THE INCIDENCE, PATHOGENESIS AND TREATMENT OF CYSTOID MACULAR EDEMA FOLLOWING CATARACT SURGERY*

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INTRODUCTION

Cystoid macular edema (CME) following cataract surgery was first recognized over 4 decades ago by Irvine.[1] Macular edema was mentioned in the 20th century, and CME was identified and studied earlier in the 20th century.[2-6] However, the report of Irvine represents the first clinical description of CME following cataract surgery as a distinct entity.[1] Following this initial description, the syndrome was further studied and described with new methods including fluorescein angiograms.[7,8] Today, this postoperative complication is frequently referred to as the Irvine-Gass syndrome. It is recognized as the most common cause of decreased vision in patients following cataract surgery with or without the implantation of an intraocular lens.[9-17] This syndrome is responsible for a greater and a more frequent loss of vision than many of the more commonly discussed postoperative complications, including retinal detachment and endophthalmitis.[10,11] Despite over 40 years of clinical and laboratory investigative effort, the incidence and pathogenesis of this syndrome remain obscure, and its treatment continues to be controversial.

The purpose of this thesis is to provide a current and comprehensive review of the literature on the Irvine-Gass syndrome and to describe previously unpublished investigations that extend our knowledge about the incidence, pathogenesis, and treatment of this syndrome. The literature review supports the hypothesis that the incidence, pathogenesis, and treatment of CME following cataract surgery are poorly understood. The overall goal of the 7 laboratory and clinical studies described within this thesis is to provide new information concerning the incidence, pathogenesis, and treatment of CME following cataract surgery.

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More specifically, the original results and data that are reported within the new investigations section following the literature review include:

I. Incidence of CME Following Cataract Surgery

II. Correlation of Anterior Ocular Inflammation with CME Following Cataract Surgery

III. Topical NSAID Treatment of CME Following Cataract Surgery With Topical NSAIDs

- A. Comparison of Topical NSAIDs and Their Ability to Stabilize the Blood-Aqueous Barrier (BAB) of Rabbits Following Paracentesis
- B. Comparison of Ketorolac Tromethamine 0.5% and Diclofenac Sodium 0.1% Ophthalmic Solutions in Reducing Postoperative Inflammation After Cataract Extraction and Intraocular Lens Implantation
- C. The Effect of Patient Characteristics on Response to Topical NSAID Treatment of Chronic Clinical CME Following Cataract Surgery
- D. Treatment of Acute-Onset Clinical Cystoid Macular Edema Following Cataract Surgery With Topical NSAIDs

IV. Oral Acetazolamide and the Treatment of Chronic Clinical CME Following Cataract Surgery

These original laboratory and clinical efforts consist of 5 studies (I, IIIA, IIIB, IIID, IV) that have not been previously published. In addition, two studies (II, IIIC) are included that have been previously published in part. However, they are reported here in more detail and with a different emphasis in support of this thesis.

A summary and conclusions section derived from both the literature review and the new investigations is placed at the end of this thesis. This section attempts to place the findings of the new investigations and their relationship to the literature review into perspective in a concise manner.

REVIEW OF LITERATURE

INCIDENCE

Although CME following cataract surgery is recognized as the most common cause of decreased vision in the postoperative period, the reported incidence of this postoperative complication has been and continues to be quite variable. Many review articles mention factors that may contribute to the difference in the reported incidence of CME.[15,17-31] These comments are derived from more than 60 published papers, each of which mentions or discusses the incidence of this syndrome. These publications are summarized in the Appendix of this paper.[9-11,14,24,25,28-90] In spite of the extensive effort reflected in these reports and reviews, the incidence of this syndrome remains uncertain. Furthermore, frequently the reasons for the differences

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in reported incidence continue to remain a mystery. For example, 2 well-designed studies performed in the same city, including patients with similar characteristics who were operated on by the same surgeon using the same technique and medications, report an incidence of 5.6% and 18.8%, respectively, for angiographic CME in eyes with intact posterior capsules and intraocular lenses lacking UV filters.[14,91] The explanation for this difference in incidence is unclear.[92] Therefore, some of the coexistent variables that can affect the incidence of CME have not been identified.

However, in spite of this uncertainty, it is important to recognize as many of the known variables as is possible for at least 2 reasons. First, it seems prudent to identify factors tending to increase the incidence of CME and to omit them in an attempt to minimize the incidence of this postoperative complication.[92] Second, it is important to identify these variables and recognize their potential impact on the interpretation of results from therapeutic trials that evaluate potential treatments for CME. The presence of these variables and their potential influence on the observed incidence of CME make it unwise to use retrospective controls when evaluating the potential merits of a new therapeutic approach, because the observed difference may reflect the presence of the coexistent variable and not a therapeutic effect. Furthermore, when evaluating the results of a prospective, randomized, double-masked therapeutic trial, one must confirm that these variables are present in both the treatment and control groups in similar numbers at the conclusion of the study to prevent misinterpretation of the results.

