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Assessment of the effect of cyclosporine-A 0.05% emulsion on the ocular surface and corneal sensation following cataract surgery

Samer Hamada[a,b,c], Tara C.B. Moore[a], Jonathan E. Moore[a,d], Madonna G. Al-Dreihi[e], Anas Anbari[c,e], Sunil Shah[a,b,f,*]

[a] School of Biomedical Sciences, University of Ulster, Coleraine, NI, UK
[b] Birmingham and Midland Eye Centre, Birmingham, UK
[c] Corneo Plastic Unit and Eye Bank, Queen Victoria Hospital, East Grinstead, UK
[d] Cathedral Eye Clinic, Belfast, NI, UK
[e] Manar International Hospital, Damascus, Syria
[f] Midland Eye, Solihull, UK

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ABSTRACT

Aim: To assess the effect of cyclosporine-A (CsA) 0.05% ophthalmic emulsion on corneal sensation and ocular surface problems following cataract surgery.
Design: Prospective, randomized, double masked clinical trial.
Methods: Consecutive case series of patients attending for bilateral cataract surgery. Subject's eyes were randomized to receive either topical CsA or carboxymethylcellulose 0.5% (CMC) eye drops twice daily for one month following routine cataract surgery. Subjective and objective assessments were performed pre-operatively, one week, and one month after surgery. Primary safety parameters included best spectacle-corrected visual acuity and incidence of adverse events. Objective assessments included tests of tear film (osmolarity, tear break-up time, and Schirmer's type-I test), ocular surface staining, corneal sensitivity and a subjective assessment: ocular surface disease index (OSDI) questionnaire.
Results: 30 subjects (60 eyes) were recruited. At one month following cataract surgery, osmolarity, ocular surface staining, TBUT, Schirmer's results showed a greater improvement after CsA drops compared to CMC and this was statistically significant for all measures ($p < 0.05$). All corneal sensation measurements were reduced after one week and one month. Eyes receiving CsA had higher recovery of corneal sensation at both time points post operatively and this was statistically significant at one month. OSDI questionnaire results did not show a statistically significant difference between the two eyes.
Conclusions: CsA is effective and safe in the management of ocular surface problems after cataract surgery and allows faster recovery of corneal sensation. This recovery of sensation may be relevant to the improvement in ocular surface problems in all patients.

1. Introduction

Recent advances in ophthalmology, in particular those relating to cataract surgery have led to an increasing focus on the qualitative outcomes of cataract surgery. Measurement of patient's satisfaction after cataract surgery now includes not only the visual outcomes but also ocular comfort and the patient's experience of surgery [1].

The occurrence of dry eye in the first few months following cataract surgery has been frequently reported [2,3]. Several factors could exacerbate a dry eye condition or lead to a new transient status of dry eye in patients following cataract surgery including disruption of corneal nerves [4], ocular surface toxicity from topical ophthalmic medications [5,6], and the surgical procedure itself [7]. Khanal et al. described a deterioration in corneal sensitivity and tear physiology immediately after small incision cataract surgery, which does not return to preoperative levels until three months postoperatively, whereas the tear function recovers within one month [3]. Lyne has also demonstrated anaesthesia in the upper half of the cornea even after one year [8].

Suboptimal visual outcomes in the period immediately after cataract surgery (particularly with premium intraocular lenses) are

* Corresponding author at: Midland Eye, 50 Lode Lane, Solihull, West Midlands B91 2AW, UK.
E-mail address: sunilshah@doctors.net.uk (S. Shah).

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sometimes felt to be related to a dry ocular surface and tear film instability with the presence of superficial corneal punctate erosions [2].

Topical cyclosporine-A (CsA) is an immunomodulator and anti-inflammatory agent. It is a fungal peptide which inhibits expression of various immune mediators such as Interleukin (IL) 2, IL-4 and Interferon (IFN) gamma, and through interaction with T cells inhibits lymphocyte proliferation [9]. In doing so CsA may well protect the goblet cell, a key player in providing a healthy ocular surface [10]. Studies have confirmed increased numbers of goblet cell in patients using topical CsA [11]. CsA has been shown to improve dry eye symptoms by restoring the tear film equilibrium and volume in dry eye patients [12].

The aim of this study was to assess the safety and efficacy of topical CsA ophthalmic emulsion used after cataract surgery to improve the ocular surface and hence surgical outcomes, and also to explore the possibility of CsA accelerating the recovery of corneal sensation.

