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Title page

The long-term effect of cataract phacoemulsification on the inflammation control and clinical outcome in uveitis patients

Running title: Effect of phacoemulsification on uveitis

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Abstract

Importance: Cataract is one of the most common complications associated with uveitis, and is the leading cause of vision loss in these patients.

Background: The study aimed to evaluate the effect of phacoemulsification on the long-term clinical outcome and inflammation control in uveitis patients.

Design: Longitudinal study

Participants: Of 1907 eyes with uveitis, 309 eyes underwent phacoemulsification were compared to a control group of 300 phakic eyes with uveitis.

Method: Visual acuity of pseudophakic eyes over the follow-up period was compared to the early (1st week) postoperative vision and to the control group. The rates of corticosteroids administration and uveitis relapse were also measured in pseudophakic eyes and compared to preoperative period.

Main Outcome Measures: Change in uveitis activity post phacoemulsification by measuring rate of uveitis relapse and use of topical and systemic steroids. Also, to measure the risk of vision loss and macular oedema post surgery.

Results: Over a median follow up time of 6.7 years or 2249 Eye-Years [EY], pseudophakic eyes had a greater risk of vision loss (hazard ratio [HR] 2.4, C.I. 1.4-4.0; $p<0.001$) and macular oedema (HR 2.2, C.I. 1.4-3.4, $p<0.001$) compared to the phakic uveitis group. Over five years, there was a reduction in the annual rate of uveitis relapses (-1.2, 95% C.I -2.0 to -0.2, $p=0.012$) following cataract surgery compared to the same period prior to surgery with no significant change in the annual rate of using topical and systemic prednisolone >7.5mg/day.

Conclusions and Relevance: There was no significant increase in uveitis relapse rate over the long term post phacoemulsification compared to the time before surgery with the use of current prophylactic inflammation control measures.

KEY WORDS: Uveitis, phacoemulsification, vision impairment, cataract surgery

Introduction:

Cataract is one of the most common complications associated with uveitis, seen in up to 50-78% of patients and is the leading cause of vision loss in uveitis [1,2]. It is more common in eyes with chronic anterior uveitis such as Fuchs' heterochromic iridocyclitis, juvenile idiopathic arthritis as well as intermediate uveitis [3,4]. In a study involving 1799 eyes with uveitis, 474 (26%) required cataract surgery in an average of 7.5 years from the time of uveitis diagnosis [1]. Cataract surgery in the setting of uveitis can be associated with additional challenges and risks due to the higher incidence of postoperative complications [5]. In a prospective study, eyes with active uveitis within three months prior to cataract surgery had a higher risk of postoperative macular oedema, a risk which was significantly reduced upon the use of short course of oral corticosteroids few days prior to surgery [6].

While there have been several studies looking at the visual outcome of uveitic eyes following cataract surgery [7], few have explored the long term effect of cataract surgery on the rate of uveitis relapse and the use of topical and systemic immunosuppressants. The aim of this study was to assess the long-term visual outcome and ocular complications in uveitic eyes post cataract surgery and the influence of cataract surgery on uveitis activity through examining changes in the rate of uveitis relapse and the use of topical and systemic corticosteroids.

Materials and methods:

The initial stage of the research involved reviewing hospital case notes of all patients with uveitis who attended the tertiary clinic of a single consultant (S.L.) at Moorfields Eye Hospital, London, United Kingdom, between January 2012 and December 2013. This clinic treats patients form both secondary referrals and primary care cases. [1]. The study followed the Tenets of the Declaration of Helsinki and received institutional review board approval

(ethical approval for data collection: ROAD16039, visual loss in uveitis; Clinical Trials registry no., NCT01983488). Using a database of 1907 eyes, of 1169 patients, with uveitis we included eyes if they were non-infectious uveitis, had cataract surgery using phacoemulsification with intraocular lens (IOL) insertion and a minimum follow-up period of one year prior to and following surgery. Exclusion criteria included infectious causes of retinitis or choroiditis, extracapsular cataract extraction, aphakia and history of vitrectomy or retinal detachment prior to cataract surgery. As a control group we included phakic uveitis eyes in order to address the impact of cataract surgery on eyes with uveitis.

