Review Article

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Alternatıve Treatment Methods In Eyes Wıth Pseudophakıc Cystoıd Macular Edema

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Abstract: Cystoid macular edema is a common cause for unexplained painless vision loss after cataract surgery. Even the pathogenesis of pseudophakic cystoid macular edema (PCME) still remains undefined, it can most frequently occur in eyes with high vasoactive profile and risk of inflammation. Increased inflammation, ultimately leading to the breakdown of the blood-retinal barrier and cystic accumulation of extracellular intraretinal fluid. The natural history of PCME is spontaneous resolution without any treatment in most of patient, but it may take weeks or months, in addition permanent visual morbidity may occured in some cases. Therefore there is lack of consensus regarding treatment approach for this common ocular condition.

In this review treatment alternatives of PCME and its relation with underlying patho-physiologic mechanism are evaluated.

Key words: pseudophakic cystoid macular edema, Irvine-Gass syndrome, steroid, non-steroidal anti-inflammatory drugs, ozurdex, Anti- Vascular endothelial growth factors.

Introduction:

Pseudophakic cystoid macular edema (PCME) also known as Irvine-Gass syndrome (IGS), was initially reported by Irvine in 1953. Gass and Norton subsequently reported its characteristics with fluorescein angiography. (1-4) IGS remains an important cause of painless decrease in vision following uneventful cataract extraction and intraocular lens (IOL) implantation. This syndrome is present in around 4–12 weeks after cataract surgery and often resolves spontaneously in 70-90 % of the cases; which can takes from 2 months to a year. Epidemiological studies show that, 50% of these cases have resolution within 6 months after surgery, and 90% of them in 2 years. (3-7)

The Patho-Physiologic Mechanism:

The patho-physiologic mechanism for IGS is multifactorial including excessive surgical trauma increased inflammation, vitreous disturbance, hypotony. Surgical trauma triggers the cascade of inflammatory reactions, leading to conversion of arachidonic acid to prostacyclins, prostaglandins thromboxanes, leukotriens and other inflammatory mediators. These inflammatory mediators cause the breakdown of the blood–retinal barrier that ultimately increased retinal capillary permeability and extracellular fluid accumulation mainly in the outer plexiform and inner nuclear layers characterized by petalloid perifoveal leakage on fluorescein angiography (FA) (Fig.1)

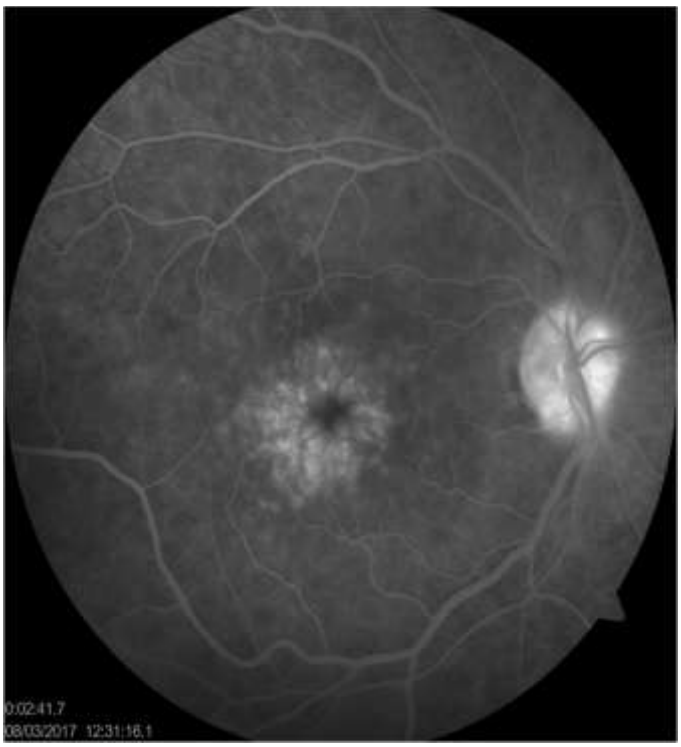

Figure 1: Petalloid perifoveal leakage on fluorescein angiography (FA)

