Assessment of Efficacy of Non-Steroidal Anti-inflammatory Drugs in the prevention of Pseudophakic Cystoid Macular Edema in Diabetic Patients

Thesis

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BRB:……..Blood retinal barrier

BRVO:.....Branch retinal vein occlusion

CME:…….Cystoid macular edema

COX:……..Cyclooxygenase

CNV:……..Choroidal neovascularization

CRVO:.....Central retinal vein occlusion

CSME:……..Clinical significant macular edema

DM…….Diabetes mellitus

DME:…….Diabetic macular edema

DR:…….Diabetic retinopathy

ELM:……..External limiting membrane

FA:…….Fluorescein angiography

FDA:……...Food and drug administration

GCL:……..Ganglion cell layer

ILM:……Internal limiting membrane

IVTA:…….Intra-vitreal triamcinolone acetonide

ME:…….Macular edema

NSAID's:……...Non-steriodal anti-inflammatory drugs

OCT:…….Optical coherence tomography

PCME:……..Pseudophakic cystoid macular edema

PTSS :.....Posterior sub-tenon triamcinolone
Acetonide

RD:……....Retinal detachement

RPE:……..Retinal pigmented epithelium

RVO:…….Retinal vein occlusion

VEGF:……Vascular endothelial growth factor

INTRODUCTION

Macular edema(ME) is the result of an accumulation of fluid in the retinal layers around the fovea. It contributes to visual loss by altering the functional cell relationship in the retina and promoting an inflammatory reparative response.**(Coscas., 2010)**

ME may be intracellular or extracellular. Intracellular accumulation of fluid, also called cytotoxic edema, is an alteration of the cellular ionic distribution. Extracellular accumulation of fluid, which is more frequent and clinically more relevant, is directly associated with an alteration of the blood-retinal barrier (BRB). **(Coscas., 2010)**

The relevant parameters to evaluate ME include: extent of the macular edema (i.e., the area that shows increased retinal thickness); distribution of the edema in the macular area (i.e., focal versus diffuse macular edema); central foveal involvement with central area 500 µ; fluorescein leakage (evidence of alteration of the BRB or 'open barrier') and intraretinal cysts. Signs of ischemia (broken perifoveolar capillary arcade and/or areas of capillary closure); presence or absence of vitreous traction; increase in retinal thickness and cysts in the retina (inner or outer), and chronicity of the edema as the time elapsed since initial diagnosis and response to therapy are also important parameters for ME.**(Coscas., 2010)**

ME is a common, final pathway for many different ocular and systemic diseases especially diabetic retinopathy (DR), retinal vascular disorders (such as central and branch retinal vein occlusion), and uveitis. The complex and multi-factorial patho-physiological mechanisms leading to ME, are still poorly understood. Inflammation plays a crucial role as demontrsated by significant increase of different cytokines and chemokines, (besides vascular endothelial growth factors-VEGF) in ocular fluids**.(Vujosevic and Midena., 2015).**

Macular edema secondary to uveitis is also a common problem, occurring in up to 48% of uveitic eyes.**(Prieto et al.,2001).**

Cystoid macular edema (CME) is a serious consequence of cataract surgery and other ocular procedures, resulting sometimes in transient or sometimes permanent visual loss. **(Solomon., 1995)**

Clinically significant CME has been reported from 1%–2% of patients following uncomplicated phacoemulsification. (Ray and D'Amico.,2002 and Wolf at al.,2007) while , the incidence of subclinical, angiographic CME is approximately 20%–30% of uncomplicated cataract surgery cases **(Ursell et al,. 1999)**

Pseudophakic cystoid macular edema (PCME) remains the most common cause of poor visual outcome following cataract surgery. The incidence of PCME ranges from 4% to 11% in optical coherence tomography (OCT) after uneventful phacoemulsification cataract surgery and peaks at approximately 4 to 6 weeks**.(Bélair et al.,2009 and Vukicevic et al.,2012).**