2. Materials and methods

Full ethical approval was obtained from the University of Ulster and procedures carried out were in accordance with the ethical standards of the local Research Ethics Committee and with the Declaration of Helsinki.

A prospective, randomized, double masked, single-centre clinical trial recruited a consecutive case series of 30 subjects attending a tertiary referral eye centre for bilateral cataract surgery. Subjects included adults with cataract with normal lid position and closure and no known ocular disease. Informed consent was obtained from all subjects after discussion of the risks and possible consequences of the study.

A thorough history was taken to ensure that any subject with potential contra-indications to the study medication was excluded. Those with ocular surface disease, systemic or an ocular disorder that could possibly interfere with the interpretation of study results, prior usage of CsA or a systemic or topical steroidal or non- steroidal anti-inflammatory drugs during the previous 90 days before surgery, or had complicated surgery were also excluded from the study.

Subjects were randomized, via a computer-generated randomization schedule, into two treatment groups. The first group received topical CsA 0.05% ophthalmic emulsion (Restasis®, Allergan Inc., Irvine, CA) twice daily for one month following surgery in the first eye undergoing cataract surgery. The second group used carboxymethylcellulose 0.5% (CMC) preservative free (Refresh Plus®, Allergan Inc., Irvine, CA) drops on the same regimen following cataract surgery in the first eye to be operated. After a minimum of two months, the second eye of each subject underwent cataract surgery and received the other drop i.e. if first eye had received CsA then the second eye had CMC; and vice versa.

In both groups, subjects used CsA or CMC in addition to the standard postoperative treatment. Both Restasis® and Refresh Plus® look the same and have similar vials and the drugs labelling was masked in both groups.

All patients underwent standard small incision cataract surgery by the same surgeon, whereby the corneal incision was made in the

Table 1
Outcomes comparing all parameters between the CMC eyes and CsA eyes.

	Parameter	CMC (Mean ± SD)	CsA (Mean ± SD)	*P*-value
Pre-op	BSCVA (LogMAR)	0.8 ± 0.6	0.6 ± 0.5	0.17
	Osmolarity (mOsmol/L)	304.6 ± 20.2	306.6 ± 19.1	0.06
	TBUT (seconds)	7.1 ± 4.3	7.3 ± 4.5	0.87
	Staining	0.3 ± 0.5	0.4 ± 0.6	0.66
	Schirmer's 1 Test (mm)	17.0 ± 8.1	15.3 ± 6.7	0.26
	Sensation Central (mm)	4.4 ± 1.2	4.3 ± 1.1	0.71
	Sensation Q1 (mm)	4.2 ± 1.2	4.0 ± 1.2	0.54
	Sensation Q2 (mm)	4.4 ± 1.1	4.2 ± 1.3	0.49
	Sensation Q3 (mm)	4.4 ± 1.1	4.3 ± 1.3	0.51
	Sensation Q4 (mm)	4.3 ± 1.2	4.2 ± 1.2	0.59
	OSDI	38.7 ± 13.2	40.3 ± 12.3	0.17
One week post-op	Osmolarity (mOsmol/L)	318.6 ± 22.7	300.6 ± 13.7	<0.01*
	TBUT (seconds)	5.8 ± 3.1	8.3 ± 3.2	0.01*
	Staining	0.6 ± 0.9	0.2 ± 0.4	0.04*
	Schirmer's 1 Test (mm)	14.1 ± 5.9	17.6 ± 5.0	<0.01*
	Sensation Central (mm)	3.5 ± 1.5	3.6 ± 1.3	0.70
	Sensation Q1 (mm)	2.0 ± 1.3	2.5 ± 1.5	0.26
	Sensation Q2 (mm)	3.7 ± 1.2	3.4 ± 1.6	0.49
	Sensation Q3 (mm)	4.1 ± 1.1	4.2 ± 1.1	0.63
	Sensation Q4 (mm)	4.0 ± 1.1	4.1 ± 0.9	0.81
One month post-op	BSCVA (LogMAR)	0.3 ± 0.4	0.2 ± 0.4	0.49
	Osmolarity (mOsmol/L)	312.3 ± 24.1	298.7 ± 20.7	0.01*
	TBUT (seconds)	7.4 ± 3.9	9.6 ± 4.1	0.02*
	Staining	0.9 ± 1.3	0.3 ± 0.7	0.04*
	Schirmer's 1 Test (mm)	15.6 ± 7.7	20.0 ± 6.8	0.02*
	Sensation Central (mm)	3.5 ± 1.2	4.1 ± 1.1	0.03*
	Sensation Q1 (mm)	2.2 ± 1.3	2.9 ± 1.2	0.03*
	Sensation Q2 (mm)	3.5 ± 1.0	4.2 ± 0.9	0.01*
	Sensation Q3 (mm)	4.2 ± 1.1	4.1 ± 1.2	0.73
	Sensation Q4 (mm)	4.2 ± 1.1	4.2 ± 1.2	0.80
	OSDI	19.1 ± 16.6	13.6 ± 15.4	0.17