Increased macular thickness in optical coherent tomography (OCT) is one of the significant finding of postoperative CME. (Fig 2)

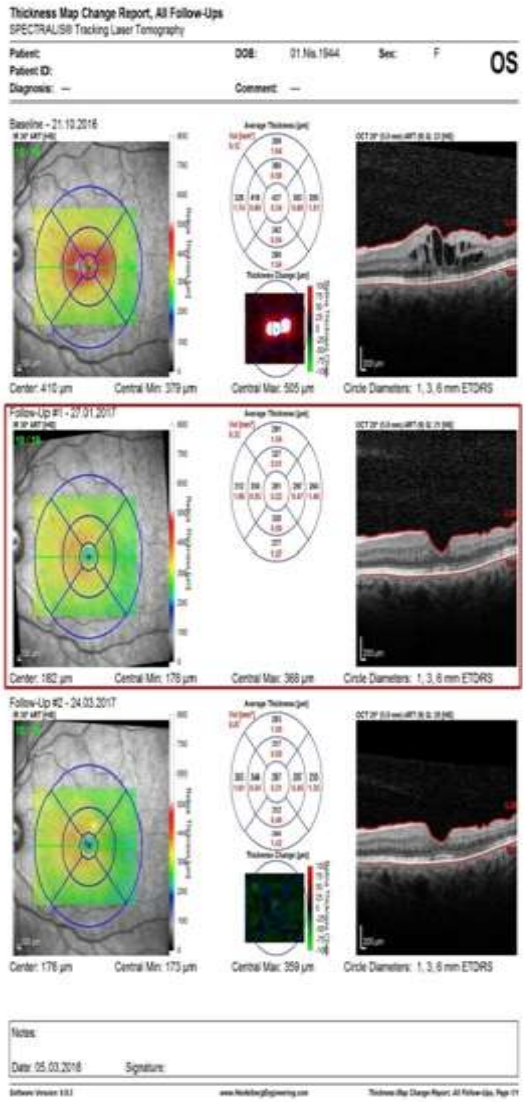

Figure 2: Differential map between the first and the last OCTs showed a foveal thickness reduction after treatment with dexamethasone implant (Ozurdex)

Increased prostaglandins within the eye also cause vasodilation and leukocyte migration. With these process, Müller cells become swollen and lysed than eventually developed cystic changes that result in varying degree of decrease in visual acuity. This detrimental effect on visual acuity may occasionally persist and lead to permanent vision loss.(3,5,7-9)

Prophylaxis and Treatment:

Prophylaxis:

Prophylaxis is recommended mainly for patients who have the risks of developing cystoid macular edema after cataract surgery, such as patients with diabetes, retinal vein occlusion, and uveitis. The incidence of IGS has been reported 0.1- 5% according to different reports, Several meta-analyses and systematic reviews have reported that a significant reduction in incidence of CME after cataract surgery with prophylactic use of topical nonsteroidal anti-inflammatory drugs (NSAID), including ketorolac 0.4%, bromfenac 0.1%, nepafenac 0.1% and diclofenac 0.1%. Topically applied nonsteroidal NSAIDs reduce prostaglandin synthesis by inhibiting the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) result in anti-inflammatory effect. (10-14) In systematic reviews and meta-analysis of randomized controlled trials have reported the effects of prophylactic topical NSAIDs; either as monotherapy or combined with topical corticosteroids, appear to be more effective than topical corticosteroids such as betamethasone, fluorometholone, dexamethasone or prednisolone asetonide alone for reduce the risk of developing PCME within 3 months after surgery. Similarly, results of controlled trials showed that the prevalence of CME 1 month after surgery was significantly lower among patients treated with NSAIDs (3.8%) comparing to patients treated with either potent or weaker corticosteroids (25.3%). (12-17)

Treatment Alternatives:

There is no standardized treatment protocol for Irvine-Gass syndrome due its multifactorial pathogenesis and spontaneous resolution, in most of the cases. Spontaneous resolution without any treatment, may take weeks or months, so for patients, especially those who have vision-dependent occupations and live active lifestyles, treatment should start as early as possible. (10-13)

