Concise Practice Points

Post-operative macular oedema (PMO)

The ROYAL COLLEGE of OPHTHALMOLOGISTS

Date of Publication: January 2026
Date of Review: January 2029

Context

Epidemiology

The incidence of clinically recognised post-operative macular oedema (PMO) has been reported to be 1-2% following cataract surgery, with increased risk from surgical complications or pre-existing conditions such as diabetes, epiretinal membrane, previous retinal detachment or retinal vein occlusion. (1) The incidence of PMO identified on optical coherence tomography (OCT) after uncomplicated cataract surgery is reported as 10.7% in people with diabetes and 3.5% in those without. (2) PMO results in additional hospital visits, prolonged topical therapy, additional procedures and, despite these measures, worse visual acuity outcomes.

Current practice

There is lack of uniformity in clinical practice in the management of PMO including in mode of treatment, therapeutic agents, the duration of treatment and escalation for persistent PMO. This reflects the limited evidence on the management of PMO. Most published studies on the subject are retrospective case series, or randomised trials with small samples and significant risk of bias. Various modalities of treatment are available, including non-steroidal anti-inflammatory (NSAID) drops, topical, periocular and intraocular steroids, anti-VEGF injections and carbonic anhydrase inhibitors.

Objective

The objectives of this CPP are to review the published literature on management of PMO and present recommendations on case identification, referral to secondary care, initial treatment and management of refractory cases. Research recommendations may arise from gaps in the knowledge base.

Contents

Methods

We conducted a PUBMED search for publications with the terms:
("post operative macular"[All Fields]) OR
(("post operative cystoid macular edema"[All Fields]) OR
("post operative cystoid macular oedema"[All Fields])) OR
(("pseudophakic cystoid macular oedema"[All Fields]) OR
("pseudophakic cystoid macular edema"[All Fields])) OR
("irvine gass syndrome"[All Fields])

We limited the initial search to papers published since 2003. Further relevant articles were identified from review of references, retrieved and added to the cited list.

We excluded case reports and studies investigating prevention, but not management of PMO. A total of 41 articles were included.

Recommendations

Definition and nomenclature

- PMO is defined as the presence of intraretinal fluid cysts within the central macula (ETDRS grid central subfield) on spectral domain OCT in a patient within 1 year of intra-ocular surgery, where no other cause is evident.

  There is no evidence that a central macular thickness threshold is indicative of clinical significance. Clinicians should make a clinical judgement about the significance of PMO after considering symptoms and visual acuity, bearing in mind that any intra-retinal fluid which is new post-operatively is abnormal.

  Level of evidence: 4

- There are multiple names for PMO. We recommend dropping unneeded descriptors (eg "cystoid") and eponymous labels, and the adoption of post-operative macular oedema to align with other forms of macular oedema.

Diagnosis

- The following patients should have examination with dilated slit lamp biomicroscopy and OCT macular scan between 3 and 8 weeks post-operatively to identify PMO:
  - vision has not improved as expected following cataract surgery,
  - patient reporting dissatisfaction with quality of vision after intra-ocular surgery,
  - high risk of PMO due to complicated surgery, or history of PMO in the fellow eye
  - history of retinal vein occlusion, diabetic maculopathy or moderate non-proliferative retinopathy or worse.

  Level of evidence: 4

Referral

- All patients with PMO should be referred by the community care provider to ophthalmology to be seen preferably within 2 weeks but at most within 4 weeks. Referral pathways which are direct from community optometry to ophthalmology are preferable, to prevent delay from referring via the patient's GP.
- Patients should be referred to their original provider of intra-ocular surgery.

  Level of evidence: 4

Initial treatment

- Initial treatment for PMO should be with steroid and NSAID eye drops for 8 to 12 weeks from diagnosis. The steroid should be potent and penetrate intraocularly e.g. prednisolone acetate 1% or dexamethasone 0.1%; and used three to four times per day.(3,4) There is no evidence that any NSAID eye drop is superior to others (Appendix 2).(5–11)

  Level of evidence: 1+

Treatment for persistent PMO

- a) If PMO is persistent or insufficiently improved after 8-12 weeks of topical steroid and NSAID then offer periocular steroid injection with sub-tenon's or orbital floor triamcinolone 40mg or methylprednisolone suspension 40mg.(12–15) Earlier peri-ocular steroid may be justified if there is no improvement to topical treatment.

  Level of evidence: 1-

- b) If PMO is insufficiently improved or recurs after peri-ocular steroid injection (or peri-ocular steroid is inappropriate) consider intravitreal steroid treatment, such as dexamethasone 700µg implant (Ozurdex). (16) A patient's susceptibility to steroid-induced ocular hypertension or glaucoma needs to be considered, although in most cases it can be sufficiently managed medically. Intravitreal steroid may need to be repeated due to waning effect.