CMC: Carboxymethylcellulose.
CsA: Cyclosporine-A.
BSCVA: Best Spectacle Corrected Visual Acuity.
Corneal sensation was measured in all four quadrants (Q1 superotemporal, Q2 superonasal, Q3 inferotemporal, and Q4 inferonasal) and the centre of the cornea (central).
Corneal surgical incision was at the10 o'clock position (Q1).
OSDI: Ocular Surface Disease Index.
SD: Standard deviation.
* Denotes significance at $p < 0.05$.

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superotemporal quadrant of the right eye and the superonasal quadrant of the left eye. The postoperative care was identical in all patients and consisted of topical moxifloxacin hydrochloride 0.5% (VIGAMOX® Alcon Laboratories, Inc., Fort Worth, Texas) four times daily for two weeks, and dexamethasone sodium phosphate 0.1% (MAXIDEX® Alcon Laboratories, Inc., Fort Worth, Texas) four times daily for one week and then tapering to three times a day for one week, twice a day for one week, and finishing by once a day for one week (this was the standard regimen for the surgeon). CsA/CMC eye drops were used as an adjunctive rather than sole treatment.

All patients underwent a full clinical examination preoperatively and at one week and one month after surgery. In addition to the routine examination, the following tests were performed:

a Tear film assessment: tear osmolarity using the Tearlab osmolarity system (Tearlab, San Diego, CA) and a Schirmer's type I test.
b Ocular surface status using the Oxford staining index.
c Corneal sensitivity measurements with a Cochet–Bonnet Aesthesiometer (Luneau Ophthalmology, Paris, France). Measurements were taken at five different areas within each cornea: the four quadrants (Q1: superotemporal, Q2: superonasal, Q3: inferotemporal, and Q4: inferonasal) and the centre of the cornea (C).

Patients were also asked to complete the OSDI questionnaire [13] at baseline and then one month after surgery.

2.1. Statistical analysis

Descriptive statistics and various statistical tests were performed using SPSS (SPSS Inc, Chicago, IL Version 20.0). Paired *t*-test between eyes for osmolarity was performed. Ordinal data like the Oxford grading scale was assessed using the Kruskal–Wallis test. For the OSDI, the Mann–Whitney test was performed. *P* value of less than 0.05 was considered to be statistically significant.

3. Results

The study enrolled 30 subjects (60 eyes) with a mean age of 64.5 years +/−11.3 years standard deviation (SD) with a range of 23–80 years. 19 subjects were female and 11 male. 12 right eyes and 18 left eyes received CsA eye drops with the contra lateral eye receiving CMC eye drops in addition to the standard regimen of drops.

The results preoperatively and at one week and one month postoperatively are detailed in Table 1.

3.1. Safety

Mean best spectacle corrected visual acuity (BSCVA) was 0.80 ± 0.62 LogMar preoperatively and improved to 0.30 ± 0.43 LogMar one month after surgery in the CMC eyes. In the CsA eyes, BSCVA improved from 0.60 ± 0.54 LogMar to 0.22 ± 0.40 LogMar one month after cataract surgery. None of the eyes lost any BSCVA.

No complications or side effects were reported at any stage during the study including allergy or intolerance to any of the products used in the study.

