

Pseudophakic Macular Edema (Irvine-Gass Syndrome): Has the Treatment Changed?

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INTRODUCTION

Cataract surgery is the most common ophthalmic surgery and is generally associated with good visual outcomes. Nevertheless, cystoid macular edema may develop resulting in suboptimal visual results. The post-surgical macular edema (PSME) is one of the most important causes of suboptimal visual acuity that can occur after any intraocular surgery, even in uncomplicated cases, namely cataract surgery. In this setting, it is also called Irvine-Gass syndrome (IGS) or pseudophakic cystoid macular edema (PCME). It was first described by Irvine, AR in 1953 and later defined by Gass et al. The inflammatory insult after cataract surgery, caused by the release of inflammatory mediators, such as mediated by prostaglandins and cytokines, leads to the breakdown of blood-retinal barrier (BRB) and to increase vascular permeability and fluid leakage to the extracellular intraretinal space. Other factors as light toxicity, mechanical irritation have also been implicated [1, 2]. Other factors can cause BRB disruption such as diabetes mellitus, hypertension, history of central retinal vein occlusion, recent history of uveitis, pre-existing epiretinal membrane or following complicated cataract surgery.

The rate of IGS was very high in the past with intracapsular cataract extraction and subsequently decreased with the widespread adoption of extracapsular cataract surgery. The implementation of phacoemulsification as the gold-standard technique for cataract removal, with the adoption of more physiological and less invasive techniques for intraocular lens (IOL) insertion, such as the insertion of foldable-IOLs in the capsular bag, lead to further reduction of IGS rates. However, with the recent technological advances and their implementation in daily office practice, as the optical coherence tomography (OCT) lead to the detection of much more cases of

pseudophakic macular edema than those able to be detected by clinical evaluation and fluorescein angiography (FA), even subclinical PSME, facilitating early detection and OCT is also useful to guide treatment and to give insight to the underlying mechanism of this retinal disorder [3]. At least one in five patients subjected to uncomplicated cataract surgery develop PME detected by FA. The advent of spectral-domain OCT (SD-OCT), a noninvasive and fast exam that provides a remarkable amount of retinal in vivo imaging detail elevated the rate of detection of central macular edema after cataract surgery even further to a level as high as 41%, because it is able to detect even minor amounts of intraretinal fluid [1]. However, the incidence of clinical significant PCME is much lower, approximately 0.1% to 2.35% [4-6]. A recent study found an incidence of 1.17% in non-diabetic patients and a 4-fold increase in diabetic patients [6]. The risk is higher in diabetic patients, even those without diabetic retinopathy and it is highest in the most severe grades of diabetic retinopathy [6]. This study questioned the role of the history of prostaglandin use before surgery as an important risk factor, in disagreement to previous retrospective smaller studies, but confirmed well-established risk factors. Complicated cataract surgery (posterior capsule rupture, vitreous loss) is associated with very high rates of IGS.

Femtosecond laser-assisted cataract surgery (FLACS) is a new promising technique, specially in hard cataracts and patients with preoperative low endothelial counts [7]. Two studies evaluated the macular changes in FLACS as compared to standard phacoemulsification [8, 9]. Ecsedy, KM et al. studied the changes of macular thickness after FLACS compared to standard phacoemulsification [9]. This study included a small sample of 20 eyes of 20 patients in each group and they found that in the FLACS group the macular thickness did not increase sig-

nificantly at 1 week after surgery, in contrary to what occurred in the standard phaco group, where the macular thickness increased, after adjusting for age and baseline macular thickness. The macular thickness at 1 week after surgery was significantly lower in the FLACS group compared to standard phaco group, but this difference between groups became marginally significant at 1 month [9]. This suggests that FLACS is associated to less immediate or short-term inflammatory reaction after uneventful surgery than standard phacoemulsification. More recently, Conrad-Hengerer, Fl and colleagues studied in 2014 one hundred and four patients, that underwent FLACS in one eye ($n = 104$) and standard ultrasound phacoemulsification in the fellow eye ($n = 104$) with macular OCT [8]. They also evaluated anterior segment flare with laser photometry. They found similar macular thickness changes in both groups at 4 days, 1 month, 3 months and 6 months after surgery. They found higher levels of short-term anterior chamber inflammation in standard phacoemulsification group by laser flare photometry at 2 hours after surgery. They concluded that FLACS did not obviously influenced the incidence of postoperative macular edema. Another study found that both techniques achieved similar safety and efficacy outcomes, with similar postoperative macular thicknesses in every evaluation but in eyes with FLACS had lower flare values at six months postoperatively [10]. A meta-analysis concluded that there was no evidence that FLACS and lens removal contributed to a higher incidence of postoperative macular edema than manual phacoemulsification and found similar postoperative macular thicknesses between both groups in all included studies [7]. Although, there is not any well-designed epidemiologic study about the incidence of IGS after FLACS, it is expected that the incidence of this complication after FLACS is similar to the incidence in manual phacoemulsification.