Whereas subacute PCME may resolve spontaneously, some patients will suffer from vision impairment and will be difficult to treat. As broad as the mechanisms, as many are the treatment options. Topical non-steroidal anti-inflammatory drugss (NSAID's) and corticosteroids either as mono- or combined therapy are a commonly used first line approach in the treatment. When ineffective, systemic treatment with these agents may be an option. Alternatively, intravitreal application of corticosteroids and anti-vascular endothelial growth factor (anti-VEGF) may offer an effective option, if first-line treatment fails. A critical evaluation of the current literature revealed that the optimal treatment of PCME remains unclear and requires further investigation. In addition, prevention should be of foremost importance and remains an open issue. Identification of risk factors, application of NSAID's and consequent follow-up are potential essential steps in the avoidance and treatment of this complication**.(Grzybowski et al.,2015).**

Aim of the Study

To assess the efficacy of topical NSAID's for prevention of CME after cataract surgery in diabetic patients.

Anatomy of The MACULA

Macula Lutea:

The macula lutea appears as a darkened region in the central retina and may seem to have a yellow hue because of the xanthophyll pigments, lutein, and zeaxanthin. These pigments are located throughout the retina, but the greatest concentration is in the macula. These pigments apparently act as filters, absorbing short wavelength visible light to reduce chromatic aberration but may also have an antioxidant effect suggesting a protective role against Ultraviolet radiation damage(Patton and Thibodeau.,2013).

The macula lutea is approximately 5.5 mm in diameter ;its center is approximately 3.5 mm lateral to the edge of the disc and approximately 1 mm inferior to the center of the disc.(Fig 1).

The pigment epithelial cells are taller and contain more pigment than cells elsewhere in the retina, contributing to the darkness of this area. The choroidal capillary bed also is thicker in the macula lutea than elsewhere. The entire macular region consists of the foveola, the fovea, and the parafoveal and perifoveal areas (both are annular areas).(Picaud.,2003)

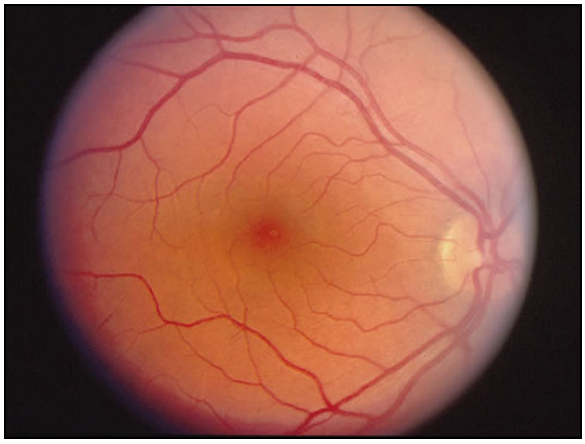

Figure 1. Ophthalmoscopic appearance of the fundus to show the macula lutea. (Picaud.,2003)

Fovea (Fovea Centralis):

The shallow depression in the center of the macular region is the foveal centralis and is formed because the retinal neurons are displaced,leaving only photoreceptors in the center. The fovea has a horizontal diameter of approximately 1.5 mm. The curved wall of the depression is known as the clivus(Fig 2). The fovea has the highest concentration of cones in the retina. The ratio between cone cells and ganglion cells approaches 1:1 (Forrester et al.,2015).

Within the fovea is a capillary-free zone 0.4 to 0.5 mm in diameter. The lack of blood vessels in this region allows light to pass unobstructed into the photoreceptor outer segment. The only photoreceptors located in the center of the fovea are cones. The external limiting membrane(ELM) is displaced vitreally because of the lengthening of the outer segments. (Ahnelt.,1998).

The cells of the inner nuclear layer and ganglion cell layer are displaced laterally and accumulate on the walls of the fovea. The photoreceptor axons become longer as they deviate away from the center; these fibers are called Henle's fibers. This region of the outer plexiform layer is known as Henle's fiber layer.(Duker et al.,2014).

