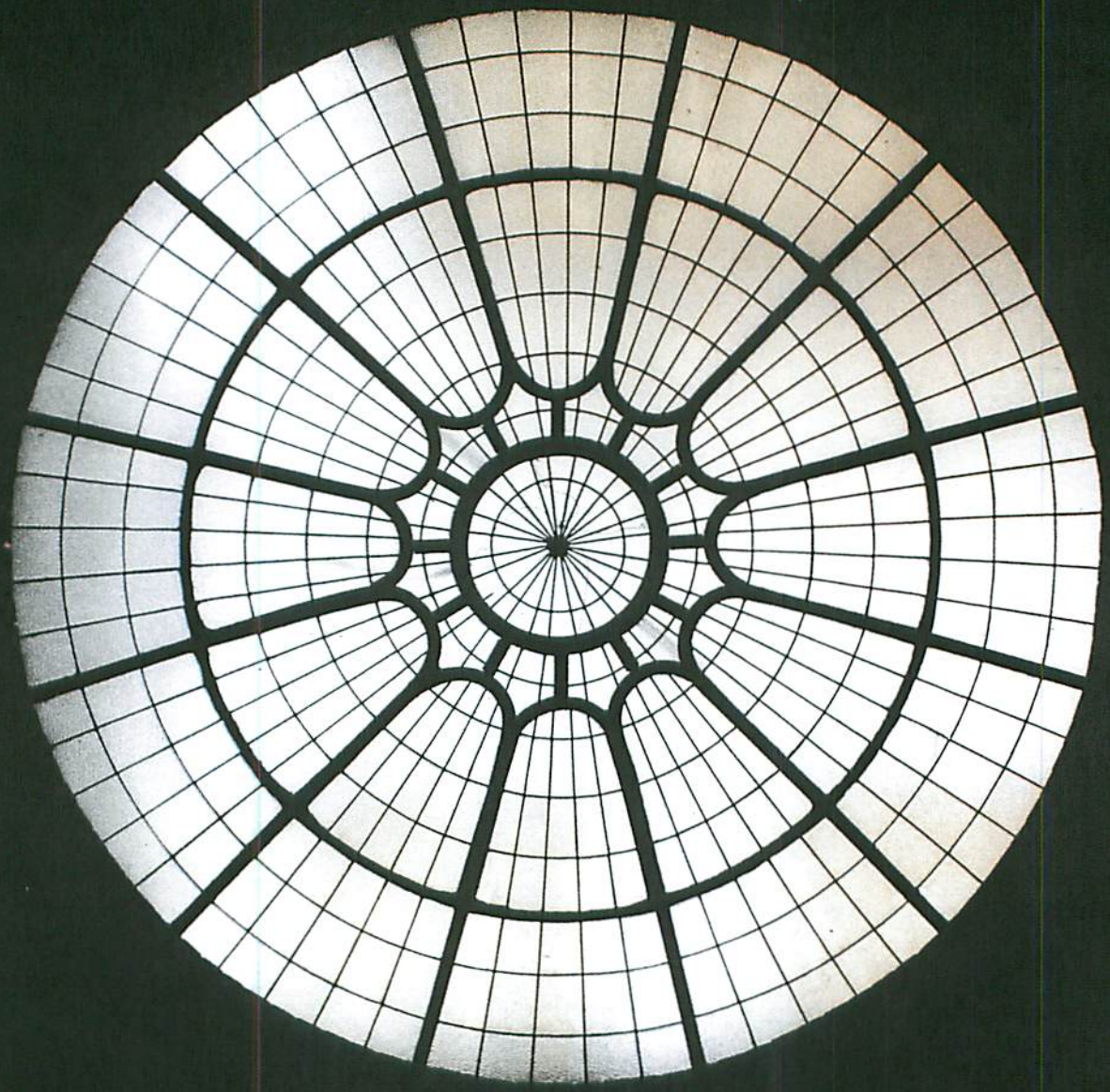
eyenews

THE BIMONTHLY REVIEW OF OPHTHALMOLOGY
FEBRUARY / MARCH 2015 • VOL 21 NO 5 • UK £10.00



www.eyenews.uk.com

ISSN: 1368-8952

A paradigm shift in the way we approach cataract surgery

BY N LEE

Cataract surgery is the most common elective surgical procedure in the UK [1], with in the region of 350,000 cases being conducted each year. With an ageing population, this figure will only continue to rise over time.

