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Adult orbital tumors: a Southeast-Asian experience

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Abstract

Aim: *A study of the prevalence, demographics, clinical and histopathological features of orbital tumors biopsied in Serdang Hospital, a national Oculoplastic referral center in Malaysia.*

Methods: *This was a retrospective, observational study on all the orbital biopsies performed in Serdang Hospital from January 2008 to December 2014. Outcome measures included demographic data and histological diagnosis of the biopsied orbital lesions.*

Results: *Among the 136 cases, there is slight male preponderance (59.6%). Malays were the commonest racial group (58.8%) followed by Chinese (32.4%). Lymphoproliferative lesion was the most common category (34.6%), followed by inflammatory (10.3%) and lacrimal lesion (9.6%). Benign lymphoid hyperplasia (16.9%) and non-Hodgkin lymphoma (NHL) (16.2%) were the most common histology diagnoses. Benign lymphoid hyperplasia was seen among younger patients (mean 56 years) compared to NHL cases (60.6 years old). Benign lymphoid hyperplasia occurred with the same frequency in the orbit and lacrimal gland, while NHL was mostly located within the orbit. Lymphoproliferative disorders were more common among Chinese males. Cavernous haemangioma, pleomorphic adenoma and solitary fibrous tumor were seen at an earlier age than their Western counterparts. Benign orbital lesions were most common, but may be associated with significant visual and orbital comorbidities.*

Conclusions: *Lymphoproliferative lesions occur at a higher incidence among Southeast-Asian patients, especially among Chinese and male. Our patients also develop cavernous haemangioma, pleomorphic adenoma and solitary fibrous tumor at an earlier age compared to their Western counterparts. There was an ethnic difference among different orbital pathologies. Delayed presentation of benign orbital lesions lead to significant morbidity and even exenteration. Financial restraints may hinder precise histological diagnosis in developing countries.*

Introduction

Orbital tumors encompass a broad spectrum of benign and malignant lesions. It can be intrinsic to the orbit, like cavernous haemangioma, Schwannomas, glioma and inflammation, or it can also arise from adjacent periocular structures such as skin, nose, sinuses and cranial bones with secondary orbital invasion. Metastasis from breast, lung, prostate and skin are also reported. Lymphoproliferative lesions are common.[1]

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Orbital tumors can cause a variety of symptoms. Their space-occupying nature can lead to proptosis, eye displacement, swelling, diplopia, conjunctival congestion, chemosis and exposure keratopathy with associated pain and discomfort. The impingement on adjacent structure can lead to visual loss, dilated pupil and diplopia. The involvement to bone or nerve can also lead to pain. The malignant nature of some disease may even lead to mortality.

Histological examination of orbital biopsies are required to achieve a diagnosis. Orbital biopsy can be incisional or excisional depending on potential diagnosis, size of the lesions and level of infiltration towards normal structures. The surgical incision approach towards orbital biopsy usually depends on the location and size of the lesions. The recent advances in immunohistochemical staining and gene arrangement studies have helped to further characterize lesions and allow more targeted treatment. The classic examples are CD34 used to characterize haemangioma, haemangiopericytoma and solitary fibrous tumor, S100 protein for Schwannoma, neurofibroma, desmin for smooth and skeletal muscle[2] and the recently much discussed Ig G4 staining of IgG4 related disease in idiopathic sclerosing orbital inflammation.[3] Demonstration of light chain restriction using *in- situ* hybridization together with Immunoglobulin heavy chain gene monoclonal rearrangement via southern blot hybridization analysis allows B cell lymphoma to be identified from benign lymphoid hyperplasia.[2]

The types and frequencies of orbital tumors cited in studies vary according to sources, geographical location and age of the study cohort. While there are several publications addressing the incidence of space occupying lesions of the orbit in developed countries[1,4-7] and other parts in the world,[8-10] there is no such data describing incidences of space occupying tumor in South East Asia regions. Malaysia is a country consisting of three main different ethnic groups: Malay (67.4%), Chinese (24.6%), and Indian (7.3%)[11] with a relatively even distribution which provides a meaningful comparison between ethnicities.

The main objective of this retrospective study is to identify the incidence, clinical and histopathological features of orbital tumor among adult patients who had orbital biopsies in Serdang Hospital, a national Oculoplastic referral center in Malaysia. The secondary objective is to identify demographics data associated with various orbital pathologies in Malaysia and to compare the prevalence of orbital tumor with various published data in the world.

Subjects and methods

This is a retrospective, observational study on all the consecutive orbital lesions biopsies performed from January 2008 to December 2014. The informed consent was obtained orally and the subjects do not receive any stipend. This research adhered to the tenets of the Declaration of Helsinki as amended in 2008. The data is obtained via computer data surgical record. The setting is Serdang Hospital, a tertiary referral center for the orbital cases.

Serdang Hospital has been the national oculoplastic referral center for Malaysia since 2006. It receives referrals from all over Malaysia in relation with suspicious

orbital tumors. Therefore data from Serdang Hospital will serve as a useful reference point on the demographics of orbital tumor in Malaysia.

Data collected included patients' age at the time of orbital diagnosis, gender, race, ophthalmic symptoms, laterality, best corrected Snellen visual acuity, location of involved orbital contents (extraocular muscle, lacrimal gland, conjunctiva, eyelid), general histopathological category diagnosis, treatment and follow-up period. The statistical comparison with various countries was based on reports of case studies in those countries.

Inclusion criteria were age above 18, patients who had orbital biopsy and confirmed histology findings. Those who were under 18 years old and declined orbital biopsy were excluded.