PCME most often presents after 4-6 weeks after cataract surgery, but in rare cases it can occur months or even years after surgery [1, 2, 11]. It is diagnosed by decreased or suboptimal visual acuity, by the classic appearance of perifoveal petaloid staining with or without late leakage from the optic disk and by the presence of macular thickening and cystic spaces in the outer plexiform layer on OCT, occasionally with subfoveal fluid [1]. Although PCME can resolve without treatment, its detection implicates initiation of anti-inflammatory treatment. When managing PCME we should look if there is an underlying cause for its occurrence. The physician should rule out IOL subluxation, because its haptics can traumatize the iris with secondary release of prostaglandins. Vitreous or iris incarceration in corneal surgical wounds and retained lens fragments should also be ruled out. In the case of vitreous incarceration

in the corneal wound, a Nd: YAG vitreolysis or vitrectomy could be performed. If there is posterior capsule rupture, the posterior segment of the eye should be inspected to identify the presence of retained nuclear fragments, even they can be small and difficult to detect. Fundoscopy at slit-lamp with a 90D-lens and a 3-mirror lens and also fundoscopy with indirect ophthalmoscope with scleral depression to inspect the vitreous base for small retained lens fragments are important procedures for a comprehensive ophthalmological examination for ruling out an underlying cause for the PCME. Ocular Ultrasound can be valuable when visualization of the ocular fundus inadequate or impossible.

Concerning the treatment, if an underlying cause is identified, it is important to remove it, because anti-inflammatory treatment alone is not sufficient in these cases. So, in cases of complicated cataract surgery, if retained lens fragments are identified, patients need a secondary pars plana vitrectomy to remove them and also the vitreous, in order to remove all the sources of recurrent ocular inflammation. If a dislocated IOL is identified, its repositioning or removal may be necessary. The options may range from single-piece in the bag IOL with optic capture in the rhexis, if posterior capsule rupture (PCR) is minimal and posterior capsular support is adequate, to sulcus-placed 3-piece IOL if the PCR is extensive but the referred kinds of is preserved, to iris-sutured 3-piece IOL or iris-claw aphakia IOLs if both kinds of IOL support are absent. When vitreous incarceration into the surgical wound is detected, a Nd:YAG vitreolysis or pars plana vitrectomy is necessary. When vitreous adhesions to anterior segment structures or iris capture of the IOL exists, pars plana vitrectomy may resolve persistent PCME and may improve visual acuity [12]. Even if cataract surgery was uneventful but an epiretinal membrane or significant vitreomacular traction are identified, patients should be submitted to pars plana vitrectomy for induction of posterior vitreous detachment (if not already present) and for peeling of epiretinal and internal limiting membranes, to remove all sources of traction and to let the edema resolve subsequently with anti-inflammatory therapy.

When an identifiable cause for the PCME is absent, a step-wise approach should be employed. Besides the 80% rate of spontaneous resolution of PCME without underlying cause, when it is diagnosed, medical anti-inflammatory treatment should be initiated first [11]. Acute IGS is the PCME occurring at 2 months or less after surgery and chronic IGS refers to the IGS occurring at more than 2 months after surgery. For acute IGS, first-line therapy involves a topical NSAI (ketorolac, bromfenac, nepafenac, flurbiprofen) for more than 2 months, with or without a topical steroid. As prostaglandins have a fun-

damental role in the pathophysiology of PCME, a NSAID must always be present in the topical therapy and a steroid alone is generally insufficient or less efficacious, as confirmed by the literature. If after 3 months, the PCME persists, a topical steroid must be added to the NSAID therapy, if not employed previously. If after 4 months of treatment PCME persists, intravitreal injections of triamcinolone or anti-VEGF or a novel sustained-release corticosteroid intravitreal implant must be used.