Cataract surgery is associated with a low risk of serious complications and with recent advancements in technology and the surgical procedure itself, this safety profile is only expected to improve. However, no matter how sophisticated the technology, how good the surgery and how perfect the patient, any complications that might occur can be minimised if the postoperative treatment of the patient is optimised.

Cystoid macular oedema is a relatively common condition and when its aetiology is related to the cataract surgery itself, it is known as Irvine Gass Syndrome or pseudophakic cystoid macular oedema. This complication is the most common cause of visual loss following cataract surgery [2], and although it is usually self-limiting, in cases of chronic, persistent or recurrent forms of the disorder, photoreceptor damage with permanent deterioration of central vision can ensue [3].

Irvine Gass Syndrome was first reported in 1953 by Dr AR Irvine and then later confirmed by Dr JD Gass in 1969 through utilisation of the invasive procedure, fundus fluorescein angiography (FFA). Its nomenclature is therefore derived from these important contributors to ophthalmology [4,5].

Risk factors

Risk factors for developing the disorder include a number of pre-existing systemic and ocular conditions such as diabetes mellitus and uveitis, in addition to any complications occurring during the surgical procedure itself such as iris damage, capsular rupture or vitreous loss. The presence of diabetes mellitus, even in the absence of any diabetic retinopathy, has been proven to increase the risk of the development of this disorder significantly [6].

Diagnosis

Diagnosis of this painless condition is made through observation of swelling or thickening of the central retina (at the macula) and can be determined through either direct observation, the invasive technique of fundus fluorescein angiography or through the newest innovation to assist in the detection of this disorder, optical coherence tomography (OCT).

Slit-lamp biomicroscopy reveals an irregular foveal light reflex, retinal thickening and / or intraretinal cysts in the foveal region whilst the findings observed with fundus fluorescein angiography and OCT show characteristic appearances associated with the disorder. The advent and utilisation of OCT technology which provides high resolution, cross-sectional and real-time images of the macula region has heralded an increase in the sensitivity and specificity of the detection of the condition. The incidence of cystoid macular oedema being reported using OCT is as high as 14% in post-cataract patients [7]. This increase in sensitivity in the diagnosis of the disorder provides support for the routine use of this non-invasive, objective measure in the assessment of post-cataract patients. Moreover, it could be argued that the specificity in detection would be further enhanced if OCT was conducted both pre and postoperatively, in the case of adequate imagery being possible in the presence of any lenticular opacity. Using this objective measure in this way would help to ensure the correct diagnosis of the disorder, and to rule out the presence of pre-existing macula disease that may not be detectable through direct observation, but that may be mistaken for forms of Irvine Gass Syndrome post-surgery. Indeed this is supported by some members of the ophthalmology community to assist in improving patient care and allowing for improved counselling and management of patient expectations post-surgery [8].

The onset of post-surgical macular oedema or Irvine Gass Syndrome usually occurs around four to 12 weeks post-surgery with the incidence of it peaking at four to six weeks. The duration of the condition assists in the classification of the disorder with it either being acute or chronic in nature. The more persistent it is, however, the worse prognosis it has for the patient's long-term visual function [6]. Most cases recover spontaneously with 80% of cases resolving within three to 12 months [9].

Pathogenesis

The pathogenesis of the disease is related to the surgical trauma itself which initiates an inflammatory response. Surgically induced anterior segment inflammation and disruptions to the blood aqueous barrier result in the release of inflammatory mediators. These then go on to diffuse through the vitreous to the retina where they cause disruption to the blood retinal barrier, which then leads to the accumulation of fluid in the perifoveal retina causing this oedema [10].

