle trekking. The common ocular manifestations were not present in our case. Although steroids have no proven role on visual outcome,[4] we used steroids in two of the cases to reduce the inflammatory response and to treat the underlying immune-mediated cause, which resulted in a better visual recovery and outcome. On completion of treatment, the visual response of our cases was satisfactory due to prompt aetiological diagnosis and management. As the pathogenesis of ocular infections and optic neuritis related to leptospirosis is still controversial, there is still no standardized treatment in managing ocular leptospirosis. A prospective multicentric study considering the aetiological factors and outcomes of the standardized treatment may provide a better insight into the aetiopathology, diagnosis, and management of *Leptospira* neuroretinitis.

Conclusion

Leptospirosis presenting as neuroretinitis without systemic manifestations has not been well reported or published. Hence, the knowledge of this condition and institution of prompt treatment may result in full visual recovery.

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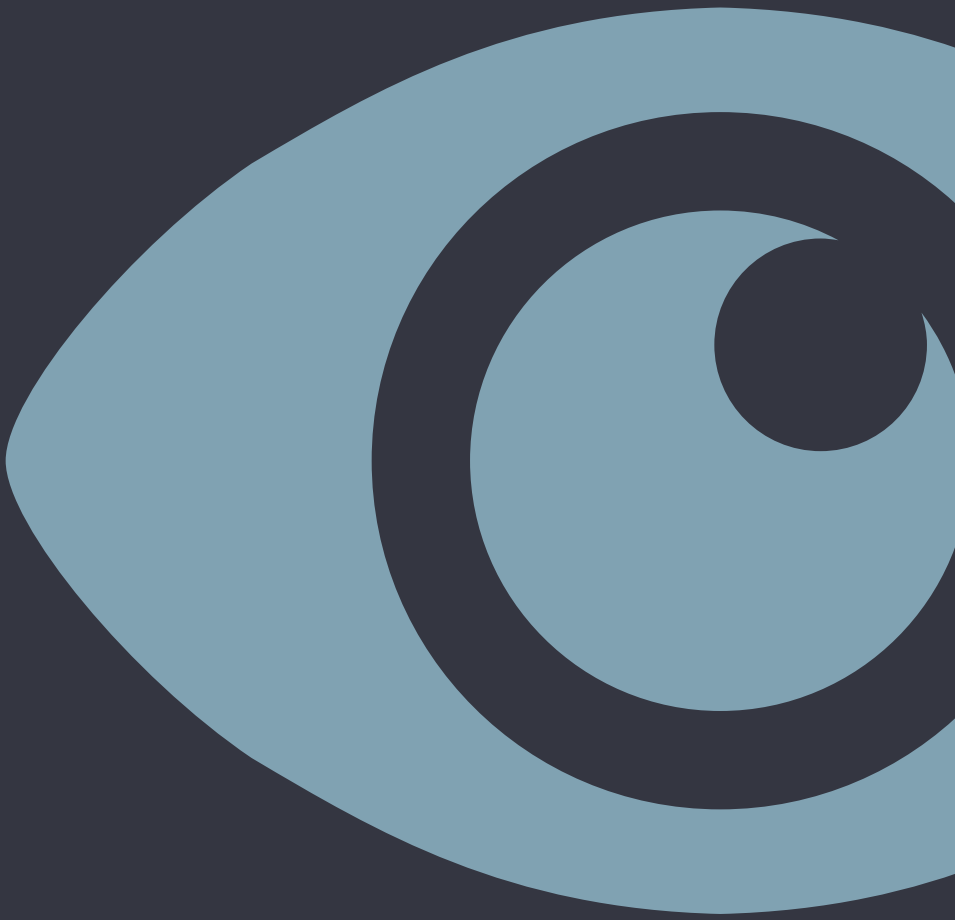

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