Insofar as the factors that influence the incidence of CME are relevant to therapeutic trials concerning this syndrome, a review of these variables is of great practical value. Factors that investigators have considered *potentially* capable of influencing the incidence of CME following cataract surgery include:

1. The thoroughness of the search for this syndrome, including the performance and examination of multiple angiograms[20]
2. Whether the investigators report a retrospective study designed to assess patients with poor vision or a prospective study including fluorescein angiograms[30]
3. The introduction of new instrumentation or technology permitting more careful or complete diagnostic examinations[20]
4. A changing definition of CME following cataract surgery[23]
5. Whether the investigators are reporting clinical CME (angiographic CME associated with a decrease in visual acuity) or only angiographic CME[15,17,19,20,22,28]
6. How long after surgery the patient is examined[20,39,40,45,137,138]
7. Patient characteristics, including age,[20,34,68,73,77,93,94] presence of vascular disease,[7,20,29,34,39,45,50,86,89,90,95,96] race and eye color,[83,97] and a history of

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alcoholsim[95]

8. A history of CME following surgery in the contralateral eye[8,20,28,56,99]
9. Comparisons of results following intracapsular cataract extraction (ICCE) and extracapsular cataract extraction (ECCE) with or without the presence of an intraocular lens[17,24,25,28,29,42,47,49,53,55,57,59,62,65,72,81,87,100]
10. The administration of retrobulbar hyaluronidase[101,102]
11. The presence of intraoperative complications, including vitreous loss[9,11,52,54,63,64,72,84,87,103,104]
12. The presence of vitreous to the wound[1,20,104-110]
13. The presence of a peaked pupil in the postoperative period[19,27,93,111-113]
14. The influence of coexistent drug use or other ocular irritants[17,26,51,58,75,83,101,102,114-119]
15. The presence or absence of an intact posterior capsule[31,52,54,59,60,65,69,70,78,98,120-123]
16. The presence of specific intraocular lens qualities such as a polyvinlypyrrolidone coating,[124] metal loops,[125] and UV blockers,[91,98] lens defects,[126] iris clip and rigid anterior chamber (AC) lens[27,30,94]
17. Exposure to excessive intraoperative or postoperative light[79,91,98,122,127-131]
18. The performance of a postoperative yttrium-aluminum-garnet (YAG) capsulotomy[120,132]
19. The lapse of time between cataract extraction and secondary intraocular lens implant[133]
20. Secondary lens implantation compared with primary lens implantation[133]

There is agreement that the incidence of CME is greatest in *prospective* studies reporting *angiographic* CME including *multiple* angiograms performed *1 to 3 months* following an *ICCE* with implantation of an *iris clip* lens in an *older* population of patients with systemic *vascular disease*. Furthermore, the incidence can vary with how, when, and why an investigator looks for this syndrome. However, investigators have not been in agreement concerning the importance of several of the potential variables listed previously. Therefore, the evidence suggesting that these factors may or may not influence the development of angiographic or clinical CME following cataract surgery is summarized in Table I.

CLINICAL CHARACTERISTICS

CME following cataract surgery consists of a maldistribution of the retinal intravascular fluid within the macula. The leakage of the intravascular contents from dilated perifoveal capillaries initially causes thickening of the macula, which may progress to cystoid expansions within the outer plexiform (Henle's) layer and inner nuclear layer of the retina. These cystoid

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TABLE I: FACTORS INFLUENCING THE INCIDENCE OF CME FOLLOWING CATARACT SURGERY

VARIABLE	RESULTS OF COMPARISON	ANGIOGRAPHIC CME	CLINICAL CME	REFERENCES
Type of surgery	ICCE>ECCE	Increased	Increased	35,50,51,53,56, 57,59,60,62,65, 69,71,72
Placement of IOL	Iris clip>AC>PC*	Increased	Increased	27,28,30,56,94, 125,134
Integrity of posterior capsule	Absent > present†	Increased	Same	78
Hyaluronidase in retrobulbar	Absent = Present ‡	Same	Same	102
Operating microscope light	UV filter = no filter§	Same	Same	79
Environmental light	IOL without UV filter > IOL with UV filter	Increased	Same	91,98
Contralateral CME	Present>absent	Increased	Increased	8,20,56, 98,99
When examined	1-3 mo greatest incidence	Increased	Increased	20,39,40,45
Age	Older > younger‖	Increased	Increased	20,68,73,77, 93,94
Systemic vascular disease (diabetes, hypertension)	Present > absent¶	Increased	Increased	7,20,29,34, 39, 45,50, 95,96
Vitreous loss	Present > absent#	Increased	Increased	9,11,52,54, 63,64,72,84, 87,103,135
Vitreous to wound	Present > absent	Increased	Increased	1,20,104,105, 106,107,109, 110
Abnormal pupil shape	Present > absent	Increased	Increased	19,27,112,113
Iris incarceration in wound	Present > absent	Increased	Increased	113
Race	White > black	Increased	Increased	83,97
Epinephrine	Present > absent**	Increased	Increased	114,115,116, 117,118,119

AC, anterior chamber; CME, cystoid macular edema; angiographic CME, visual acuity normal; clinical CME, visual acuity abnormal; ECCE, extracapsular cataract extraction; ICCE, intracapsular cataract extraction; IOL, intraocular lens; PC, posterior chamber; UV, ultraviolet.

* Initially investigators observed no difference.[52,57,62,72,136] Subsequently good evidence for AC > PC,[28,134] iris-supported lenses poorer prognosis,[30] iris clip lenses particularly

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