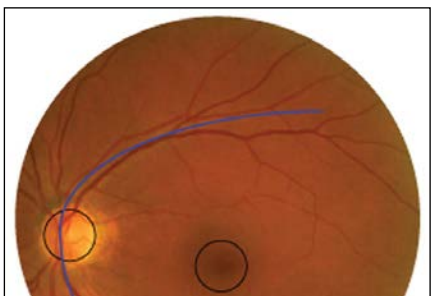

Fig.2: A digital color fundus photograph with a circle marking the optic disc (left) and another circle in the center of which is the fovea. The vascular arch marked in the image is formed by the major arteries and veins that leave the optic disc up- and downwards. **(Abràmoff et al.,2007)**

Foveola:

The diameter of the foveola is approximately 0.35 mm. At the foveola, the retina is approximately 0.13 mm thick, compared with 0.18 mm at the equator and 0.11 mm at the ora serrata. The foveola contains the densest population of cones that have the smallest cross-sectional diameters of all the photoreceptors.(Forrester et al.,2015)

The layers present in the foveola are the:

RPE(Retinal pigmented epithelium), photoreceptor layer, ELM, Outer nuclear layer (which contains about 10 rows of cone nuclei), Henle's fiber layer and the Internal limiting membrane(ILM)(Forrester et al.,2015).

Parafoveal and Perifoveal Areas

The annular zone surrounding the fovea can be divided into an inner parafoveal area and an outer perifoveal. The width of the parafoveal area is 0.5mm and of the perifoveal area, 1.5 mm (Forrester et al.,2015).

The terms used to describe the macular area differ between the histologist and the clinician. The histologist uses the word fovea to describe what a clinician would name macula, and the histologist calls the foveola that which a clinician would name the fovea. The term macula is purely approximately the same size as the optic disc; clinically, the term fovea then refers to the very center of this area clinical one and usually refers to the area of darker coloration(Yanoff and Sassani.,2015).

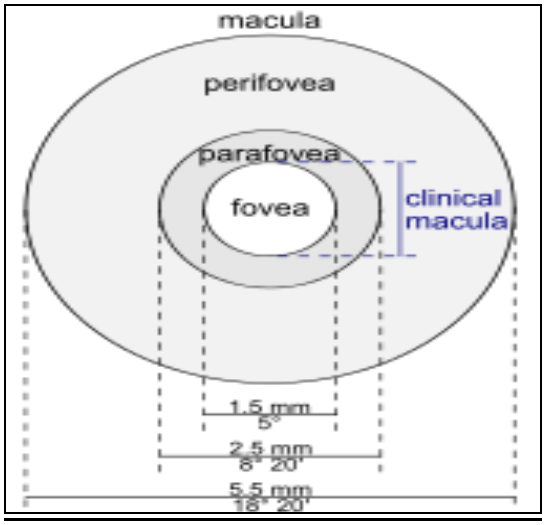

Fig.3: The macula lutea of the retina, showing perifovea, parafovea, fovea, and clinical macula

Causes of CME:

- **<u>Postoperative cystoid macular edema</u>:**

CME following cataract surgery was initially reported by Irvine in 1953 and is known as the Irvine–Gass syndrome . However, a clinically significant decrease in visual acuity is seen only in about 1% of these eyes . If cataract extraction is complicated by posterior capsule rupture and vitreous loss, severe iris trauma or vitreous traction at the wound, there is a significantly higher incidence (up to 20%).(Tsangaridou et al.,2015).

Transient corneal edema detected within the first week after routine cataract surgery is a predictive factor for development of PCME. Close postoperative observation and intervention is recommended in patients with transient corneal edema. (Do et al.,2015).

Topical NSAID's and corticosteroids are widely used and, when combined, may have a synergistic effect.(Fernández-Ferreiro et al.,2015).