Uveitis was classified based on the Standard Uveitis Nomenclature (SUN) Working Group classification of uveitis as anterior, intermediate, posterior and panuveitis [8]. Demographic data as well as time of uveitis diagnosis and the interval to cataract surgery was noted. Patients with any documented history of CMO during their follow-up, or a diagnosis of non-infectious panuveitis, are considered to have an increased risk of postsurgical flare. Therefore these patients were given pre or peri-operative prophylactic steroid cover. [9] When indicated, prophylaxis treatment was given in the form of oral prednisolone at a dose of 40mg per day for two weeks prior to surgery and then tapered down postoperatively according to the inflammation status. In cases where systemic prednisolone use was not applicable, an alternative prophylaxis method was used in the form of intravitreal triamcinolone acetonide (IVTA) at time of surgery except for cases known to be steroid responders or at risk of increased intraocular pressure (IOP) [9].

All patients had their best corrected visual acuity (BCVA) measured while looking through a pinhole or with patient's glasses prescription and the result was recorded in Snellen acuity format. For the purpose of longitudinal data analysis, the BCVA measurements were converted from Snellen acuity into the negative value of the decadal logarithm of the minimal angle of resolution (LogMAR) [10]. In the pseudophakic eyes, change in BCVA from the

baseline (1st week postoperative vision) was measured during 1 month, 3 months, 6 months, and 12 months postoperatively and then annually afterward until last visit. Vision loss was defined as BCVA ≤6/15 according to the SUN working group criteria [8].

Uveitis relapses in this study were defined as the presence of active inflammation which required an administration or increase in local or systemic immunosuppressive therapy. Uveitis relapse rates were calculated by counting the number of relapses per eye per year (EY) [11]. The rate of using topical and systemic corticosteroids were measured by counting the number of months being on treatment per EY [12,13]. Intraoperative complications such as posterior capsule rupture and the need for anterior vitrectomy were documented if present.

Postoperative complications were also noted including cystoid macular oedema (CMO), posterior capsular opacity (PCO) and the date of capsulotomy if done, elevated IOP >30mmHg, hypotony, and any other sight threatening complications. The presence of CMO within the first three months postoperatively and over the follow-up period was also documented. This was mainly based on the optical coherence tomographic (OCT) findings of central retinal thickness of >300μm and the presence of low-reflective intraretinal spaces [14]. For cases with no available OCT scans, the presence of CMO was based either on the presence of significant macular leakage during late stage fundus fluorescein angiography or based on clinical examination findings as described in patient's notes.

Continuous data are presented as median and interquartile range (IQR), whereas categorical data are presented as proportions. Repeated measurement analysis of BCVA was done using a multivariate linear regression method obtained from the generalized estimating equation (GEE) test. The hazard ratio (HR) and 95% confidence interval (C.I.) for vision loss and CMO was measured using Cox proportional hazards regression analysis. The incidence rates

per EY for uveitis relapse and use of topical and systemic corticosteroids were calculated using negative binominal regression with log link model.

Results

We identified 1907 eyes with uveitis from electronic database of which 619 eyes (32.5%) had cataract surgery. A total of 246 psedophakic eyes were excluded mainly due to a short follow-up or, past history of retinal detachment, infectious posterior uveitis, aphakia and those underwent vitrectomy or extracapsular cataract extraction. In addition, clinical notes from 32 patients were inaccessible and had to be excluded.

A total of 309 eyes from 217 patients were included in the study. A control group of 300 phakic eyes (210 patients) were randomly selected from the uveitis cohort for comparison with the pseudophakic group. The clinical and demographic data of both case and control groups is presented in Table 1. The median follow-up time for pseudophakic eyes post surgery was 6.7 years or 2249 EY, which was not different from the control group (5.8 years, p=0.052). The median time from uveitis diagnosis to cataract surgery was 6 years (IQR 3.2-13.3). Prophylactic corticosteroid cover prior or during cataract surgery was administered in 195 eyes in the form of systemic prednisolone (39.4%) or IVTA (24.1%).

The median BCVA in the two months prior to cataract surgery was 0.60 LogMAR (IQR 0.30-1.00). This improved significantly in the 1st postoperative week to a median BCVA of 0.18 LogMAR (IQR 0.18 – 0.30, p<0.001). The majority of eyes (93%) managed to achieve more than 2 Snellen lines improvement in BCVA following cataract surgery when compared to the preoperative vision. The average change in the BCVA from the 1st week postoperatively (baseline) continued to be significantly better even up to 5 and 10 years follow-up postoperatively (Figure 1).