3.2. Objective assessment of efficacy

1) Tear film assessment
   a. Osmolarity
      i. In the eyes that received CsA, tear osmolarity decreased from 306.6 ± 19.1 to 300.6 ± 13.7 mOsmol/L at one week and 298.7 ± 20.7 mOsmol/L at one month as shown in Fig. 1.
      ii. In the eyes that received CMC, tear osmolarity increased from 304.6 ± 20.2 to 318.6 ± 22.7 mOsmol/L and 312.3 ± 24.1 mOsmol/L after one week and one month, respectively. The difference between CsA and CMC eyes was statistically significant at both 1 week and 1 month (Table 1).
   b. Tear break up time
      i. TBUT values increased in the CsA eyes from 7.3 ± 4.5 s (s) to 8.3 ± 3.2 s after one week and to 9.6 ± 4.1 s after one

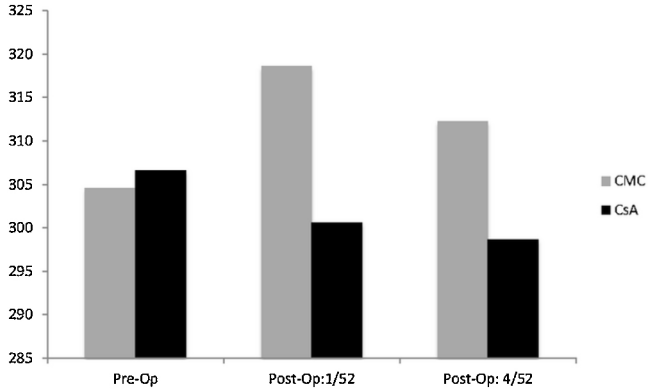

Fig. 1. Osmolarity values before and after cataract surgery (one week and one month) in both CsA and CMC groups.

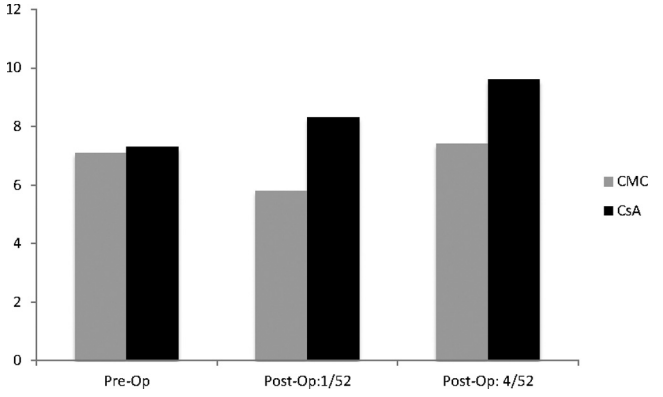

Fig. 2. Tear film break-up time before and after cataract surgery (one week and one month) in both CsA and CMC groups.

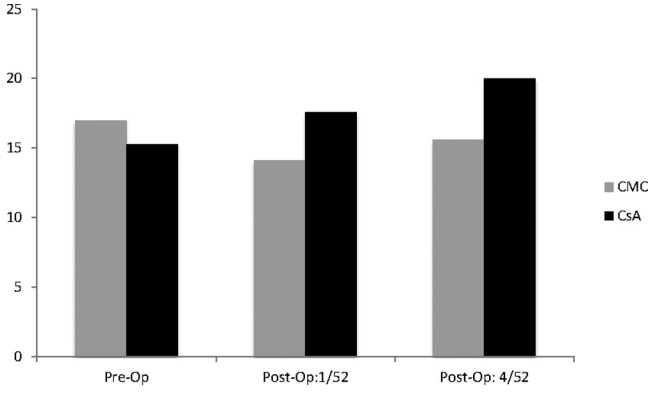

Fig. 3. Schirmer's I test before and after cataract surgery (one week and one month) in both CsA and CMC groups.

month, but in CMC group they reduced from 7.1 ± 4.3 s to 5.8 ± 3.1 s at one week and then increased to the preoperative values at one month (7.4 ± 3.9 s) (Fig. 2). The difference between CsA and CMC eyes in mean TBUT was statistically significant at both time points (Table 1).

c. Schirmer's type 1 test
   i. Schirmer's values increased from 15.3 ± 6.7 millimetres (mm) to 17.6 ± 5.0 mm and 20.0 ± 6.8 mm after one week and one month, respectively, with CsA as shown in Fig. 3. The values reduced from 17.0 ± 8.1 mm to 14.1 ± 5.9 mm and 15.6 ± 6.8 mm at the same time points postoperatively with CMC. The difference between CsA and CMC eyes was statistically significant at both time points (Table 1).