Results

In total, 136 patients had orbital tumors biopsied during this period with slight male preponderance (59.6%) as compared to female 40.4%. Sixty-eight patients (50%) had lesions on the right compared to 66 patients (48.5%) patients had lesions in the left, two patients (1.5%) had bilateral lesions. Eighty patients were Malay (58.8%), 44 were Chinese (32.4%), nine were Indians (6.7%), two were Indonesians (1.5%) and one was from Myanmar. The mean follow up period was 7.67 months (median: two months, ranges: one day to 76 months). The presenting symptoms are proptosis 96 (70.6%), reduced vision 80 (59%), eyelid swelling 11 (8%) and ophthalmoplegia 38 (28%).

All patients had CT and MRI scans prior to biopsies. 27.2% of the lesions were intraconal compared to 61.8% extraconal and 11% of the lesions located both intraconally and extraconally. CT/MRI can usually diagnose lymphoproliferative disease well. However, it does not differentiate lymphoma from benign lymphoproliferative lesion. The other lesions that correlate well with CT/MRI are cavernous haemangioma and adenoid cystic carcinoma. Otherwise, CT/MRI more serves to outline the location of lesions rather than informing us about the nature of the lesion.

Seventy (51.5%) patients had incisional biopsies and 55 patients (40.4%) underwent excisional biopsies, whilst 11 patients (8.1%) had exenteration. All patients who had exenteration had malignant lesions except for one patient who had an arteriovenous malformation leading to orbital apex syndrome with no perception of light.

The demographic details of different categories are in Table 1.

Table 1. Classification of 136 consecutive patients with orbital lesions.

Category	No. of patients (%)	Mean age (years; median, range)	Race
Lymphoproliferative	47/136 (34.6%)	57.5 (57; 27-87)	M:25 C: 20 I: 1. Indo 1
Inflammatory	14/136 (10.3%)	44.7 (44; 24-69)	M:11 Chinese 2 Myanmar 1
Lacrimal gland lesion	13/136 (9.6%)	42.8 (36; 21-65)	M: 7 C:2 I: 3, Indo 1
Secondary orbital tumor	10/136 (7.4%)	58.77 (56; 41-86)	M: 10
Vasculogenic lesion	9/136 (6.6%)	42.9 (41: 26-60)	M: 7 C: 2
Cystic tumor	6/136 (4.4%)	35.5 (38; 24-44)	M: 2 C: 1 I: 1
Optic nerve sheath/ meningeal lesion	6/136 (4.4%)	46.8 (45; 29-50)	M:2 C: 2 I: 1
Fibrocystic lesion	4/136 (2.9%)	31.2 (32.5; 25-33)	M: 2 C: 2
Peripheral nerve lesion	4/136 (2.9%)	32 (33.5; 23-38)	M: 2 C: 2
Lipocytic/myxoid lesion	3/136 (2.2%)	48.7 (52; 27-62)	M: 2 C:1
Fibro-osseous lesion	1/136 (0.7%)	23	M: 1
Myogenic lesion	1/136 (0.7%)	32	M: 1
Melanocytic lesion	1/136 (0.7%)	66	M: 1
Metastatic lesion	1/136 (0.7%)	67	C: 1
Histiocytic lesion	1/136 (0.7%)	40	I: 1
Miscellaneous	14/136 (10.3%)	47.3 ($2; 37-72)	M: 3 C: 9 I: 2

M: Malay; C: Chinese; I: Indian.

As for the specific histological diagnosis, lymphoid hyperplasia and NHL constitute 16.9% and 16.2% respectively. Median age of patients who develop benign lymphoid hyperplasia (57 years old) was younger than that of NHL (60 years old). This is followed by chronic inflammation (10.3%), cavernous haemangioma (5.1 %), and pleomorphic adenoma (3.7%). Dermoid cyst, Schwannoma extra pleural solitary fibrous tumor and pleomorphic adenoma shared the same occurrence (2.9%) (Table 2).

Stratification of orbital lymphoproliferative lesions was performed to further characterize the lesions (Table 3). Benign lymphoid hyperplasia usually affected the

orbit (7.4%) and lacrimal gland (6.6%) equally. Patients with lacrimal gland involvement were slightly older (63.4 years old) compared with orbital involvement (58.6 years old). In comparison, NHL usually affect orbit only (14% of total orbital lesions) with a mean age of 59.7 years.

Table 2. Frequency of patients with orbital lesions according to histology diagnosis (commonest nine only).

	Diagnosis	No. (%)	Mean age (yrs, median, range)	Sex	Race
1	Benign lymphoid hyperplasian (BLH)	23 (16.9%)	56 (57; 27-79)	M: 18 F: 5	M: 13 C: 9
2	Non-Hodgkin lymphoma (NHL)	22 (16.2%)	60.6 (60; 42-87)	M: 13 F: 9	M: 11 C: 9 I: 1
3	Chronic inflammation	14 (10.3%)	45.8 (46; 24-71)	M: 7 F: 6	M: 11 C: 2 Myn: 1
4	Cavernous haemangioma	7 (5.1%)	42.9 (41; 33-64)	M: 1 F: 6	M: 5 C: 2
5	Pleomorphic adenoma	5 (3.7%)	38.2 (34; 26-65)	M: 5	M: 3 I: 1 Indo: 1
6	Dermoid cyst	4 (2.9%)	35.5 (38; 24-44)	M: 3 F: 1	M: 2 C: 1 I: 1
7	Schwannoma	4 (2.9%)	52.2 (51.5; 29-77)	M: 4	M: 2 C: 2
8	Extrapleural solitary fibrous tumor	4 (2.9%)	31.2 (32.5; 25-35)	M: 2 F: 2	M: 2 C: 2
9	Ca ex pleomorphic adenoma	4 (2.9%)	53 (50; 33-74)	M: 3 F: 1	M: 2 C:2

Table 3. Stratification of 47 patients with lymphoproliferative lesions.