The incidence rate of persistent vision loss post cataract surgery was 0.02/EY and occurred at a median of 19.6 months post cataract surgery in 58 pseudophakic eyes (18.8%) compared to 22 phakic eyes (7.4%) from the control group. Among the 80 pseudophakic eyes with CMO, 24 eyes (35%) were associated with persistent vision loss and accounted for 41.4% of eyes with vision loss. Other causes of vision loss included retinal pigment epithelial atrophy in 17 eyes (29.4%), epiretinal membrane in 6 eyes (10.3%), advanced glaucoma in 5 eyes (8.6%), retinal detachment in 3 eyes (5.1%), optic neuropathy in 2 eyes (3.4%) and corneal decompensation in 1 eye (1.7%). The pseudophakic uveitic eyes had a greater risk of vision loss compared to the control group (HR 2.4, C.I 1.4- 4.0; p<0.001). CMO was associated with a two fold increase in the risk of vision loss in pseudophakic eyes compared to eyes without incidence of CMO and such risk persisted even after adjusting for the presence of other risk factors for vision loss (HR 2.1, C.I 1.1- 3.9, p = 0.01) (Table 2).

Over the follow-up period, the incidence rate of CMO in pseudophakic eyes was 0.03/EY and occurred at a median of 5.3 months (IQR 1.4 – 21.7) following surgery. Of the 80 eyes (26.9%) that had CMO over follow up period, 33 (10.6%) occurred within the first three months postoperatively. The risk of CMO in pseudophakic eyes was found to be twice that of the control group (HR 2.2, C.I. 1.4 – 3.4, P<0.001). Previous history of CMO prior to cataract surgery was associated with an increased risk of developing CMO in pseudophakic eyes (HR 2.3, 95% C.I 1.4- 3.7, p<0.001). Prophylactic corticosteroid cover was given prior to surgery in 197 eyes (63.7%), in the form of either systemic prednisolone 40mg /day for two weeks preoperatively in 123 eyes (62.5%), or IVTA for 74 eyes (37.5%). There was no significant correlation between type of prophylactic corticosteroid cover and the incidence of postoperative CMO (HR 1.52, 95% C.I 0.82- 2.80, p=0.17). When examining the subgroup of 118 eyes with a history of CMO prior to surgery, 109 eyes (92.4%) who received prophylaxis

steroid cover had a reduced risk of vision loss compared to those not receiving prophylaxis therapy (HR 0.22, 95% C.I 0.06 – 0.80, p= 0.02).

The incidence rate of high IOP>30mmHg in pseudophakic eyes was 0.01/EY. PCO occurred in 104 eyes (33.7%) at a median of 8 months (IQR 4.8 – 38 months) post cataract surgery and required capsulotomy within a median of 15 months (IQR 5.5 to 54 months) post cataract surgery. Other intraoperative and postoperative complications include IOL subluxation/dislocation in four eyes (1.3%), hypotony in two eyes (0.6%), sterile endophthalmitis with intraoperative IVTA use in two eyes (0.6%), corneal decompensation in one eye (0.3%), and retinal detachment in one eye (0.3%). Intraoperative rupture of posterior capsule occurred in one eye (0.3%) and resulted in dropped nucleus.

When examining the average number of uveitis relapses (Figure 2), we found that the median number of relapses within the first year following cataract surgery did not differ significantly from the same preoperative period (-0.01, 95% C.I -0.3 – 1.2, p= 0.50, Poisson loglinear model). This changed when looking at the annual rate of relapses over 5 years pre surgery (median 0.4 relapse/EY, IQR 0.0 – 1.0) compared to the same period post surgery (median 0.2 relapse/EY, IQR 0.0 – 0.6) with a significant reduction in the annual number of relapses/EY following surgery by an average of -1.2, 95% C.I -2.0 to -0.2, p=0.012.