Topical Nsaid Treatment:

A number of meta-analyses and systematic reviews have reported several treatment alternatives included, topical NSAIDs and steroids application, intravitreally or sub-Tenon's injections of triamcinolone acetonide, intravitreally Anti-VEGF injections, oral carbonic anhydrase inhibitors, immunomodulators therapy and in cases secondary to vitreous traction, other surgical approaches such as Nd: Yag laser vitreolysis, vitrectomy. (9,12,13)

The most frequently applied treatment choice include aggressive topical steroids, with or without NSAIDs, aimed at minimizing inflammation. Even in an analysis of several placebo-controlled trials, macular edema was reported in 0.7% in eyes receiving bromfenac 0.09% while 1.4% of patients receiving placebo, the benefits of topical NSAIDs in treating PCME are not well demonstrated

comparing to their prophylactic effects. In addition combination therapy with corticosteroids and topical NSAIDs significantly more effective than corticosteroids alone in treating IGS. (12-16)

Corticosteroid Treatment:

Administration of corticosteroids through various routes, other than topical application have been used for several years mostly. But still there is a little consensus on the efficacy of various therapeutic options such as, peribulbar, retrobulbar, or intravitreal in patient with foveal thickness more than 250 μm lasting for at least 90 days after the initiation of topical treatment. (16-18)

Randazzo et al [19] reported a significant devreased in foveal thickness after 0.8 cc of 4 mg betamethasone sub-Tenon injections. They also observed reduction in metamorphopsiaafter and better color sensitivity with this treatment.

The sub-Tenon route is considered equal to the retrobulbar route in terms of efficacy, in addition the sub-Tenon route is generally considered safer with respect to IOP elevation. On the other hand result of several studies showed a significant IOP rise with the use of triamcinolone acetonide (TA) that did not correlate with the route of application. According to most of reports in the literature, there is a common opinion about a higher incidence of IOP elevation beyond 30 mm Hg following intravitreal triamcinolone acetonide (IVTA) injection which has higher intravitreal concentration compared to peribulbar injection. (17-19)

Dexamethasone as an other corticosteroid has a 6-fold more potent anti-inflammatory effect than TA. One of the other disadvantages of IVTA is the transient therapeutic effect necessitating repeated injections. Sustained-release dexamethasone implant (Ozurdex) (Allergan, Inc.) have been developed to overcome this problem which sustained steroid levels and biological activity for 6 months, with peak levels of drug remains in the first 3 months. (20-24) This biodegradable systems made of poly lactic acid-co-glycolic acid (PLGA) matrix material which dissolves completely in the vitreous and provides sustained release of 0.7 mg of preservative-free dexamethasone during 6 months period. (20-22)

Williams et al. [21] observed a considerable improvement in BCVA from 0.3 pre-Ozurdex injection to 0.8 post-Ozurdex injection. Similarly Mayer et al [22] reported that the mean VA increased from 30.2 letters at baseline to 50.4 with the ozurdex treatment while the foveal thickness decreased from 520.8 ± 71.4 μm to 232.7 ± 26.6 μm at 12 months. Landré et al [23] reported a significant improvemed in term of macular edema treatment in which the mean central foveal thickness decreased from 598 μm. to 286 μm at month 1, 338 μm at month 3, and was 441 μm at month 12 with Ozurdex injection. They reported that some of their patients needed another dexamethasone implant injections. Klamann et al. [24] reported that 66% of their patient out of 12 patients needed more than one injection and recurring macular edema had been completely reduced by re-injection

Bellocq [25] reported that even 49% of 50 patient received a second Ozurdex injection neither functional nor anatomical recurrence was observed at least 1 year followed-up. They reported a significant decreament in macular thickness which was 544±117.2 μm before treatment and decreased to 302 μm and 61.2% of patients had an increase of more than 15 letters with the Ozurdex treatment. A good anatomic and functional response and safety patterns were similar in each injection which demonstrating Ozurdex's reproducibility.