2) Oxford staining index
   a. The ocular surface staining index decreased from 0.4 ± 0.6 to 0.2 ± 0.4 and 0.3 ± 0.7, after one week and one month respectively, with CsA (Fig. 4). In contrast, the values in the CMC group increased from 0.3 ± 0.5 to 0.6 ± 0.9 and 0.9 ± 1.3 after one week and one month, respectively. The difference between CsA and CMC eyes was statistically significant at all postoperative time points (Table 1).
3) Corneal sensitivity measurements
   a. All corneal sensation measurements were reduced at one week and one month post surgery, in particular centrally and in Q1 and Q2. However, recovery of corneal sensation was noticeably different between the CsA and CMC eyes and the difference in recovery of corneal sensation was statistically significant for the measures within the central cornea, Q1 and Q2 in CsA eyes at one month (Table 1).

3.3. Subjective assessment of efficacy

The OSDI questionnaire [13] (scoring: 100 = Complete disability; 0 = No disability) results showed better scoring postoperatively in the CsA group (preoperative scores were 40.3 ± 12.3 and 38.7 ± 13.2 in the CsA and CMC groups, respectively, which decreased after one month of treatment to 13.6 ± 15.4 and 19.1 ± 16.6) but subjective improvement was not statistically significant between the CMC and CsA eyes for this sample size.

4. Discussion

Dry eye after cataract surgery is a common complaint that has been described in numerous studies [4,5,6] but yet is rarely managed proactively [2]. Outcomes of cataract surgery can be improved by decreasing the symptoms of ocular dryness [2].

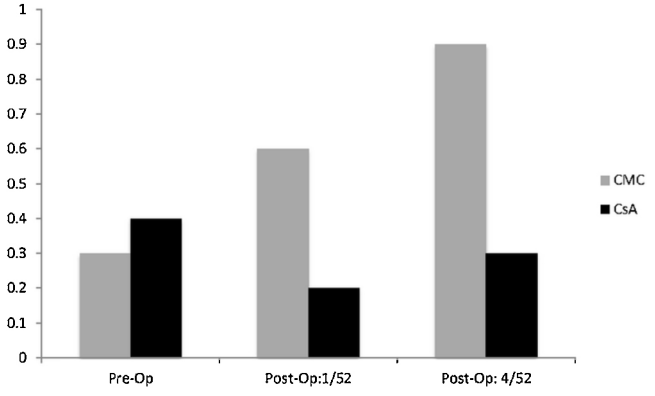

Fig. 4. Ocular surface staining (Oxford scoring system 0–5) before and after cataract surgery (one week and one month) in both CsA and CMC groups.

Topical CsA has been shown to be beneficial in various ocular surface conditions such as vernal keratoconjunctivitis, atopic keratoconjunctivitis, blepharokeratoconjunctivitis and dry eye [14]. Other studies [12] have reported that CsA improves the quality of vision in patients with dry eye and decreases their dependency on artificial tears. A large trial in dry eye patients comparing CsA with its vehicle showed that CsA significantly improved the signs and symptoms of dry eye [15]. A different and additional mechanism of action has also been postulated in a study by Peyman where treatment with CsA demonstrated an earlier recovery of corneal sensation after LASIK. This additional action of CsA may contribute to earlier recovery of dry eye symptoms [16].

We hypothesized that CsA may be effective on dry eye post cataract surgery and potentially on the recovery of corneal sensation. To test this hypothesis, we randomly assigned one eye of patients undergoing cataract surgery to receiving either CsA (treatment group) or CMC (control group as known to have corneal protective properties) as adjunctive treatment after cataract surgery. We used various objective and subjective parameters in assessing all subjects.

Objective assessment of ocular surface parameters showed that CsA was universally better than just lubrication in terms of tear film stability, aqueous tear production and ocular surface damage at one week and one month after cataract surgery ($p < 0.05$) (Figs. 2–4). This was despite only a twice daily dosage regimen with no pre-treatment.

At one week and one month post-op, there were more eyes with ocular surface damage i.e. Oxford ocular surface score 2, 3 and 4 in the lubricant drops group compared to CsA group. Moreover, there were more patients with no visible corneal changes at one-month post-op in the CsA group (87% of eyes) (Fig. 3).

An indicator of a healthy ocular surface after CsA is tear film osmolarity [17,18]. Osmolarity is felt to be one of the best single metrics, both to diagnose and classify dry eye disease. Lemp et al. have demonstrated that tear hyperosmolarity was of superior accuracy when compared to other single tests [17]. From meta-analysis data, the cut off reference of normal osmolarity is 316 mOsmol/L [18].