Category	No. (% of patients)	Mean age (median, range)	Race
Benign lymphoid hyperplasia			
Orbital	10 (7.4%)	58.6 (60.5; 27-78)	M: 6, C: 4
Orbital, lacrimal gland	4(2.9%)	46 (49.5; 27-58)	M: 3 C: 1
Lacrimal gland	9 (6.6%)	63.4 (39-79)	M: 5 C: 4
Non-Hodgkin lymphoma			
Orbital	19 (14%)	59.7 (57; 42-87)	M: 9 C: 9
Orbital/lacrimal gland	1 (0.7%)	61	M: 1
Lacrimal gland	1(0.7%)	75	C: 1

For those who had NHL, the majority (18/22 or 81.8%) had low grade lesions (namely extranodal marginal zone B cell lymphoma, small lymphocytic B cell lymphoma and nodular low grade B cell lymphoma). All those with aggressive lymphoma had diffuse large B cell lymphoma. Only two patients had pre-existing orbital lymphoma and none had systemic NHL prior to diagnosis. As for pre-existing disease prior to diagnosis, three patients had diabetes mellitus and one patient had a history of intravenous drug use but a negative test for HIV. All patient had localized orbital disease except for one with diffuse large B cell lymphoma with lung nodules. All were referred to an oncologist for further management.

Chronic inflammation presented as a heterogeneous group involving various structures in the orbit. All of our patients had either proptosis or dysmotility. Pain was not a predominant feature. Four lesions (30.7%) involved the lacrimal gland with others affecting the intraconal area, extraocular muscle such as inferior rectus and also extraconal lesions. As for the histological appearance, majority of the lesions (8/14 or 61.5%) were of lymphocytic lineage. Intense fibrosis was found to be present in 5/14 (38.5%) of the sample. One patient was pANCA positive and subsequently developed lupus nephritis.

With regard to the prevalence of benign lesion compared with malignant lesions, 86/136 (63.2%) of the patients were benign compared with 50/136 (36.8%) being malignant. Morbidities among benign lesions were proptosis 61/86 (70.9%), eyelid swelling 27/86 (31.4%), ophthalmoplegia 22/86 (25.6%) and reduced vision 26/86 (30.2%). Most of our patients with lymphoproliferative lesions present with proptosis in the absence of any inflammatory symptoms. Some of them were not reversible even after surgical removal. The authors had attempted to analyze the correlation of different ocular symptoms (proptosis, reduced vision and diplopia) and systemic symptoms (*e.g.*, loss of appetite/weight), but were unable to find any correlations between them. We believe the different symptoms are more related

with the location of lesions rather than the nature of the lesions.

Various techniques have been adopted to remove orbital masses. The choice of procedure, whether through subbrow, lateral orbitotomy or subciliary incision depends on the location of lesion. Eleven patients with malignant lesions had exenteration.

Discussion

This is the first data for adult orbital tumor in South East Asia region. There was a wide variety of tumors encountered. The commoner frequency of benign lesion (61.8%) among our patients was comparable to Bonavoluta *et al.* data (68%),[4] but was slightly different from Shinder's data[7] (37%) (Table 4).

Table 4. Comparison incidence with other published data.

Name of data	Country	Benign *vs* malignant	Type of tumor	Commonest tumor
Shinder *et al.*[7]	Texas, USA	37% benign; 63% malignant	64% primary orbital; 26% secondary orbital; 10% metastasis	1) Secondary orbital tumor 26%; 2) Lyphoproliferative 25%; 3) Metastasis 10%; 4) Epithelial lacrimal gland tumor 10%; 5) Inflammation 8%
Shields *et al*[1] (1264)	Wills Eye Hospital, USA	52.5% benign; 47.5 % malignant		1) Lymphoid tumor 11%; 2) Idiopathic orbital inflammation 11%; 3) Cavernous haemangioma 6%; 4) Lymphangioma 4%; 5) Meningioma 4%
Johansen[5] 1974-1997	Denmark	55% benign; 45% malignant	43% primary orbital; 48% secondary orbital; 9% metastasis	
Bonavolunta[4] (2480) (1976-2011)	Italy	68% benign; 32% malignant		1) Dermoid cyst 14%; 2) NHL 12%; 3) Cavernous haemangioma 9%

Name of data	Country	Benign *vs* malignant	Type of tumor	Commonest tumor
Shikishima[8]	Japan	65% benign; 35% malignant	47% primary; 30% secondary; 22% inflammation	1) Inflammatory pseudo-tumor 18%; 2) Malignant lymphoma 12%; 3) Pleomorphic adenoma 7%
Ni[9] 1953-1992	China			1) Cavernous haemangioma 36%; 2)Malignant lacrimal gland tumor 32%; 3) Malignant lacrimal sac tumor 26%
Our study	**Malaysia**	**63.2% Benign; 36.8% malignant**	**92.6% primary; 7.4% secondary**	**1) BLH 16.9%; 2) NHL 16.2%; 3) inflammation 10.3%**

As for the category of lesion, lymphoproliferative lesions were the most common pathology, just like our western counterparts.[1,7] However, our prevalence of 34.6% was much higher compared to Western country counterparts, 10% in Shields' data[1] and 25 % in Shinder's.[7] Both benign lymphoid hyperplasia and NHL were the most common lesions found. As benign lymphoid hyperplasia and NHL falls within the same spectrum of the disease,[12-14] it is understandable that benign lymphoid hyperplasia occurs at slightly a younger age (57 years old) compared to NHL (60 years old). One patient with benign lymphoid hyperplasia progressed to extranodal marginal zone lymphoma within the period of two years. Hence if there is any suspicion on progression of lesion, further biopsy is required. The majority (81.8%) of our patients had low-grade lymphoma which was very similar to the published literature.[15,16] However, systemic work-up for staging is important, especially those with high grade lymphoma, as the patient was found to have a concurrent lung disease.