There are multiple options for clinical management and will be discussed in details in chapter of treatment of CME.

- **Diabetes mellitus:**

Diabetic macular edema (DME) is the major cause of vision loss in diabetic persons. DR , a common complication of DM, is the main cause of blindness in the active population. Diabetic macular edema (DME) may occur at any stage of DR, and is characterized by vascular hyper-permeability accompanied by hard exudates within the macula. Medical and surgical therapies have dramatically reduced the progression of DR, and timely intervention can reduce the risk of severe vision loss by more than 90 % (Calvo et al.,2015)

DME is a condition which involves fluid accumulation in the inner portion of the retina. It often follows changes in retinal blood vessels which enhance the fluid to come out of vessels. Although it may be asymptomatic, symptoms are primarily painless loss of central vision, often with the complaint of seeing black spots in front of the eye.It is reported that CME may resolve spontaneously, or fluctuate for months, before causing loss of vision. If left untreated, progression of CME may lead to permanent visual loss.(Sahoo et al.,2015).

Alteration of the blood-retinal barrier is the hallmark of this disease, characterized by pericyte loss and endothelial cell-cell junction breakdown. Multiple cytokines and chemokines are involved in its pathogenesis , with multiple cellular involvement affecting the neurovascular unit. . Early detection and successive treatment may improve the visual acuity. DME is mainly graded into non-clinically significant macular edema and clinically significant macular edema(CSME) according to the location of hard exudates in the macula region.(Das et al.,2015)

Patients with DME and submacular fluid, intraretinal cysts, severe thickening, or renal disease respond poorly when untreated and respond well to ranibizumab treatment. Elimination of submacular fluid, intraretinal cysts and severe thickening are important goals of DME treatment, and in patients with renal disease, treatment should be very aggressive, with a goal of eliminating all macular fluid. Several NSAID’s such as ketorolac 0.5%, bromfenac 0.09%, and nepafenac 0.1%, have therefore also been used topically to treat chronic diabetic CME.(Sophie et al.,2015).

With the introduction of anti- VEGF agents, the treatment of DME has been revolutionized, and the indication for laser therapy has been limited. However, the response to anti-VEGF drugs in DME is not as robust as in proliferative DR, and many patients with DME do not show complete resolution of fluid despite multiple intravitreal injections. Potential novel therapies targeting molecules other than VEGF and using new drug-delivery systems currently are being developed and evaluated in clinical trials. (Mookiah et al.,2015)

- **Uveitis:**

ME represents a major cause of visual loss in uveitis and its adequate management is crucial for the maintenance of useful vision in patients with uveitis. Macular edema may complicate anterior, intermediate, and posterior uveitis, which may be due to various infectious, tumoral, or autoimmune etiologies. Breakdown of the internal or external blood-retinal barrier is involved in the pathogenesis of inflammatory ME. (Voide and Borruat.,2015).

Treatment of inflammatory ME requires specific treatment in cases of infectious or tumoral etiologies. If it remains persistent, anti-inflammatory treatments are needed. Steroid treatment, available in intravitreal, subconjunctival and sub-Tenon's routes, are widely used. Triamcinolone acetonide (Kenacort) is a corticosteroid that can be administrated by subconjunctival injection, with an extended release for up to three months.(Liu and Zhang.,2015).

Bilateral chronic sight-threatening posterior uveitis often requires systemic treatment, and steroids represent the classic first-line therapy. In order to reduce the daily steroid dose, immunosuppressant or immuno-modulatory drugs may be added. Certain of these compounds are now available intra-vitreally. Long term and sustained release implantation is the newest administration for steriod therapy. The immunosuppressant such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil can be used specially for chronic and intractable uveitic CME. Moreover, some newly developed biological agents, for example, anti-VEGF, interferon-α, anti-TNF and acetazolamide will provide new options for the pharmacotherapy. (Tomkins-Netzer et al.,2015)