Treatment

Currently there are no firmly established treatment protocols for the prophylactic

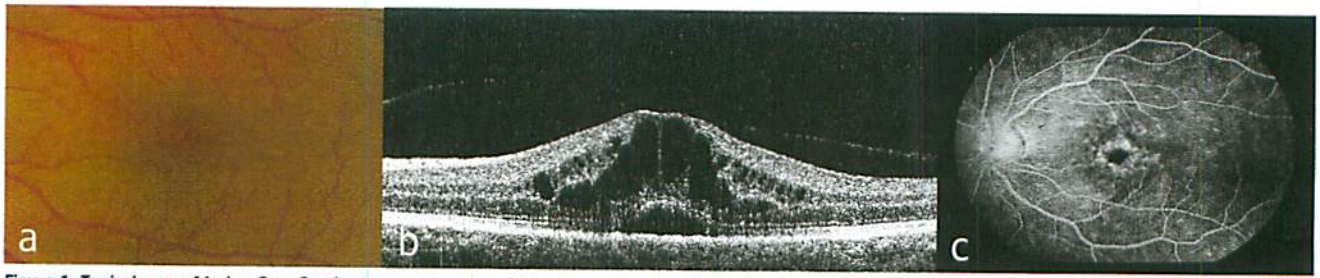


Figure 1: Typical case of Irvine Gass Syndrome as seen using a) biomicroscopy, b) optical coherence tomography (OCT), and c) fundus fluorescein angiography (FFA). (Images provided by the author.)

prevention of cystoid macula oedema in post-cataract patients. In fact, current focus lies on the treatment of the disorder once the fluid has accumulated, vision has deteriorated and the diagnosis of cystoid macular oedema has been made. The treatment goal then lies in the reduction in the inflammatory response to try to reduce the retinal thickening and swelling and to restore vision to the patient. The rationale of treating patients with Irvine Gass Syndrome is to inhibit the inflammatory cascade, and as such first line treatment modalities include the use of topical corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDS) [11]. In addition carbonic anhydrase inhibitors and anti-VEGF agents can also be considered for the treatment of the disorder and will be briefly discussed in this overview although these are generally not used as first line treatment options for these patients.

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors have been used in the treatment of cystoid macular oedema for some time. These agents work by stimulating the passage of fluid across the retinal pigment epithelium from the sub-retinal space to the choroid, thereby reducing the amount of fluid accumulation and thus the degree of oedema. The carbonic anhydrase inhibitors induce acidification of the sub-retinal space, increasing the fluid absorption through the retinal pigment epithelium and choroid [3]. Side-effects experienced with these drugs, however, are high and therefore place limitations on their use.

Anti-VEGF

Anti-VEGF treatments have represented a significant evolution in the treatment of age-related macular degeneration, and its efficacy in other ocular neovascular disorders shows promise. VEGF is a critical mediator in neovascularisation throughout the body, but it has also been found to play a part in the inflammatory and permeability of the capillaries that all contribute to the development of cystoid macular oedema. Studies investigating its use in the treatment of this disorder have revealed improvements in chronic or persistent versions of the condition [12].

Topical corticosteroids

Topical corticosteroids used to treat ocular inflammation include betamethasone, dexamethasone, flurometholine and prednisolone, all of which inhibit the enzyme phospholipase A2, an inflammatory mediator, which in turn reduces inflammation and pain. However, these steroids can be associated with side-effects including increases in the intraocular pressure, slowing of wound healing and increased risks of ocular infection [13]. Another consideration in the long-term use of these steroids for chronic forms of the disease are the complications associated with its prolonged use, including corneal thinning and the increased risk of infection through changes in the normal immune response of the eye.

Non-steroidal anti inflammatory drugs (NSAIDS)

NSAIDS also inhibit inflammation and pain but they do this through inhibition of the cyclooxygenase (COX) pathway which is responsible for the production of the inflammatory mediators thromboxane and prostaglandin. Studies have proven the efficacy of these agents in controlling inflammation in the anterior segment post cataract surgery [14].

NSAIDs available for use in the treatment of Irvine Gass Syndrome include Ketorolac, Bromfenac, Diclofenac and the newest addition to this class of drug, Nepafanac.