The annual rate of using topical corticosteroid drops did not vary significantly in the year following cataract surgery compared to the year preceding it, and remained steady throughout 5 years of follow-up. Meanwhile, the annual rate of using maintenance dose of systemic corticosteroids at a dose $\leq$ 7.5 mg/day was increased over one (0.25 months/EY, 95% C.I 0.02 to 0.4, p=0.02) and five years (0.6 months/ EY, 95% C.I 0.2 to 0.9, p=0.002) following cataract surgery compared to the same period prior to surgery (Table 3).

During the time up to cataract surgery, 170 eyes (40.0%) required high dose of systemic corticosteroids. Following surgery, this was significantly decreased to 107 eyes (21.7%, p=0.007, McNemar test) over follow-up period post surgery. This did not include prophylactic corticosteroids given prior to surgery and reduced over postoperative period. Likewise, immunomodulatory agents were initiated in 46 eyes (14.9%) during the time up to cataract surgery compared to only 18 eyes (5.8%) that were started during follow-up period post surgery (p<0.001, McNemar test).

Discussion

This study examined the influence of cataract surgery on the visual outcome and the uveitis activity following cataract surgery. The results showed that (1) Pseudophakic eyes had a higher risk of vision loss and CMO compared to a control group of phakic uveitic eyes. (2) CMO increased the risk of vision loss by two folds in pseudophakic uveitic eyes. (3) Cataract surgery was associated with a lower uveitis relapse rate over five years following surgery compared to the five years prior to surgery.

The risk of vision loss in our pseudophakic uveitis cohort was significantly more compared to the control group of phakic uveitic eyes. This risk was strongly associated with the occurrence of CMO and despite no significant increase in the rate of uveitis relapses following surgery. This suggests that cataract surgery on its own can be associated with an increased risk of vision loss secondary to CMO, a complication which was more associated with the pseudophakic group when compared to phakic uveitic eyes. This is supported by a recent multi-centered study in the UK of 81984 eyes that underwent cataract surgery, which concluded that CMO occurs commonly after phacoemulsification cataract surgery, even in the absence of complications and risk factors such as diabetes and uveitis.[15] It should also be acknowledged though that the worse visual outcome in our pseudophakic eyes' cohort is

attributed to the likelihood of cataract occurring in patients with more severe forms of uveitis with a greater tendency to develop sight threatening complications than phakic uveitis patients. Additional information regarding surgical technique and intra-operative findings, such as iris manipulation, synechiolysis or compromised lens capsule, may further impact on the incidence of post-operative CMO. However, the limited numbers reported in this study were not sufficient enough for the analysis. Furthermore, our control group included diverse aetiologies and does not reflect the specific risk related to certain conditions, such as Fuch's heterochromic iridocyclitis and multifocal choroiditis.

In our study, the rate of CMO post cataract surgery was 26.9%, including 28.4% of eyes with intermediate uveitis that had CMO post surgery. This is in agreement with previous report on the rate of CMO following cataract surgery in eyes with pars planitis which has been reported to range from 12 to 59% [16]. We also found that a previous history of CMO preoperatively in eyes with uveitis can be associated with a 2.5 fold increase in the risk of CMO postoperatively. This conclusion has been similarly drawn by Agrawal *et al.* who suggested an increased risk of developing CMO postoperatively in eyes with previous episodes prior to surgery [17]. The frequency and timing of other postoperative complications such as PCO and the need for capsulotomy has been measured in this study as it can have an impact on the length and frequency of follow-up needed following surgery in such patients.

Postoperative relapse rates can vary widely according to the aetiology and anatomic type of uveitis, ranging between 5% [9] and 41% [18]. In our cohort the annual rate of uveitis relapse following cataract surgery was lower compared to the period prior to surgery. Interestingly, this was combined with an increased rate of using systemic corticosteroids after surgery, possibly used to counter the risk of CMO following surgery, but also affecting the lower relapse rate.