  Preserved triamcinolone is not suitable for intravitreal use.

  Level of evidence: 2+

- c) Evidence is poor with regards to intravitreal anti-VEGF therapy in patients with refractory PMO. Retrospective case series, mainly evaluating bevacizumab, with high risk of bias showed anatomical and vision improvements with treatment.(17–24)

  Intravitreal anti-VEGF therapy is an option in patients with refractory PMO in whom intravitreal steroids are contraindicated, such as in a patient with IOP steroid response and advanced secondary glaucoma.

  Level of evidence: 2-

Post-operative Macular Oedema (PMO)

Definition and management of PMO

CASE DEFINITION

Presence of intraretinal fluid cysts within the central macula (ETDRS grid central subfield) on OCT in a patient **within 1 year** of intra-ocular surgery, where no other cause is evident.

CASE FINDING

Perform **slit lamp biomicroscopy** and **macular OCT 3-8 weeks postoperatively** in the following patients:

- Vision has not improved as expected following cataract surgery
- Reporting dissatisfaction with quality of vision after intra-ocular surgery
- Complicated surgery, or history of PMO in fellow eye
- History of retinal vein occlusion, diabetic maculopathy or moderate non-proliferative retinopathy or worse

REFERRAL

Refer from community care to ophthalmology to be seen preferably within **2 weeks** (but at most within 4 weeks)

Refer directly to ophthalmology and to the patient's original provider of intra-ocular surgery

INITIAL TREATMENT FOR 8-12 WEEKS FROM DIAGNOSIS

- **Steroid** - prednisolone acetate 1% or dexamethasone 0.1% eye drops 3-4 times a day

AND

- **NSAID** - any NSAID eye drop at indicated frequency

TREATMENT FOR PERSISTENT PMO

Persistent or insufficiently improved PMO after 8-12 weeks of topical treatment:

- **Periocular steroid injection** - sub-tenon's or orbital floor triamcinolone or methylprednisolone
- Earlier peri-ocular steroid may be justified if no improvement to topical treatment

Insufficiently improved, or recurs after peri-ocular steroid or peri-ocular steroid is inappropriate:

- **Intravitreal steroid** e.g. dexamethasone 700µg implant
- Consider susceptibility to steroid-induced ocular hypertension or glaucoma
- May need to be repeated due to waning effect

Recommendations for research

1. Management of PMO would benefit from an agreed definition. Research into a suitable definition would be appropriate, preferably involving multiple national or international stakeholders using a recognised consensus-building approach.
2. Health systems and implementation research could investigate the best way to identify patients with PMO and streamline their treatment pathway, particularly as patients with a high-risk of PMO may be followed up by community optometry after cataract surgery.
3. Trials on topical treatment have small numbers and do not establish categorically whether steroid alone or NSAID alone or in combination is the best initial treatment for PMO. Clinical trials are needed to answer these questions
4. Use of periocular steroid is supported mainly by retrospective case series. Clinical trials to investigate periocular steroid delivery in comparison to topical and intravitreal therapy are needed. It is recognised that supra-choroidal steroid delivery also could be investigated for PMO.
5. Use of intravitreal dexamethasone is supported by retrospective case series and clinical trials of other causes of macular oedema. Clinical trials to demonstrate whether it is superior to other modes of treatment in PMO are needed.
6. Clinical trials are needed to investigate the role of anti-VEGF therapy and carbonic anhydrase inhibitors in PMO.
7. Studies investigating other mechanisms and clinical trials on emerging non-steroidal therapeutic agents would be beneficial.
8. Research and clinical trials need to account for patients with pre-existing diabetic maculopathy or retinopathy and how their treatment pathway may differ from other PMO patients.

Appendix 1

Summary of systematic reviews and randomised controlled trials on management of post-operative macular oedema