Nepafenac (Nevanac®) was approved in the European Union on 12 November 2007 for the prevention and treatment of postoperative pain and inflammation associated with cataract surgery in adults. In February 2012 a further indication was granted by the European Medicines Agency for its use in reducing the risk of macular oedema associated with cataract surgery in diabetic patients. Nevanac® is a cyclooxygenase inhibiting drug with anti-inflammatory and analgesic properties. It is a NSAID but has been proven to have greater bioavailability, target specificity and superior penetration when compared to other NSAIDS available in the current ophthalmological arena [1].

Indications of Nevanac

Nevanac® is the first and only NSAID with an indication for its use to reduce the risk of postoperative cystoid macular oedema in diabetic patients, and as with other NSAIDS achieves its clinical effect through inhibition of the COX pathway. In order to decrease the risk of developing postoperative cystoid macular oedema one drop should be administered to the conjunctival sac of the affected eye three times daily starting one day before surgery, continuing throughout the operative day and then for up to 60 days post-surgery. An additional drop should be administered 30-120 minutes prior to the surgery itself.

In a clinical study of patients with diabetic retinopathy undergoing cataract surgery in which patients were randomised to either receive Nevanac® or a control vehicle, those patients in the treatment arm were more than five times less likely to go on to develop cystoid macula odema following the surgery, with visual acuity levels being maintained at a higher level than seen in the control groups post-surgery. Furthermore, assessment of the safety profile between the two groups revealed no significant differences between the groups [15] indicating superior efficacy and equivocal safety of this NSAID.

It is true that diabetic patients are at a much higher risk of suffering from cystoid macula oedema following cataract surgery compared with non-diabetic patients [6], begging the question why limit the approved prophylactic use of such NSAIDS to only diabetic patients? When their incorporation into the standard post-cataract medical regimen could reduce visual loss caused by this complication and therefore reduce the financial burden on the NHS. In fact reports suggest that up to 75% of ophthalmologists in the US routinely prescribe NSAIDS to all their cataract patients with only 25% of the surgeons surveyed stating that their use was reserved to only high risk patients [16].

Using NSAIDS prophylactically to reduce the risk of Irvine Gass Syndrome

The efficacy of NSAIDS in the treatment of cystoid macular oedema has been reported with studies showing superiority in the performance of NSAIDS over corticosteroids [17]. Furthermore, there have been reports to support the use of NSAIDs in the post-surgical management of inflammation in normal-risk patients using a combination of one week steroid, and up to six weeks NSAID treatment [18]. In addition, this same group of ophthalmologists suggested those patients considered as being at higher risk, to additionally receive some preoperative steroid and / or NSAID treatment [18]. Given the link between the inflammatory pathway and the development of cystoid macular oedema this prophylactic treatment could have a positive knock on effect on the incidence of Irvine Gass Syndrome in the post-cataract population.

Cost-effectiveness

The total ophthalmic costs for patients diagnosed with cystoid macula oedema following cataract surgery have been reported as being significantly higher for those patients who go on to develop the disorder. A retrospective study conducted by Schmier et al. [19] looked at the cost difference in cataract patients diagnosed with cystoid macular oedema post-surgery and compared this to a group of healthy post-cataract controls. Their findings revealed a cost differential of 41% with the affected group costing more.

We know that the development of Irvine Gass Syndrome is even higher in patients who suffer from diabetes mellitus [6]. Lucentis® is now widely used in the treatment of diabetic macular oedema, however, one could question whether

the macula oedema that develops post phacoemulsification in these patients is true diabetic macular oedema. For cases of Irvine Gass Syndrome prophylactic treatment using a NSAID could eliminate the necessity for the postoperative treatment of the macula oedema using the more costly treatment options available. As such, prophylaxis could mean an overall greater cost saving to this group of patients.

These findings in tandem with clinical evidence [18] support the need for further analysis into the potential cost savings that the prophylactic use of NSAIDs could have. If these were used as part of the standard postoperative cataract regimen for all patients then the likelihood for development of this complication could be reduced universally. If the routine postoperative use of NSAIDS could reduce the incidence of this visual threatening disorder in a cost-effective way then why would you not use it as standard on all patients?