To our knowledge there have not been previous studies looking at the rate of using systemic and topical steroids over the time period prior versus post surgery to compare our results with. However, the reduced relapse rate following cataract surgery was observed in a study in Taiwan on 62 eyes with recurrent uveitis after excluding eyes with chronic uveitis in their analysis. They found the relapse rate of 0.48 relapses per year postoperatively to be significantly less when compared to the preoperative relapse rate of 1.32 relapses per year [19]. The lower relapse rate post cataract surgery compared to the period prior to surgery might reflect the natural trend of reduced uveitis activity over time. However, our results suggest that phacoemulsificaton surgery in uveitic eyes under the current management protocol does not increase the long-term rate of uveitis relapse. Those with prior history of CMO and received prophylactic steroid cover had less risk of vision loss following cataract surgery. The adequate control of inflammation prior to cataract surgery and the use of prophylactic steroid cover is crucial in preventing CMO and the associated risk of poor visual outcome [20]. This is supported by a previous meta-analysis by Mehta, et al., who concluded that patients with active inflammation at the time of cataract surgery had a worse visual outcome, highlighting the role of controlling inflammation for at least two months prior to cataract surgery. [7]

In conclusion, the risk of vision loss can be significantly higher in uveitic eyes undergoing cataract surgery when compared to phakic uveitic eyes, with CMO being a major risk factor. Such risk occurred in the absence of a significant increase in the rate of uveitis relapse. The role of CMO following cataract surgery as a major risk factor for vision loss in pseudophakic uveitic eyes reflects the need to provide adequate prophylactic measures in such cases. It also reflects the need to improve treatment strategies and to assign resources to better manage CMO in uveitic pseudophakic eyes.

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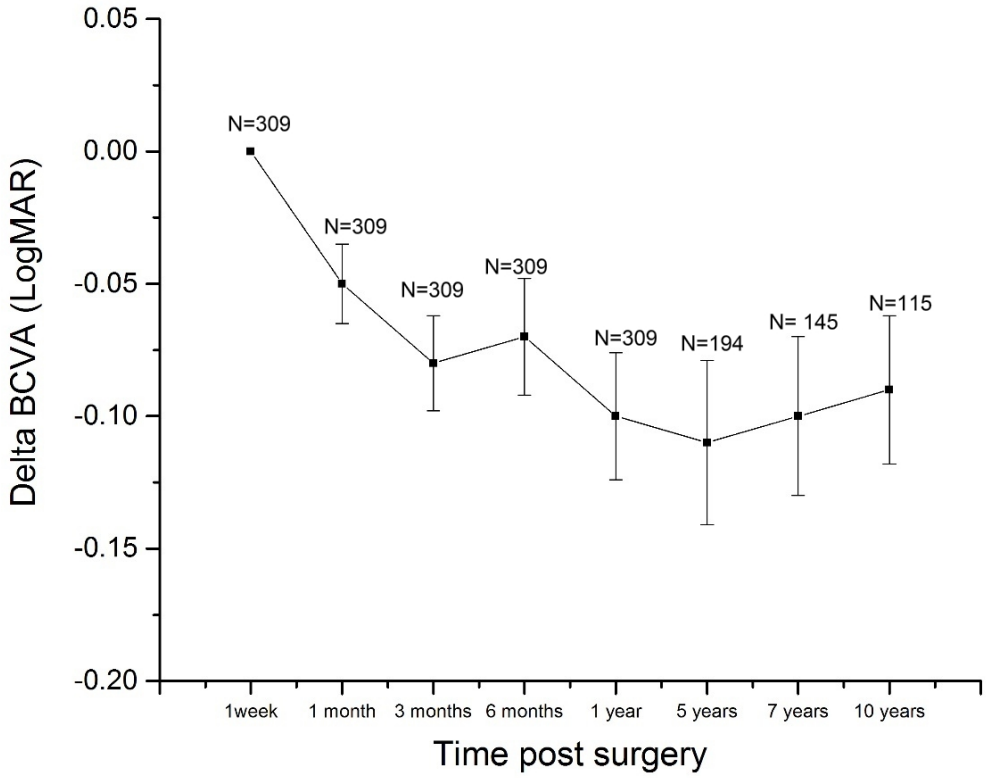

Figure 1 Mean changes (and standard error) in the best corrected visual acuity following cataract surgery from baseline (first postoperative week) in uveitic eyes. N=number of eyes.