For chronic PCME, first-line therapy involves topical combined treatment with a nonsteroidal anti-inflammatory agent (NSAID) and a corticosteroid. Whittipen et al found increased efficacy of adding topical ketorolac to topical prednisolone [13]. Also, Heier et al found increased efficacy with the combined topical treatment comparatively to monotherapies with NSAID alone or steroid alone [14]. Macular spectral-domain OCT as a non-invasive and fast exam that provides a high definition cross-sectional image of the macular retina, is a convenient and useful exam to monitorize the response to the treatment. The treatment may need to be extended from several weeks to months. If after 4 months of treatment, PCME persists, intravitreal injections of triamcinolone or anti-VEGF (bevacizumab) or sustained-release corticosteroid intravitreal implant must be done. Periocular injections of steroid, have been frequently used in the past for refractory PCME, because of the benefit of locally delivering steroid into ocular tissues, but the anecdotal and transitory effect and also the steroid side effects allied to the availability of novel delivery-devices of steroid or anti-VEGF intravitreal injections, led to the replacement of this approach by these more recent treatments. Although anti-VEGF agents were not sufficiently studied yet, some studies revealed that bevacizumab injections are efficacious in the treatment of refractory IGS. In fact, VEGF is an important mediator in the inflammatory pathway that leads to IGS, but as IGS syndrome pathophysiology involves multiple inflammatory mediators. Is it sufficient to inhibit one sole inflammatory mediator to treat IGS? I do not think so. This can be the explanation for the reason the transitory beneficial effect that has been reported in the few available studies about the effect of bevacizumab in the treatment of IGS. The studies are limited by the small study samples and by the retrospective case series study design. I do not think that anti-VEGF agents alone could have a sustained benefit in most cases of refractory IGS and multiple injections may be necessary. In a study of Spitzer M et al. [15] only 1 of the 16 eyes with refractory IGS studied, had an improvement of 2 Early Treatment Diabetic Retinopathy Study lines after intravitreal bevacizumab 1.25mg, despite a slight reduction of macular thickness on

OCT, demonstrating a limited beneficial effect of this treatment. Other studies about refractory IGS found superior results for intravitreal bevacizumab and concluded that this anti-VEGF agent is safe and efficacious in the short-term [16-18]. A multicentered, retrospective study reported that 72 percent of the eyes with refractory pseudophakic CME treated with at least one intravitreal bevacizumab injection had improvement in visual acuity with a reduction in mean central macular thickness at 12 months [17]. Forty-three percent of the eyes required more than one injection for best visual acuity [17]. I think that anti-VEGF could be useful as a complementary therapy to recalcitrant IGS under treatment with the novel dexamethasone sustained-release intravitreal implant. In this setting, continuing topical treatment with NSAID and steroid is beneficial [19]. Corticosteroids permit inhibition of multiple inflammatory mediators, but has significant side effects that limit its use, as secondary ocular hypertension and glaucoma, cataract progression in phakic eyes. Intravitreal injections of triamcinolone are efficacious in the short-term. But adverse side-effects of triamcinolone the need of frequent injections and the possibility of simulating infectious endophthalmitis, by causing sterile endophthalmitis due to an immune reaction to the solvent of the triamcinolone preparation or even causing pseudoendophthalmitis, due to the deposition of triamcinolone crystals in anterior chamber creating pseudohypopyon and also the availability of new devices for delivering steroids continually at low doses for many months into the posterior segment, had decreased the use of intravitreal injections of triamcinolone [20-33]. These new sustained-release steroid intravitreal implants have the advantage of reducing, at least in theory, the risk of adverse side effects by delivering steroids locally and continually potent steroids at low doses for many months, reducing the number of intravitreal injections needed with previous intravitreal injections. Many studies found promising results of these new intravitreal steroid implants for treatment of recalcitrant IGS [1, 23, 34-43]. The EPISODIC study included 50 patients with refractory PSME treated with 0,7mg intravitreal dexamethasone implants [34]. This study found significant functional and anatomical benefits, with no recurrences till the third month after treatment. After 3 months, recurrences were detected and this study found that the effect of a second injection was similar to the first injection, demonstrating the reproducibility of this treatment. However, more than half of the patients followed-up for at least 1 year presented neither functional nor anatomical recurrence. From these encouraging results, they found that dexamethasone intravitreal implants appear to be an interesting alternative therapy for treating post-surgical macular oedema, including Irvine-Gass syndrome refractory to first-line