Considerations

Evidence confirms that cystoid macular oedema following phacoemulsification leads to decreased vision [17] and this could impact negatively on the quality of life of patients following cataract surgery. The primary symptom of the condition is the presence of blurred vision, but this patient group in general tends to be less visually aware or more accepting of blurred vision, especially given that they have had a cataract for a period of time that they may well have become used to. It therefore follows that this group of patients may incorrectly disregard any symptoms they have and assume that it is due to normal recovery, that the cataract has returned (however impossible) or that a secondary cataract has developed (posterior capsule opacification). With this in mind it could lead to delays in the detection of the disorder which, in turn, could result in delays in its treatment, thereby increasing the time to recovery and potentially influencing the long-term prognosis of the patient. Follow-up for low risk cataract patients means that this sub-set are seen less frequently, and as such maybe the prophylactic treatment of such disorders could provide ophthalmologists with greater piece of mind and confidence that their patient outcomes are optimal with the likelihood for postoperative visual loss being minimised.

The NSAID, Nevanac®, is indicated for its use to reduce the risk of postoperative cystoid macular oedema in diabetic patients and as such its first line use in this patient group can be rationalised. For non-diabetic patients, however, there is no licensed preparation for the reduction of cystoid macular oedema, only for the reduction of pain and inflammation (Nevanac® (Nepafenac), Yellox (Bromfenac), Voltarol (Diclofenac), and Acular (Ketorolac)). Use of these drugs in the prevention or treatment of cystoid macular oedema is thus largely anecdotal. It has been reported, however, that both Diclofenac and Ketorolac are five times weaker in their potency when compared to Bromfenac [20] which may affect the NSAID clinicians consider for such usage. Furthermore, there are differences in reported patient comfort following administration of various NSAID drops [21] that could influence patient compliance and thus clinician choice. Consideration of all these aspects thus factors in on the choice of NSAID agent being prescribed in non-diabetic cataract patients. It is also of note that there are no formal prescribing recommendations for the postoperative NSAID regime in these patients and question lies over what should be advised. Our experience over three years at The Hillingdon Hospital has been to use Bromfenac twice per day for one month following surgery together with a tapering dose of TobraDex over two weeks. Since our introduction of the routine use of this postoperative medication regime, our incidence of confirmed cystoid macular oedema has been seen to decrease from 50 cases a year to less than five.

It is known by the author of this article that there is currently an European Society of Cataract & Refractive Surgeons (ESCRS) led multicentre randomised control trial (RCT) study underway to investigate the relative benefits of NSAIDS as a prophylaxis for the prevention of Irvine Gass Syndrome in both diabetic and non-diabetic patients. PRevention of Macular EDema After Cataract Surgery (PREMED). The study is expected to complete in July 2015 [22]. The results from this study could prove interesting and serve as further evidence that prophylaxis is clinically beneficial for all cataract patients.