The high prevalence of chronic inflammation also warranted attention especially as the majority of the inflammation is of lymphocytic lineage and pain is not a predominant complaint among those patients. Of our patients, 38.5% had sclerosing orbital inflammation, which may represent a different subtype and separate entity, such as IgG4-related disease.[17] Unfortunately, we are yet to have the financial resources for the IgG4 staining in the public hospital in Malaysia. The recent case report of IgG4-related dacryoadenitis that regressed without steroid but with anti-allergic administration may provide a useful alternative treatment for our patients who are not able to tolerate steroids.[18] Recent evidence has suggested that chronic inflammation may lead to or mimic lymphoma, three patients who had

the histological appearance of IgG4 disease also showed immunoglobulin heavy-chain rearrangement and light chain restriction.[19,20] Regular vigilant follow-up is required to monitor the progress of the patients and re-biopsy may be required if the disease progresses.

Another important observation is that there were four cases of orbital extrapleural solitary fibrous tumors (SFT), which is being increasingly recognized. It is a rare spindle-cell benign lesion with only 80 cases encountered in the orbit so far.[21] It is commonly described as a slow-growing painless orbital mass and/or facial deformity. On imaging, it presents as a well-defined soft tissue mass with strong enhancement on CT and MRI imaging.[22] If extensive bone remodeling is present or a long-standing lesion is noted, the possibility of malignant transformation should be suspected, particularly if a partial excision had been attempted.[22] Histologically, it displays haphazardly arranged fibroblast like cells (spindle) indistinct nucleoli, variable stromal collagen, and prominent vasculature with perivascular fibrosis which shares many similarities with other pathologies.[21] However, it has a characteristic immunohistochemical staining pattern which is strong positivity towards CD34 (90-100%) and CD 99 (70%) with about one third positive for Bcl-2. It is not immunoreactive for S100 protein like Schwannoma.[21] It is a benign lesion if completely excised. Unfortunately, in three of our four patients, they were recurrent lesions previously operated elsewhere and adhered to periosteum and extraocular muscle making complete excision impossible. Lifelong follow up is required as there is risk of malignant transformation.[21]

Age distribution for various types of lesions was also analyzed and compared with the western counterparts in the published literature. Pleomorphic adenoma occurs at a younger age (mean age 38 years old) compared to Western counterparts (48 years old[1]). A similar trend was noted with cavernous haemangioma (42.9 years old vs 48 years old[1]) and extrapleural solitary fibrous tumor (31.2 years old vs 43 years old[21]).

As for racial distribution, it is found that lymphoproliferative disorder seems to have equal distribution between Malay and Chinese. However, if one takes into account the constitution of races in Malaysia in which Malay constitutes 60.3% and Chinese only constitutes 22.9% of population,[11] it is clear that there is a preponderance of such condition among Chinese. Our results share similarity with Shikishima's data from Japan where no obvious reasons can be found.[8] Hence there should be a low threshold to perform orbital biopsy for some patients with these demographics who present with symptoms of orbital tumor. Malays had a higher incidence of orbital chronic inflammation and secondary orbital tumors at 78.6% and 100% respectively in our study which is yet to be reported.

In the west, adult patients were more likely to have a higher incidence of orbital metastases and lymphoma.[6] However, in our series, patients were more likely to have lymphoproliferative disorders and inflammation.

Orbital tumors including those of a benign nature can create a significant amount of morbidity among patients. Whilst they may not be related with reduced lifespan, morbidities such as proptosis, ophthalmoplegia and reduced vision may not be

reversible despite surgical intervention.

The advent in immunophenotyping of orbital diseases have allowed rare lesions such as solitary fibrous tumor to be recognized. It also aided in differentiation of benign lymphoid hyperplasia from lymphoma. The recent recognition of IgG4 as a subgroup of orbital inflammation[3] will provide more insight onto orbital inflammation although we are yet to have the relevant immune-essays and immunostaining to analyze this disease due to financial constraints. Our series highlighted the common problems faced by clinicians in developing countries in which financial constraints in obtaining tissue staining are one of the huddles of getting a precise diagnoses of orbital lesions.

We admit the limitation of the retrospective nature of our study and we are in the process of establishing national orbital biopsy data with prospective collection of data including those from the private sector. We also admit that we may miss out on a group of patients who may decline orbital biopsy or has been treated empirically with steroid by medical practitioners elsewhere. It is hoped that the publication of this data will educate the local clinicians to refer patients with orbital tumors to qualified oculoplastic surgeons for further investigative management. We will also seek to collaborate with hematologist to identify the long-term survival outcome of those with lymphoproliferative orbital lesions.

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Conflict of interest: Ho SF, None; Radzlian Othman, None.
Dr Ho SF conceived the ideas of this research, collected the data, wrote and edited the manuscript. Dr Radzlian Othman edited the manuscript. Dr Ho SF and Dr Radzlian Othman had full access to the data.