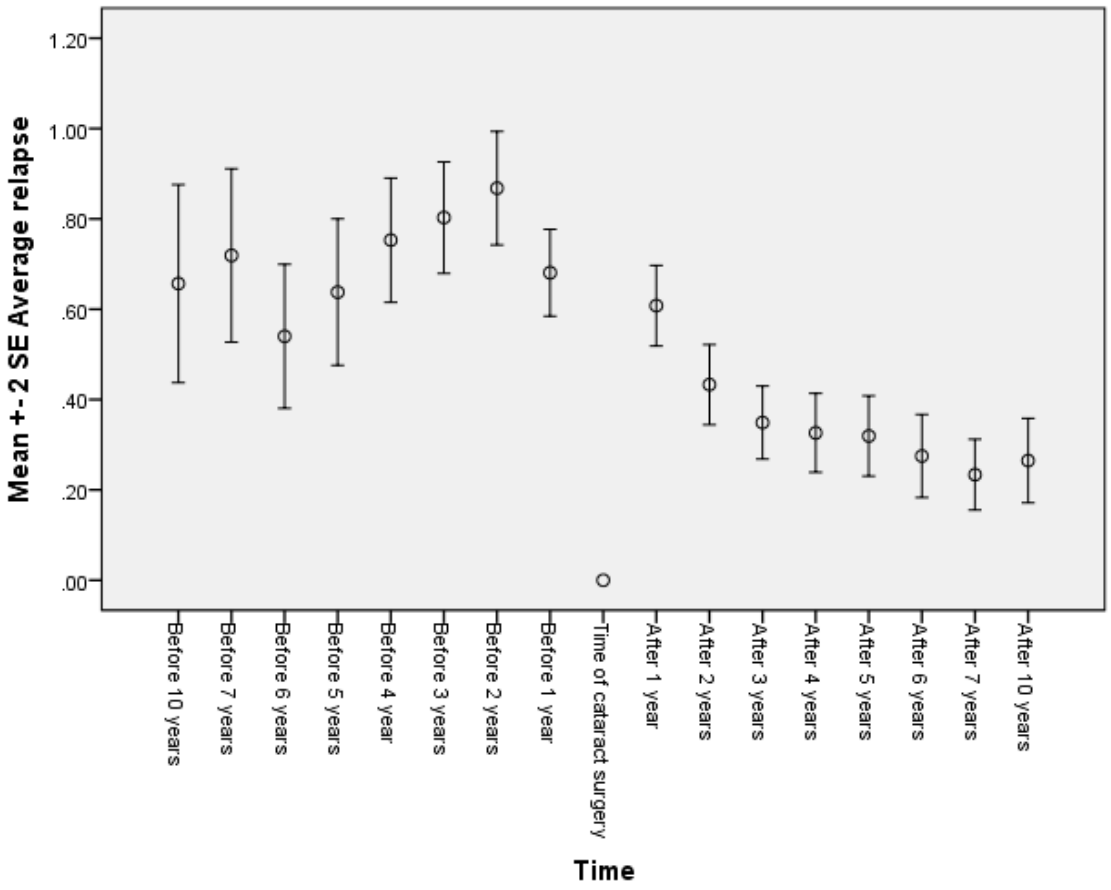

Figure 2 The mean and standard error bars of uveitis relapse over 10 years before and after cataract surgery.

Figure Legend

Figure 1 Mean changes (and standard error) in the best corrected visual acuity following cataract surgery from baseline (first postoperative week) in uveitic eyes. N=number of eyes.

Figure 2 The mean and standard error bars of uveitis relapse over 10 years before and after cataract surgery.

Table 1 Demographic and clinical characteristics of pseudophakic uveitic eyes and their phakic control group

Variables	Cases group 309 eyes, 217patients	Control group 300eyes, 210patients	P value*
Follow-up time, Median (IQR), Years	6.7 (3.9-10.6)	5.8 (3.0- 10.0)	0.052
Female; n patients (%)	136 (62.7)	127 (60.5)	0.35
BCVA LogMAR first visit, Median (IQR)	0.18 (0.00-0.48)	0.00 (0.00-0.30)	<0.001
BCVA LogMAR last visit, Median (IQR)	0.18 (0.00-0.30)	0.00 (0.00-0.18)	<0.001
Classification of uveitis; n eyes (%)			
• Anterior uveitis	96 (31)	114 (38)	0.23
• Intermediate uveitis	134(43.4)	92 (30.6)	
• Panuveitis	79 (25.6)	94 (31.4)	
Aetiological causes of uveitis; n eyes (%)			
• Idiopathic	147 (47.6)	220 (73.3)	
• Sarcoidosis	44 (14.2)	25 (8.3)	
• HLA-B27	35 (11.3)	15 (5)	
• Tuberculosis hypersensitivity	14 (4.5)	14 (4.7)	
• Behcet's disease	11 (3.6)	7 (2.3)	
• Fuchs' heterochromic iridocylitis	13 (4.2)	0 (0)	
• Multifocal choroiditis	12 (3.9)	0(0)	
• Herpes virus	9(2.9)	6 (2)	
• ANCA positive	6 (1.9)	2 (0.7)	
• Multiple sclerosis	8 (2.6)	0(0)	
• Rheumatoid arthritis	5 (1.6)	2 (0.7)	
• Vogt Koyanagi Harada syndrome	5 (1.6)	9 (3)	