Altintas et al.[26] reported a significant reduction in macular thickness with a single Ozudex implantation from 733 u to 197 u in eyes with unresponsive to intravitreal Anti-VEGF who is using inhaler steroid.

The intravitreal dexamethasone implant promising alternative therapy to achieve rapid resolution in recalcitrant post-surgical cystoid macular edema, refractory to topical treatments. It has a relatively better safety profile, reduce complications with low recurrence rate. (27-29)

Antı-Vascular Endothelıal Growth Factors (Vegf):

Despite the treatment options for IGS include NSAID and corticosteroids new fields of clinical research including the use of anti-vascular growth factors considered a good therapeutic choice.(30)

Vascular endothelial growth factors (VEGF) are inflammatory mediators which reduce vascular permeability by their indirect effect on vascular endothelial cells. They have a beneficial effect on the macular architecture, in the onset of macular edema because the inflammation is the major etiologic factor in the development of IGS. Successful treatment of IGS with intravitreal injection of either 1 mg or 1.25 mg bevacizumab (Avastin), a monoclonal antibody against all VEGF isoforms have been reported. (30-32)

According to Mitropoulos et als [33] report, single injection of Anti-VEGF was sufficient for the resolution of ME, while recurrence was observed in 1 patient out of 7 eyes.

Demirel et al [34] reported a significant reduction in CMT after Intravitreal (0.5 mg/0.05 mL) ranibizumab injection in 2 eyes. Mason et al [35] reported 2 patients with persistent IGS who had nearly immediate improvement of visual acuity 4 to 5 lines and a complete resolution of ME after a single intravitreal injection of 1.0 mg bevacizumab without further treatment. In contrast to this promising success rate Spitzer et al[36] reported that visual functional improvement did not observed in most eyes with neither single nor repeated injection at least when the drug is used as a mono-therapy. They reported that eye received repeat injections had fluctuating levels of central retinal thickness with significantly lower thickness after each injection but it increased again 6 to 10 weeks later.

Result of these clinical outcomes intravitreal ranibizumab, and bevacizumab have been shown to be effective in some, but not all cases.

Other Treatment Choise:

Mineralocorticoid receptor antagonists and spironolactone therapy, have been reported by Matet and coworkers[37] as an efficient combination with topical dexamethasone in refractory cases following complex cataract or retinal detachment surgery.

IFN alpha-2a at a dose of 3 million IU/day subcutaneously for 4 weeks has been demonstrated to be a successful treatment option for resistant chronic PCME in without any systemic or local side effects. (38)

Vitrectomy with removal of epiretinal membrane should be considered as a treatment modality in eyes had vitreomacular traction since tractional component may have adverse effect on the pathogenesis of PCME. (39)

Long-lasting, recalcitrant postoperative macular edema is a therapeutic challenge therefore early diagnose and optimal treatment regimens will help to gain visual functions prevent persistent visual disturbance.