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Comparison of efficacy and safety of Difluprednate 0.05% and Nepafenac 0.1% in reducing macular thickness and volume after cataract surgery

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Abstract

Aim or Purpose: *To evaluate and compare efficacy and safety of topical Difluprednate ophthalmic emulsion 0.05% with Nepafenac ophthalmic suspension 0.1% in patients of uneventful cataract surgery with respect to postoperative macular thickness and volume.*

Design: *A prospective, single centric, tertiary care center-based, comparative, interventional study from August 2013 to July 2014.*

Subjects: *Total 206 (Group N = 106, Group D = 100) patients were followed-up, who completed their 12 weeks follow-up.*

Methods: *Surgery was performed by phacoemulsification technique by clear corneal incision with foldable PCIOL implantation by a single surgeon having ten years of surgical experience. Postoperative patients were divided into two groups. Group N were given topical treatment with Nepafenac ophthalmic suspension 0.1% TID starting 24 hours before surgery and continued postop four weeks. Group D were given Difluprednate ophthalmic emulsion 0.05% QID post-surgery for two weeks followed by BID for two weeks.*

Main outcome measures: *Postoperative assessment of patients were done on first day and on first, eighth and 12th weeks after the surgery for best corrected visual acuity (BCVA) by logMAR, intraocular pressure by applanation tonometry and macular thickness and volume by SD-OCT.*

Statistical test used was sample unpaired and paired 't' test and statistical analysis was done with SPSS 20.0 (IBM, USA).

Results: *There was increase in the measured mean central subfield thickness (CST) at eight and 12 weeks as compared to one week, in both study groups ($P < 0.05$). On comparing the volume (in mm^3) and average thickness (in µm) at one week, it was observed that the thickness of group N (266.82 ± 25.06 µm) was statistically higher than that of group D (253.14 ± 22.21 µm) ($P = 0.03$). The comparison of best corrected visual acuity (LogMAR) and the intraocular pressure recordings showed no difference between the patients of two studied groups recorded at one, eight and 12 weeks.*

Conclusion: *Both Nepafenac ophthalmic suspension 0.1% and Difluprednate ophthalmic emulsion 0.05% are equally effective in controlling macular thickness change after uneventful cataract surgery.*

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Introduction

Incidence rate of increase in macular thickness post cataract surgery ranges from 1-6% in uncomplicated cataract surgery to 5-10% after posterior capsule rupture.[1,2] Therapeutic interventions are based on the proposed pathogenesis of edema, mainly inflammation and vitreous traction.[3] Inflammation after cataract surgery is generally managed by topical anti-inflammatory drugs such as corticosteroids or NSAIDS.[4] The majority of physicians employ a prophylactic regimen of anti-inflammatory medications in the pre-operative and post-operative period.

Currently, no standardized protocol exists for the prophylaxis and management of increased macular thickness because of a lack of prospective randomized clinical trials. The purpose of this study was to evaluate and compare efficacy and safety of topical Difluprednate ophthalmic emulsion 0.05% with Nepafenac ophthalmic suspension 0.1% in patients of uneventful cataract surgery with respect to postoperative macular thickness and volume.

Material and methods

The study was done as per tenets of Helsinki. It was a prospective, single centric, tertiary care center-based, comparative, interventional study from August 2013 to July 2014**.** The sample size was calculated on the basis of the assumption of a difference of 10 nm of macular thickness between two study groups and a SD within 10% difference and 95% confidence limit. Calculated sample size for each group was 81 patients. Cases were randomized into two groups by using computer generated random numbers: Group N [n = 81] and Group D [n = 81]. All patients above 40 years of age with senile cataract grading NS I-III, undergoing cataract surgery for visually significant cataract (phacoemulsification with PCIOL implantation) in the department of ophthalmology were included in the study. Patients receiving treatment for any other co-existing ocular pathology, having a history of any recent intraocular surgery, systemic illness which may increase macular thickness, hypersensitivity to the drugs used in the study were excluded. Patients having pre-existing macular disease or taking systemic medications which may affect macular thickness were also excluded. Patients with macular disease as seen on clinical evaluation at one week were excluded from the study (especially patients with dense cataract in whom preoperative fundus evaluation was not possible).

Written informed consent was taken for inclusion from all patients for participation in the study. Assessment of patients was done on the preoperative day by detailed history and clinical examination. Surgery was performed by phacoemulsification technique by clear corneal incision with foldable PCIOL implantation by a single surgeon having ten years of surgical experience. Postoperatively, patients were assessed for iris trauma, posterior capsular rupture and/or vitreous loss. Moxifloxacin hydrochloride ophthalmic suspension 0.5% QID for two weeks starting 24 hours prior to surgery and Cyclopentolate hydrochloride ophthalmic suspension 1.0% HS for one week were given to both groups. Group N were given topical treatment with Nepafenac ophthalmic suspension 0.1% TID starting 24

hours before surgery and continued postoperatively for four weeks. Group D were given Difluprednate ophthalmic emulsion 0.05% QID post-surgery for two weeks followed by BID for two weeks. Postoperative assessment of patients were done on the first day and on one, eight and 12 weeks after the surgery for best corrected visual acuity (BCVA) by logMAR, intraocular pressure by Applanation tonometry and macular thickness and volume by SD-OCT.