N= number; SE= Standard error; IQR= Interquantile range; ANCA= Antinuclear cytoplasmic antibodies.

*p value tested using Mann-Whitney U test for continuous data, and Chi-square test for categorical data

Table 2 Risk factors for vision loss in pseudophakic eyes with uveitis

Variables	Crude HR (C.I)	P value*	Adjusted HR (C.I)	P value*
Female	0.94 (0.5-1.6)	0.85	-	-
Uveitis type				
- Anterior uveitis	-	-	-	-
- Intermediate uveitis	1.0 (0.50-1.9)	0.52	-	-
- Panuveitis	1.3 (0.69-2.6)	0.08	-	-
Prophylaxis treatment				
- None	-	-	-	-
- Systemic steroids	0.73 (0.37 – 1.4)	0.36	-	-
- IVTA	0.83 (0.5 – 1.73)	0.83	-	-
Macular oedema pre surgery	1.90 (1.12 – 3.2)	0.01	1.5 (0.92-2.7)	0.09
Macular oedema post surgery	2.4 (1.36-4.5)	0.003	2.1 (1.1- 3.9)	0.016
IOP>30mmHg pre surgery	1.59 (0.93-2.7)	0.05	1.6 (0.94-2.8)	0.07
IOP>30mmHg post surgery	2.0 (1.18– 3.5)	0.01	1.7 (1.0- 3.1)	0.045
Posterior capsular Opacity	0.79 (0.46- 1.3)	0.39	-	-
Systemic steroids post surgery	1.8 (1.08-3.2)	0.02	0.88 (0.4-1.8)	0.74
IMM use post surgery	2.7 (1.2-6.1)	0.01	2.8 (1.08-7.4)	0.03

C.I.= Confidence Interval; IVTA= Intravitreal Triamcinolone acetonide; IOP = Intraocular pressure; IMM= Immunomodulatory agents

* Hypothesis tested using Cox regression analysis.

Table 3 Changes in the rate of using topical and systemic steroids after cataract surgery in eyes with uveitis

Treatment	Time	No. Eye	The mean (SE) rates of medication use (no. months/EY) Preoperative	Postoperative	Rate Difference* (95% C.I)	P†
Steroid drops >3	1 year	309	1.0 (0.1)	1.0 (0.1)	0.08 (-0.12 -0.23)	0.53
times/day	5 years	130	0.6 (0.1)	0.5 (0.06)	- 0.84 (-1.7-0.05)	0.06
Steroid drops ≤3	1 year	309	5.8 (0.3)	5.7 (0.3)	0.04 (-0.15 - 0.24)	0.64
times/day	5 years	130	5.0 (0.4)	5.0 (0.3)	0.11 (-0.3 - 0.55)	0.61
Prednisolone	1 year	309	1.1 (0.2)	1.0 (0.2)	-0.13 (-0.38-0.12)	0.31
>7.5mg/day	5 years	130	0.4 (0.1)	0.6 (0.1)	-1.1 (-2.0 - -0.3)	**0.007**
Prednisolone	1 year	309	1.7 (0.3)	2.2 (0.3)	0.25 (0.02-0.47)	**0.02**
≤7.5mg /day	5 years	130	1.3 (0.3)	2.1 (0.3)	0.59 (0.21-0.97)	**0.002**

* After versus before surgery
† A negative binominal regression with log link model was used when the data did not fit the Poisson model satisfactorily
EY = Eye per year. C.I = Confidence Interval, SE= Standard error