References

1. Ke T-L, Graff G, Spellman JM, et al. Nepafenac, a unique non steroidal prodrug with potential utility in the treatment of trauma induced ocular inflammation: II. In Vitro bioactiation and permeation of external ocular barriers. *Inflammation* 2000;**24(4)**:371-84.
2. Yonekawa Y, Kim IK. Pseudophakic cystoid macula edema. *Curr Opin Ophthalmol* 2012;**23(1)**:26-32.
3. Rotsos TG, Muschos MM. Cystoid Macula Edema. *Clinical Ophthalmology* (Auckland, NZ) 2008;**2(4)**:919-30.
4. Irvine SR. A newly defined vitreous syndrome following cataract surgery, interpreted according to recent concepts of the structure of the vitreous. *Am J Ophthalmol* 1953;**36**:599-619.
5. Gass JD, Norton EW. Follow up study of cystoid macular edema following cataract extraction. *Trans Am Acad Ophthalmol Otolaryngol* 1969;**73**:665-82.
6. Lowenstein AA, Zue D. Postsurgical cystoid macula edema. *Dev Ophthalmol* 2010;**47**:148-59.
7. Kim SJ, Belair ML, Bressler NM, et al. A method of reporting macula edema after cataract surgery using optical coherence tomography. *Retina* 2008;**28**:870-6.
8. Kent C. Using posterior PCT in cataract surgery. The ability to uncover retinal problems before cataract surgery could improve both outcomes and patient satisfaction. *Review of Ophthalmology* August 2012.
9. Minassian D, Reidy A, Desai P, et al. The deficit in cataract surgery in England and Wales and the escalating problem of visual impairment: epidemiological modelling of the population dynamics of cataract. *Brit J Ophthalmol* 2000;**84(1)**:4-8.
10. Miyake K, Ibaraki N. Prostaglandins and cystoid macular edema. *Surv Ophthalmol* 2002;**47**:S203-18.
11. Wittpenn JR, Silverstein S, Heier J, et al. A randomised masked comparison of topial ketorolac 0.4% plus steroid versus steroid alone in low risk cataract surgery patients. *Am J Ophthalmol* 2008;**146(4)**:554-60.
12. Arevalo JF, Maria M, Garcia-Amaris RA, et al. Pan American Collaborative Retina Study Group (PACORES). Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: The Pan-American Collaborative Retina Study Group results. *Ophthalmology* 2009;**116**:1481-7.
13. Hariprasad SM, Akduman L, Clever JA, et al. Treatment of cystoid macular edema with the new generation NSAID nepafenac 0.1%. *Clinical Ophthalmology* (Auckland, NZ) 2009;**3**:147-54.
14. Lindstrom R, Kim T. Ocular permeation and inhibition of retinal inflammation: an examination of data and expert opinion in the clinical utility of nepafenac. *Curr Med Res Opin* 2006;**22(2)**:397-404.
15. Singh R, Alpern L, Jaffe GJ, et al. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy. *Clin Ophthalmol* 2012;**6**:1259-69.
16. Stuart A. NSAIDs and cataract surgery. *Eyenet* September 2011.
17. Miyake K, Ota I, Miyake G, et al. Nepafenac 0.1% versus flurometholine 0.1% for preventing cystoid macular edema after cataract surgery. *JCRS* 2011;**37(9)**:581-8.
18. Alio JL, Bodaghi B, Tassignon MJ. Guidelines for managing post-cataract surgery inflammation: can we reach a consensus? *Ophthalmol Times Europe* November 2008 (Suppl):1-12.
19. Schmier JK, Halpern MT, Covert DW et al. Evaluation of costs for cystoid macular edema with the new generation NSAID nepafenac 0.1%. *Clinical Ophthalmol* (Auckland, NZ) 2009;**3**:147-54.
20. Kida T, Ogawa T, Mcnamara TR, et al. Evaluation of the human Cox-2 inhibition of amfenac, bromfenac, diclofenac, and ketorolac. Proceedings of the American Society of Cataract and Refractive Surgery (ASCRS), San Diego, CA, USA. 27 April – 2 May, 2007.
21. Edmondson L, McKee E, Edmondson W. Comfort comparison of three ophthalmic NSAID eye drops. *Optometry – Journal of the American Optometric Association* 2006;**77(6)**:284-5.
22. ClinicalTrials.gov Identifier NCT01774474

Take home message

- Irvine Gass Syndrome is the commonest cause of postoperative deteriorations in visual acuity post cataract surgery.
- Risk factors for Irvine Gass Syndrome include diabetes mellitus, uveitis and surgical complications.
- Postoperative complications can be minimised if the postoperative treatment of the patient is optimised.
- Prophylactic treatment with the newest of the NSAIDS, Nevenac®, revealed up to a fivefold decrease in the development of cystoid macula oedema following surgery.
- The total ophthalmic costs for patients diagnosed with cystoid macula oedema following cataract surgery have been reported as being significantly higher (41% higher) for those patients who go on to develop the disorder.
- Prophylactic treatment of Irvine Gass Syndrome could provide ophthalmologists with greater piece of mind.
- Utlising an NSAID routinely gives the potential to virtually eliminate post operation CMO.

Nicholas Lee,
Consultant Ophthalmologist,
The Hillingdon Hospital and The Western Eye Hospital,
London, UK.

Correspondence:
Email: nick@leemedical.co.uk

Declaration of competing interests:
The author is a key opinion leader for Alcon & Novartis and has received educational sponsorship grants.