In this study, the average tear osmolarity prior to surgery was similar in the two groups (304.6 ± 20.2 in the CMC eye and 306.6 ± 19.1 in the CsA eye). Tear osmolarity was reduced after one month with CsA treatment to 298.7 ± 20.7 while it increased with CMC to 312.3 ± 24.1 (Fig. 1). Hence, subjects treated with ocular lubricants only, still had hyperosmolarity, indicative of dry eye one month after treatment, whilst those treated with CsA had near normal tear osmolarity.

CsA was also as effective as CMC in alleviating symptoms (rather than signs) of dry eye as evident by the outcomes of the OSDI questionnaire, although this was not statistically significant possibly because of the size of the study.

The incisions created during cataract surgery damage the cornea's neuro-architecture, reduce corneal sensation, and induce dry-eye disease. It has been postulated that there is a link between corneal innervation and aqueous tear production [19]. Damage to the sensory nerves in the ocular surface, specifically the cornea, prevents the normal reflex arc to the lacrimal gland and can result in decreased tear secretion and dry eye syndrome [20]. Significant correlations have been observed between the number of sub-basal nerves and the results of a Schirmer's test [21], and Rose Bengal staining of the cornea has been found to correlate positively with nerve density and negatively with beading. [22]

In this study, corneal sensation was reduced in both groups after surgery mainly in the central cornea and upper two quadrants (Q1 and Q2). The main corneal incision was always placed at the 10 o'clock position in Q1 and the side port 90 degrees away in the Q2. This suggests that surgical trauma to sub-epithelial nerve plexus

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may be responsible for the reduced corneal sensation. Recovery of corneal sensation as measured by the Cochet–Bonnet aesthesiometer was quicker in CsA group as demonstrated in Table 1 and this was statistically significant at one month. Whilst there was a tendency for quicker recovery even at 1 week, this did not reach significance. To our knowledge, this finding has never been reported before and could be of major significance given the numbers of cataract procedures performed worldwide each year.

No subjects treated with CsA lost best spectacle corrected visual acuity or reported side effects with CsA usage in this formulation. The use of CsA resulted in subjective and objective recovery of dry eye status. Similar findings have been reported when CsA was used after corneal laser refractive surgery [16], but this is the first description of the use of CsA in speeding up recovery of dry eye and corneal anaesthesia and hence potentially improving patient satisfaction after cataract surgery.

This is a preliminary study. One possible weakness is the small number in each group and short term follow up. CsA was only used for one month after surgery and potentially could be used for pre-treatment or at a higher frequency/concentration. In previous trials, CsA has sometimes been started before surgery or treatment extended to three months after surgery [16,23]. For patients convenience, in this preliminary study, we opted not to increase number of patient visits after cataract surgery and hence restricted to one month of treatment. Further studies with expanded usage of CsA in larger groups may be useful.

Another potential weakness of the study is that Restasis® has inactive ingredients in addition to CsA (glycerin; castor oil; polysorbate 80; carbomer copolymer type A; purified water; and sodium hydroxide to adjust pH). Castor oil has been reported to improve ocular surface in patients with meibomian gland dysfunction [24] and to increase tear film stability [25]. Our patients have no preexisting ocular surface disease. There is no direct comparison between CMC and Castor oil. We believe that the superior objective outcomes are attributable to the active CsA but further work would have to be done to confirm this. Although castor oil might prevent tear evaporation, there is no evidence that it has an effect on wound healing and corneal sensitivity. The control drop for this study (we used CMC) would ideally have comprised of the inactive portions of the CsA formulation used except castor oil. However, for the purposes of this preliminary study, we only used commercially available products. Future work could do exactly this or to use a formulation that was different from the one used for this study.

This study demonstrates that CsA is effective and safe in the management of dry eye status after cataract surgery and appears to speed return of corneal sensitivity. This may be contributory to the dry eye and is a possible new indication for the use of topical CsA in the eye. There is a price implication for using CsA routinely for cataract surgery and this would have to be weighed up against the longer recovery period particularly in patients having premium intraocular lenses.

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The authors except SS have proprietary or commercial interest in any materials discussed in this article. SS holds equity in a company licensing the intellectual property.

Conflict of interest

No conflicting relationship exits for any author.

Prior presentations

Parts of the study results have been previously presented as a poster at the American Academy of Ophthalmology Conference 2013.

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