AUTHOR AND YEAR	METHODOLOGY	KEY MESSAGE	STRENGTHS	LIMITATIONS
Wingert et al 2022	Systematic review 9 RCT	Some studies showed positive effect of NSAID in acute PMO, variable results in chronic cases	Summary of early studies 1997-2006	Old studies, no OCT data No data on results after treatment cessation
Ahmadyar et al 2022	Systematic review (2 RCT, 16 case series) on injectable options (peri-ocular or IVI steroids, anti-VEGF, IVI infliximab)	All studies reported positive outcomes	Systematic review of available literature on injectable therapies for PMO	Mainly case series or small RCTs. Significant issues found including masking, selective reporting, protocol deviation
Wielders et al 2017	Systematic review (10 RCT) On topical NSAIDs, topical and periocular steroids, oral NSAIDs and carbonic anhydrase inhibitors	Positive effect with topical NSAID, unclear effect of other agents studied	Systematic review of published literature 1977-2016	Studies included were found to be of poor-moderate quality
Falavarjani et al 2012	Systematic review (4 RCT, 4 retrospective studies, 4 case reports) on anti-VEGF use for PMO	Anti VEGF has unclear role in PMO and reserved for cases refractory to topical treatment	Systematic review of available literature on anti VEGF	Overall evidence found to be of poor quality
Shelsta et al 2010	Summary of available evidence	Positive outcomes with topical steroids and NSAIDs.Unproven role of anti-VEGF	Full summary of available literature	The quality of studies was found to be suboptimal
Sivaprasad et al 2005	Systematic review 7 RCT	Positive effect from ketorolac in PMO	Systematic review with full summary of the literature	The quality of studies was found to be suboptimal
Staurenghi et al 2018	Randomised controlled trial. Intravitreal ranibizumab vs sham in eyes with macular oedema from various causes; subgroup of PMO had 59 eyes	Visual acuity gain was superior in ranibizumab group at 2 months. All patients had open label ranibizumab 3-12 months	Randomised, sham controlled. Planned sub-group analysis.	RCT was only for 2 months, and not powered for PMO analysis.
Yuskel et al 2016	Prospective randomised trial. Sub-tenon's triamcinolone vs topical nepafenac n=48	There was significant gain of vision and reduction of CRT in both groups, Nepafenac group had more sustained effect throughout the study period	Randomised, comparative study over 6 months	Randomisation method unclear; patients and OCT assessors and retreatment decisions unmasked

Appendix 1 (continued)

AUTHOR AND YEAR	METHODOLOGY	KEY MESSAGE	STRENGTHS	LIMITATIONS
Warren et al 2010	Randomised controlled trial. All patients had intravitreal triamcinolone and bevacizumab then randomised to 1 of 4 topical NSAID or placebo. n=39	Vision gain was significant in all groups. Bromfenac and nepafenac had a significant reduction in retinal thickness at 12 and 16 weeks.	Randomised, prospective study.	Small unmasked study investigating a niche question: the effect of adding topical NSAIDs to intravitreal triamcinolone and bevacizumab in PMO.
Williams et al 2009	Randomised single masked trial of patients with uveitic macular oedema or PMO Intravitreal dexamethasone 700ug vs 350ug vs observation. Total n=41	At 90 days in all patients, 10 letter gain was seen in 54% who received 700um dexamethasone, 42% with 350um dexamethasone and 7% with observation	Randomised, multicentre study	Mixed population and results for PMO not given separately. Small study with 27 with PMO.
Rho 2003	Randomised controlled trial. Topical ketorolac vs diclofenac for PMO n=34	There was improvement in vision and reduced leakage on FFA in both groups with no significant difference	Early RCT with FFA (no OCT)	Small, single-centre, unmasked, single-author study with unclear randomisation method. No placebo
Singhal et al 2003	Randomised controlled trial. Topical ketorolac vs topical ketorolac and prednisolone n=10	No significant difference in visual acuity gain	Early double-masked RCT with FFA (no OCT)	Very small, unpowered, single-centre study with no placebo.
Heier et al 2000	Randomised controlled trial. Topical ketorolac vs topical prednisolone vs combined ketorolac and prednisolone for 3 months n=26	Combined treatment resulted in superior vision acuity improvement compared to monotherapy. No difference in visual gain between ketorolac and prednisolone	Early double-masked RCT with FFA (no OCT)	Small, unpowered, single-centre study with unclear randomisation method
Flach et al 1991	Randomised controlled trial. Topical ketorolac vs placebo n=120	Visual acuity gain was superior with Ketorolac	Placebo controlled, double-masked study. Larger sample size	Early, multi-centre, randomised study

Abbreviations:

FFA fundus fluorescein angiogram
IVI intravitreal injection
NSAID non-steroidal anti-inflammatory drug
OCT optical coherence tomography
PMO post-operative macular oedema
RCT randomised controlled trial
VEGF vascular endothelial growth factor

Appendix 2

Topical non-steroidal anti-inflammatory drugs used for treatment of post-operative macular oedema

MEDICATION	TRADE NAME	FREQUENCY
Ketorolac trometamol 0.5%	Acular	3x, 4x
Bromfenac 0.09%	Yellox	2x
Nepafenac 0.1%	Nevanac	3x
Nepafenac 0.3%	Nevanac	1x
Diclofenac 0.1%	Voltarol Ophtha	4x
Flurbiprofen 0.03%	Ocufen	4x

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