Referencs

1. Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. Curr Opin Ophthalmol. 2012;23:26–32
2. Daien V, Papinaud L, Domerg C, Lacombe S, Daures JP, Villain M. Incidence and characteristics of cystoid macular edema after cataract surgery. Ophthalmology. 2016;123(3):663–664
3. Altıntaş AGK, Coban P, Arifoğlu, HB, Koklu G, Ozcan PY, Sonmez K. Comparison of phaco parameters effect on macular thickness changes after uneventful phacosurgery in diabetic and non-diabetic patients Int Eye Sci 2016; 16 (2):201-206
4. Packer M, Lowe J, Fine H. Incidence of acute postoperative cystoid macular edema in clinical practice. J Cataract Refract Surg. 2012;38(12):2108–2111
5. Henderson BA, Kim JY, Ament CS, Ferrufino-Ponce ZK, Grabowska A, Cremers SL. Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. J Cataract Refract Surg. 2007;33:1550–1558
6. Loewenstein A, Zur D. Postsurgical cystoid macular edema Dev Ophthalmol. 2010;47:148–159
7. Lobo C. Pseudophakic cystoid macular edema. Ophthalmologica. 2012;227:61–67
8. Shields MK, Adler PA,Fuzzard DRW, Chalasani R, Teong JMY A Case of Acute Bilateral Irvine-Gass Syndrome following Uncomplicated Phacoemulsification, Demonstrated with Optical Coherence Tomography. Case Rep Ophthalmol. 2015 Jan-Apr; 6(1): 143–148
9. Kiernan DF, Hariprasad SM. Controversies in the Management of Irvine-Gass Syndrome Ophthalmic Surgery, Lasers and Imaging Retina 2013;- Volume 44 · 6: 522-527
10. Quintana NE, Allocco AR, Ponce JA, Magurno MG. Non steroidal anti-inflammatory drugs in the prevention of cystoid macular edema after uneventful cataract surgery. Clin Ophthalmol. 2014;8:1209–1212
11. Sheppard JD. Topical bromfenac for prevention and treatment of cystoid macular edema following cataract surgery: a review. Clin Ophthalmol. 2016; 10: 2099–2111
12. Sahu S, Ram J, Bansal R, Pandav SS, Gupta A. Effect of topical ketorolac 0.4%, nepafenac 0.1%, and bromfenac 0.009% on postoperative inflammation using laser flare photometry in patients having phacoemulsification. J Cataract Refract Surg. 2015;41:2043–2048
13. Walters TR, Goldberg DF, Peace JH, Gow JA, Bromfenac Ophthalmic Solution 0.07% Once Daily Study Group Bromfenac ophthalmic solution 0.07% dosed once daily for cataract surgery: results of 2 randomized controlled trials. Ophthalmology. 2014;121(1):25–33