OCT protocol

OCT 512x128 scans were done with CIRRUS SD-OCT (Zeiss, USA) for macular thickness assessment.[5] Macular thickness was reported in a modified Early Treatment of Diabetic Retinopathy Study macular map with the central subfield one mm in diameter and the inner and outer subfields having diameters of three mm and six mm, respectively [Figs.1a, 1b, 1c]. The retinal thickness in the inner and outer subfields, the central foveal thickness (CFT), the center point thickness (CPT), and the macular volume were calculated. CPT was defined as average of six radial scans centered at the foveola, whereas the CFT was defined as the average of all points within the central one mm diameter circle surrounding fixation.[6]

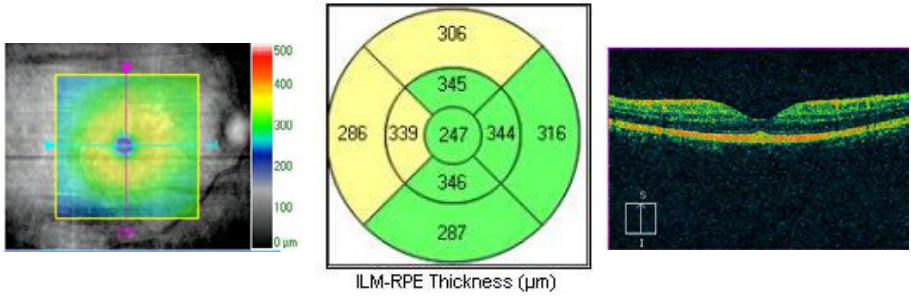

Fig. 1. Macular thickness map using ETDRS circles of one mm, three mm, and six mm showing the mean thickness in each of the nine subfields in a participant.

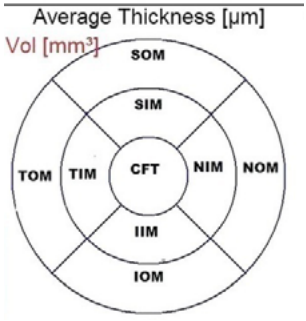

Fig. 2. The standard ETDRS subfields dividing the macula into central fovea, inner macula, and outer macula. CFT: Central foveal thickness; SIM: Superior inner macula; NIM: Nasal inner macula; IIM: Inferior inner macula; TIM: Temporal inner macula; SOM: Superior outer macula; NOM: Nasal outer macula; IOM: Inferior outer macula; TOM: Temporal outer macula.

Statistical analysis

Average macular thickness and volume by OCT were recorded on each visit for both groups and compared by statistical test by two sample unpaired and paired 't' tests. BCVA and IOP were recorded on each visit and compared between two groups by unpaired and paired 't' test. $P < 0.05$ was considered for level of significance during statistical analysis. Statistical analysis was done with SPSS 20.0 (IBM, USA).

Results

A total of 300 patients were screened. Seventy-two patients were excluded (senile cataract of grade NS-IV - 42, and diabetes mellitus and/or hypertension 30), so 228 patients were enrolled in the study: 118 in group N and 110 patients in group D. Four patients were discontinued from study after recruitment (perioperative complications - one, retinal pathology postoperatively - one, and other complications revealed on the first postoperative day - two). Two hundred twenty-four patients were included in the study for further follow-up (114 patients in group N and 110 patients in group D). Eight patients from group N were lost to follow-up before completion of 12 weeks and excluded from the study. Ten patients from group D were lost to follow-up before completion of 12 weeks and excluded from the study. A total of 206 (N = 106, D = 100) patients were followed-up who completed their 12 weeks follow-up after which the data was compiled and statistical analysis was done (Fig. 1).

There was no statistically significant difference in baseline (first day) measurements of central subfield thickness (CST), macular volume, average thickness and intra ocular pressure between group D and group N (Tables 2, 4, 6, 9). The two study groups were comparable in terms of age and the gender ratio of the study patients as shown in Table 1. No statistical difference was observed in the mean CST recorded at one, eight and 12 weeks in both the study groups ($P > 0.05$) (Table 2). There was increase in the measured mean CST at eight and 12 weeks as compared to one week, in both the study groups ($P < 0.05$). But there was no difference from one to eight and 12 weeks among the two study groups (Table 3).

On comparing the volume (in mm^3) and average thickness (in µm) at one week, it was observed that the thickness of group N (266.82 ± 25.06 µm) was statistically higher than that of group D (253.14 ± 22.21µm) ($P = 0.03$). Otherwise there was no statistical difference in the volume (in mm^3) and average thickness (in µm) of patients in two study groups at one week, eight weeks and 12 weeks ($P > 0.05$) (Tables 4 and 6). In either of the studied groups no statistical change in the volume (in mm^3) and average thickness (in µm) of patients was observed between one week and eight weeks and between one week and 12 weeks ($P > 0.05$) as shown in Table 5 and Table 7, respectively. The comparison of best corrected visual acuity (LogMAR) and the intraocular pressure recordings showed no difference between the patients of two studied groups recorded at one week, eight weeks and 12 weeks as shown in Table 8 and Table 9, respectively.

Discussion

Ocular inflammation after cataract surgery is generally managed by topical anti-inflammatory drugs such as corticosteroids and NSAIDS. Pre and postoperative treatment with anti-inflammatory drops is now standard in many centers to reduce surgically induced inflammation. Control of postoperative inflammation is important in ensuring a successful outcome after cataract surgery. Deciding which anti-inflammatory agent is to be used as standard in patients undergoing cataract surgery is important to ensure a favorable outcome. Current guidelines do not provide specific recommendations concerning the postoperative management of inflammation.[7]

There are multiple reports comparing role of various steroid (Betamethasone, Dexamethasone, Fluorometholone, Rimexolone) with different types of NSAIDs (Diclofenac, Ketorolac, Bromfenac, Indomethacin and Flurbiprofen) in controlling post cataract surgery inflammation.[8-13] To the best of our knowledge, there is only one report in which Nepafenac has been compared with a steroid (Fluorometholone).[14] Corticosteroids are typically the cornerstone of these treatment regimens because of their broad anti-inflammatory activity.[15]

Difluprednate 0.05% ophthalmic emulsion is a potent new topical synthetic difluorinated prednisolone derivative steroid that exhibits enhanced penetration, better bioavailability, rapid local metabolism, and strong efficacy with low incidence of adverse effects. It has been have incorporated into their standard anti-inflammatory treatment regimen for postoperative inflammation.[7] Difluprednate, being a steroid derivative, can also be associated with elevated IOP. Thus, standard care of practice must be employed, with frequent measurement of eye pressure for anyone using this medication.