treatments [34]. This favourable results should encourage further studies, to directly compare the effectiveness of these intravitreal implants to other options for treatment of refractory IGS. Several other intravitreal treatments (pegaptanib sodium, infliximab, diclofenac, interferon alfa) have been suggested as alternatives in case of resistance to drug-based treatment, but there are only reports of series of cases with no control groups [44-48]. Pars plana vitrectomy has been suggested for treatment of PCME refractory to all options of medical treatment with good outcomes, even if no vitreous disturbance is detected [49].

Oral carbonic anhydrase inhibitors (CAIs) can be considered in refractory IGS. CAIs are thought to improve the pumping function of the retina pigment epithelium [2, 31, 50]. They also can induce acidification of the subretinal space, and thereby increase fluid resorption from the retina through the RPE into the choroid [2, 51]. These actions could aid in decreasing the intraretinal fluid. Their role in treatment has not been stabilised [31]. However, favourable results were reported in case reports and small series, but their use can be limited by side effects [2, 31, 51-53].

Regarding the IGS prevention after uncomplicated cataract surgery in low-risk patients, there is evidence supporting the prophylactic use of topical NSAIDs or NSAIDs combined with topical steroids after surgery [54, 55]. Steroids should not be used alone in this regard, as they are less effective in preventing IGS and a higher incidence of this complication has been reported in groups treated prophylactically with topical steroid alone [54, 55]. A meta-analysis demonstrated that a combination of topical NSAIDs and corticosteroids significantly reduced the odds of developing PCME as compared to topical corticosteroids, while combination treatment did not show any benefit over topical NSAIDs in an indirect treatment comparison [54]. This study found that topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids in non-diabetic patients [54]. However, we must take in consideration that most studies included relatively weak steroids in the groups treated with steroid-alone prophylactic regimen, which could have influenced these results [54]. There is sufficient evidence supporting the initiation of NSAIDs 3 days before cataract surgery. This approach seems to hasten short-term visual recovery, but does not affect long-term visual outcomes [54, 55]. In addition, NSAIDs are used preoperatively to stabilize pupillary dilation intra-operatively and to facilitate cataract extraction. By the other way, there is no evidence supporting the addition of a topical steroid to the NSAID preoperatively. There is no sufficient evidence to support the long-term (>3 months after surgery) visual benefit of

NSAID therapy when applied solely or in combination with a steroid to prevent visual loss from PCME [55]. The suggestion from some authors that the combined effect of NSAIDs and corticosteroids could have a synergistic effect is not supported by the literature.

In patients with risk factors for IGS, the prevention should also be directed on their control or, when possible, their removal. In patients with pre-existent uveitis, should have the intraocular inflammation controlled with at least 3 months in order to undergo cataract surgery. Intravitreal or periocular steroids should be used to prevent reactivation of uveitis in the post-operative period. Immunomodulatory agents could be used in conjunction with steroids and NSAIDs to aid in ocular inflammation control in the pre, peri and post-operative periods as for steroid sparing. Acrylic or heparin-surface-modified polymethylmethacrylate intraocular lens should be used [56]. In cases of patients with pre-existent epirretinal membranes (ERM), the pars plana vitrectomy (PPV) for peeling of ERM before cataract surgery or, most frequently nowadays, combined PPV and cataract surgery could help to remove macular traction forces and reduce the risk of post-operative macular edema. Patients with diabetic macular edema should have an intravitreal anti-VEGF injection 2-3 weeks before cataract surgery.

The variability of the used criteria for diagnosis (some studies were based on OCT and other on fluorescein angiography) and for treatment of PCME among the several studies has limited accurate estimation of PSME incidence and assessment of treatment benefit with cross-trial comparisons [55].

It is expected that the use of long-lasting drug-delivery systems will provide sustained improvement of anatomic and functional results. New technologies and improvements in pharmacological agents have made significant improvement in treatment and outcomes for this serious condition. So what other advances can we expect from the near future?

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