14. Wittpenn JR, Silverstein S, Heier J, et al. A randomized, masked comparison of topical ketorolac 0.4% plus steroid vs steroid alone in low-risk cataract surgery patients. Am J Ophthalmol. 2008;146:554–560.
15. Dal D, Sarac O, Toklu Y, Kocak Altintas AG, Cakmak HB, Damar Gungor E, Simsek S. The Effect of Perioperative Topical Ketorolac 0.5% on Macular Thickness after Uneventful Phacoemulsification.J Ophthalmol. 2017;2017:4271671
16. Warren KA Bahrani H Fox JE. NSAIDs in combination therapy for the treatment of chronic pseudophakic cystoid macular edema. Retina . 2010; 30: 260–266.
17. Sivaprasad S McCluskey P Lightman S. Intravitreal steroids in the management of macular oedema.Acta Ophthalmol Scand . 2006; 84: 722–733
18. Benhamou N Massin P Haouchine B. Intravitreal triamcinolone for refractory pseudophakic macular edema. Am J Ophthalmol . 2003; 135: 246–249
19. Randazzo A, Vinciguerra P. Chronic macular edema medical treatment in Irvine-Gass syndrome: case report Eur J Ophthalmol 2010;(2): 462-465
20. Herrero-Vanell R, Cardillo JA, Kuppermann BD. Clinical applications for the sustained-release dexamethasone implant for treatment of macular edema. Clin Ophthalmol. 2011;5:139–146
21. Williams GA, Haller JA, Kuppermann BD, et al. Dexamethasone posterior-segment drug delivery system in the treatment of macular edema resulting from uveitis or Irvine-Gass syndrome. Am J Ophthalmol. 2009;147:1048–1054
22. Mayer WJ , Kurz S, Wolf A, Kook D, Kreutzer T, Kampik A, Priglinger S, Haritoglou C. Dexamethasone implant as an effective treatment option for macular edema due to Irvine-Gasssyndrome J Cataract Refract Surg. 2015 Sep;41(9):1954-1961
23. Landré C, Zourdani A, Gastaud P, Baillif S. Treatment of postoperative cystoid macular edema (Irvine-Gass syndrome) with dexamethasone 0.7 mg intravitreal implant J Fr Ophtalmol Jan;39(1):5-11
24. Klamann A, Böttcher K, Ackermann P, Geerling G, Schargus M, Guthoff R. Intravitreal Dexamethasone Implant for the Treatment of Postoperative Macular Edema. Ophthalmologica. 2016; 236(4): 181-185
25. Bellocq D, Korobelnik JF, Burillon C, Voirin N, Dot C, Souied E, Conrath J, Milazzo S, Massin P, Baillif S, Kodjikian L. Effectiveness and safety of dexamethasone implants for post-surgical macular oedema including Irvine-Gass syndrome. the EPISODIC stud study. Br J Ophthalmol 2015 ;99(7):979-83
26. Altintas AGK, Ilhan C, Citirik M. The management of Irvine-Gass Syndrome in a patient using Inhaler steroid Int J Clin Exp Ophthalmol. 2018;2:1-5
27. Medeiros MD, Navarro R, Garcia-Arumí J, Mateo C, Corcóstegui B. Dexamethasone Intravitreal Implant for Treatment of Patients With Recalcitrant Macular Edema Resulting From Irvine-Gass Syndrome Investigative Ophthalmology & Visual Science May 2013, Vol.54, 3320-3324
28. Keilani C, Halalchi A, Wakpi Djeugue D, Regis A, Abada S. Evaluation of best corrected visual acuity and central macular thickness after intravitreal dexamethasone implant injections in patients with Irvine-Gass syndrome: A retrospective study of six cases. Therapie. 2016, OCT :71(%); 457-465
29. Sudhalkar A, Chhablani J, Vasavada A, Bhojwani D, Vasavada V, Vasavada S; Medscape. Intravitreal dexamethasone implant for recurrent cystoid macular edema due to Irvine-Gasssyndrome: a prospective case series. Eye (Lond). 2016 Dec;30(12):1549-1557.
30. Fenicia V, Balestrieri M, Perdicchi A, MauriziEnrici M, DelleFave M, Recupero SM Intravitreal Injection of Dexamethasone Implant and Ranibizumab in Cystoid Macular Edema in the Course of Irvine-Gass Syndrome Case Rep Ophthalmol. 2014 May-Aug; 5(2): 243–248
31. Arevalo JF, Maia M, Garcia-Amaris RA, et al. Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: the Pan-American Collaborative Retina Study Group results. Ophthalmology. 2009;116:1481–1487
32. Mason JO, Albert MA, Vail R, et al: Intravitreal bevacizumab (Avastin) for refractory pseudophakic cystoid macular edema. Retina 2006; 26: pp. 356-357
33. Mitropoulos PG, Chatziralli IP, Peponis VG, Drakos E, Parikakis EA. Intravitreal Ranibizumab for the Treatment of Irvine-Gass Syndrome. Ocul Immunol Inflamm. 2015 Jun;23(3):225-231

34. Demirel S, Batioğlu F, Özmert E. Intravitreal Ranibizumab for the Treatment of Cystoid Macular Edema in Irvine-Gass Syndrome Journal of Ocular Pharmacology and Therapeutics. 2012, 28(6): 636-639
35. Mason JO, III, Albert MA, Jr, Vail R. Intravitreal bevacizumab (Avastin) for refractory pseudophakic cystoid macular edema. Retina. 2006;26:356–357
36. Spitzer MS, Ziemssen F, Yoeruek E, et al. Efficacy of intravitreal bevacizumab in treating postoperative pseudophakic cystoid macular edema J Cataract Refract Surg 2008;34:70–75
37. Matet A, Daruich A, Behar-Cohen F. Irvine-Gass Macular Edema Responding to the Combination of Oral Mineralocorticoid-Receptor Antagonist With Dexamethasone Drops. Ophthalmic Surg Lasers Imaging Retina. 2017 Nov 1;48(11):936-942.
38. Deuter CM Gelisken F Stubiger N. Successful treatment of chronic pseudophakic macular edema (Irvine-Gass syndrome) with interferon alpha: a report of three cases. Ocul Immunol Inflamm . 2011; 19: 216–218
39. Scarpa G. Bilateral cystoid macular edema after cataract surgery resolved by vitrectomy. Eur J Ophthalmol. 2011;21:677–679