Nepafenac ophthalmic suspension 0.1%, a topical prodrug, is the first prodrug ophthalmic NSAID formulation approved for use in the US for the treatment of postoperative pain and inflammation after cataract surgery. The theoretical advantage offered by Nepafenac over other existing NSAIDs is in corneal penetration, providing a better bio-availability. Prophylactic use of Nepafenac prior to cataract surgery may in fact lessen postoperative inflammation avoiding intraocular pressure-related complications incurred with frequent administration of high dose corticosteroids postoperatively.

This is the first study planned to evaluate and compare efficacy and safety of topical Difluprednate ophthalmic emulsion 0.05% with Nepafenac ophthalmic suspension 0.1% in patients of uneventful cataract surgery with respect to postoperative macular thickness and volume. In the present study we observed that central subfield thickness recorded in patients were reported to be the maximum at eight weeks after which there was a fall in central subfield thickness values in Nepafenac 0.1% group (group N) and unchanged in Difluprednate group 0.05% (group D) (Tables 2 and 3). Previous studies have also reported that macular thickness, as assessed by OCT in patients without pseudophakic cystoid macular edema, peaks at approximately four to six weeks postoperatively.[16-18] Our finding is supported by earlier fluorophotometric findings, that an earlier

re-establishment of the blood-aqueous barrier occurs in NSAID-treated patients compared with steroid-treated patients.[19] We failed to observe any difference in the visual acuity, macular volume and average macular thickness, between two study groups. Despite an initial fall in the central subfield thickness by Nepafenac group compared to Difluprednate ophthalmic emulsion 0.05%, the final average macular thickness, macular volume and visual acuity showed no difference in both the groups. Thus, both Nepafenac ophthalmic suspension 0.1% and Difluprednate ophthalmic emulsion 0.05% are equally effective in controlling macular thickness change after uneventful cataract surgery.

The risk of rise of IOP after steroid use has tempted many surgeons to turned to NSAIDs to control inflammation after cataract surgery.[20] But we did not observe any statistically significant difference between IOP recorded in both the groups during the 12-weeks follow-up. Also there was no evidence of increased risk of adverse events with the use of NSAID, although previous reports have indicated that prolonged use of topical NSAIDs may be associated with a risk of corneal melts and impaired corneal wound healing.[21,22]

Conclusion

Nepafenac ophthalmic suspension 0.1% offers no advantage over Difluprednate ophthalmic emulsion 0.05% in reducing macular thickness and volume post uneventful cataract surgery. Both Difluprednate ophthalmic emulsion 0.05% and Nepafenac ophthalmic suspension 0.1% are comparable in terms of elevating IOP. Thus, both have equal efficacy and safety in reducing postoperative macular thickness and volume in patients of uneventful cataract surgery.

Fig. 1. Flowchart for patient recruitment.

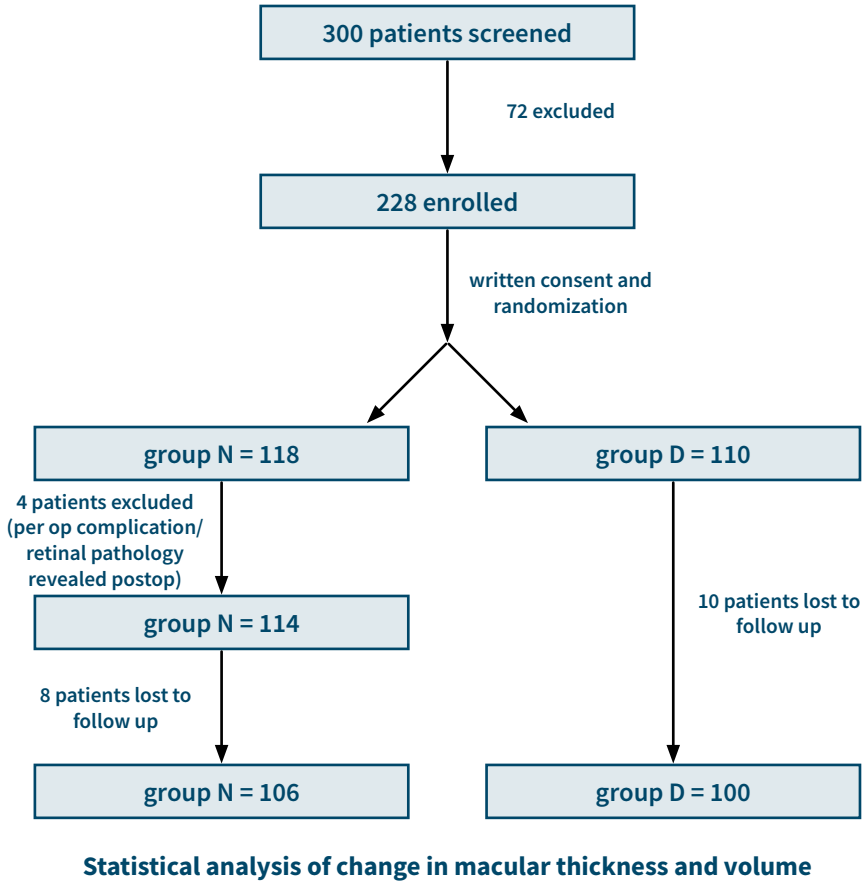

Table 1. Comparison of age distribution of the patients in two groups.

	Group N (n = 56)	Group D (n = 50)	p-value
Age in years	56.43 ± 9.11	59.00 ± 10.38	0.32[1]
Gender ratio (M/F)	20/36	16/34	M: 0.56[1] F: 0.58[1]

Group N: Nepafenac 0.1%; Group D: Difluprednate 0.05%; [1]Unpaired t-test; [2]Chi-square test.

Table 2. Comparison of central subfield thickness (in µm) between the groups across the time interval.

	Group N (n = 106)	Group D (n = 100)	p-value
Baseline (1st day) 1 week	240.36 ± 24.23 238.36 ± 25.23	241.12 ± 23.65 239.07 ± 26.74	0.86 0.91
8 weeks	248.21 ± 24.74	245.57 ± 22.24	0.67
12 weeks	244.93 ± 19.97	245.61 ± 18.95	0.89

Group N: Nepafenac 0.1%; Group D: Difluprednate 0.05%; [1]Unpaired t-test.

Table 3. Average percent change in central subfield thickness (in µm) from 1 week to 8 and 12 weeks.

	Group N (n = 106)	Group D (n = 100)	p-value[1]
1 week	-	-	
8 weeks	3.8 ± 7.1	2.7 ± 3.6	0.48
12 weeks	2.6 ± 7.4	2.7 ± 5.7	0.92
p-value[2]			
1 week to 8 weeks	0.009*	0.001*	
1 week to 12 weeks	0.05	0.02*	

Group N: Nepafenac 0.1%; Group D: Difluprednate 0.05%; [1]Unpaired t-test; [2]Paired t-test.

Table 4. Comparison of volume (in mm^3) between the groups across the time interval.

	Group N (n = 106)	Group D (n = 100)	p-value
Baseline (1st day) 1 week	9.68 ± 0.80 9.62 ± 0.80	9.42 ± 0.78 9.32 ± 0.66	0.87 0.91
8 weeks	9.46 ± 0.73	9.23 ± 0.80	0.67
12 weeks	9.51 ± 0.53	9.16 ± 0.72	0.89

Group N: Nepafenac 0.1%; Group D: Difluprednate 0.05%; [1]Unpaired t-test.

Table 5. Average percent change in volume (in mm^3) from 1 week to 8 and 12 weeks.

	Group N (n = 106)	Group D (n = 100)	p-value[1]
1 week	-	-	
8 weeks	*1.8 ± 7.3*	*0.4 ± 9.3*	*0.53*
12 weeks	*1.2 ± 8.6*	*1.4 ± 12.1*	*0.94*
p-value[2]			
1 week to 8 weeks	*0.22*	*0.98*	
1 week to 12 weeks	*0.48*	*0.73*	

Group N: Nepafenac 0.1%; Group D: Difluprednate 0.05%; [1]Unpaired t-test; [2]Paired t-test.

Table 6. Comparison of average thickness (in µm) between the groups across time interval.

Baseline (1st day)	Group N (n = 106) 264.80 ± 23.06	Group D (n = 100) 264.50 ± 22.99	p-value 0.90
1 week	266.82 ± 25.06	253.14 ± 22.21	0.03*
8 weeks	260.29 ± 24.11	257.32 ± 23.17	0.64
12 weeks	266.39 ± 19.56	256.21 ± 21.71	0.07

Group N: Nepafenac 0.1%; Group D: Difluprednate 0.05%; [1]Unpaired t-test.

Table 7. Average percent change in average thickness (in µm) from 1 week to 8 and 12 weeks.

	Group N (n = 106)	Group D (n = 100)	p-value[1]
1 week	-	-	
8 weeks	2.8 ± 9.1	1.1 ± 9.7	0.11
12 weeks	0.57 ± 11.0	0.42 ± 12.9	0.75
p-value[2]			
1 week to 8 weeks	0.13	0.35	
1 week to 12 weeks	0.93	0.60	

Group N: Nepafenac 0.1%; Group D: Difluprednate 0.05%; [1]Unpaired t-test; [2]Paired t-test.

Table 8. Comparison of best corrected visual acuity (LogMAR) between the groups across the time interval.

	Group N (n = 106)	Group D (n = 100)	p-value
1 week	0.57 ± 0.07	0.60 ± 0.17	0.07
8 weeks	0.50 ± 0.23	0.45 ± 0.25	0.44
12 weeks	0.37 ± 0.15	0.27 ± 0.24	0.06

Group N: Nepafenac 0.1%; Group D: Difluprednate 0.05%; [1]Unpaired t-test.

Table 9. Comparison of IOP (mmHg) between the groups across the time intervals.

	Group N (n = 106)	Group D (n = 100)	p-value
Baseline (1st day) 1 week	13.14 ± 2.80 13.07 ± 2.24	13.50 ± 3.00 12.42 ± 2.57	0.50 0.32
8 weeks	13.07 ± 2.26	13.09 ± 3.24	0.37
12 weeks	14.14 ± 0.91	14.18 ± 3.14	0.39

Group N: Nepafenac 0.1%; Group D: Difluprednate 0.05%; [1]Unpaired t-test.

Disclaimer- The authors have no financial interest and no competing of interest

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