

Research Article

# Efficacy of Intravitreal Injection of Etamsylate in Inflammation and Angiogenesis-dependent Ocular Diseases

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## Abstract

Etamsylate is a synthetic inhibitor of both FGF and VEGF with very promising clinical efficacy data in ocular diseases. Here we summarize the evidence supporting the efficacy of etamsylate in treating inflammation- and angiogenesis-dependent ocular diseases and provide a pharmacological rationale for clinical improvement.

**Keywords:** Etamsylate; Retinal Diseases; Fibroblast Growth Factor; Vascular Endothelial Growth Factor

## Abbreviations:

FGF: Fibroblast Growth Factor; VEGF: Vascular Endothelial Growth Factor; AMD: Age Related Macular Degeneration; DHBS: Dihydroxybenzene Sulfonate; GA: Geographic Atrophy; CME: Cystoid Macular Edema; CSR: Central Serous Retinopathy; RVO: Retinal Vein Occlusion; CRVO: Central Retinal Vein Occlusion; BRVO: Branch Retinal Veins Occlusion; RPE: Retinal Pigment Epithelium

## Introduction

Inflammation elicited by Fibroblast Growth Factor (FGF) is prone to the consolidation of a positive inflammatory feedback loop, typical of chronic diseases, since it induces the upregulation of the synthesis of COX-2 and phospholipase A2, which reciprocally promote the expression of FGF [1,2].

Generally, inflammation ends up in a healing process. However, if this process is not properly ordered, it results in persistent inflammation. Chronic inflammatory conditions have been found to mediate a wide variety of diseases including ocular disorders [3,4]. Inflammatory cells secrete growth factors such as FGF and Vascular Endothelial Growth Factor (VEGF), proteases and cytokines that induce angiogenesis. Thus, inflammation promotes angiogenesis and angiogenesis maintains inflammation [5,6].

Under hypoxic conditions, a variety of molecules are secreted onto the vitreous including growth factors, cytokines and chemokines that can direct the recruitment of leukocytes to sites of inflammation [7].

Chronic intravitreal injections of anti- VEGF agents are the first line treatment for exudative related macular degeneration (wet AMD) [8]. However, frequent intravitreal injections of anti-VEGF drugs have shown local and systemic side effects (Fig. 1). Indeed, poor vision and persistent exudation are often associated with macular atrophy and sub macular fibrotic scar formation after anti-VEGF treatment, causing further persistent vision loss in AMD patients [9-19]. Due to the side effects of these standard therapies, targeting alternative mechanism of action may be helpful to find treatment for this very common disease.

## ***Adverse effects of long-term intravitreal anti-VEGF drug administration***

<b>Local</b>	<b>Systemic</b>
<ul style="list-style-type: none"> <li>• Endophthalmitis</li> <li>• Intraocular inflammation</li> <li>• Retinal detachment</li> <li>• Intraocular pressure elevation</li> <li>• Ocular hemorrhage</li> <li>• Ischemic optic neuropathy</li> <li>• Retinal venous occlusion</li> <li>• Hemorrhagic macular infarction</li> <li>• Visual acuity loss (15% in 5 years)</li> </ul>	<ul style="list-style-type: none"> <li>• Sixth nerve palsy</li> <li>• Visual hallucination</li> <li>• Erectile dysfunction</li> <li>• Decreased kidney function</li> <li>• Myocardial infarction</li> <li>• Cerebrovascular accidents</li> <li>• Cerebral hemorrhage</li> <li>• Hypertension</li> <li>• Arrhythmias:               <ul style="list-style-type: none"> <li>• Atrial fibrillation</li> <li>• Atrial flutter</li> <li>• Ventricular fibrillation</li> <li>• Supraventricular tachycardia</li> </ul> </li> </ul>

**Figure 1:** Adverse and systemic effects in patients after chronic intravitreal injection of anti-VEGF drugs.

It has been reported that etamsylate is a well-characterized inhibitor of FGF and VEGF signalling pathways [20-22]. Thus, etamsylate is a good candidate for treating inflammation and angiogenesis-dependent diseases. In this report, we highlight the efficacy of etamsylate in several diseases affecting retina and anterior ocular segment.

### **Methods**

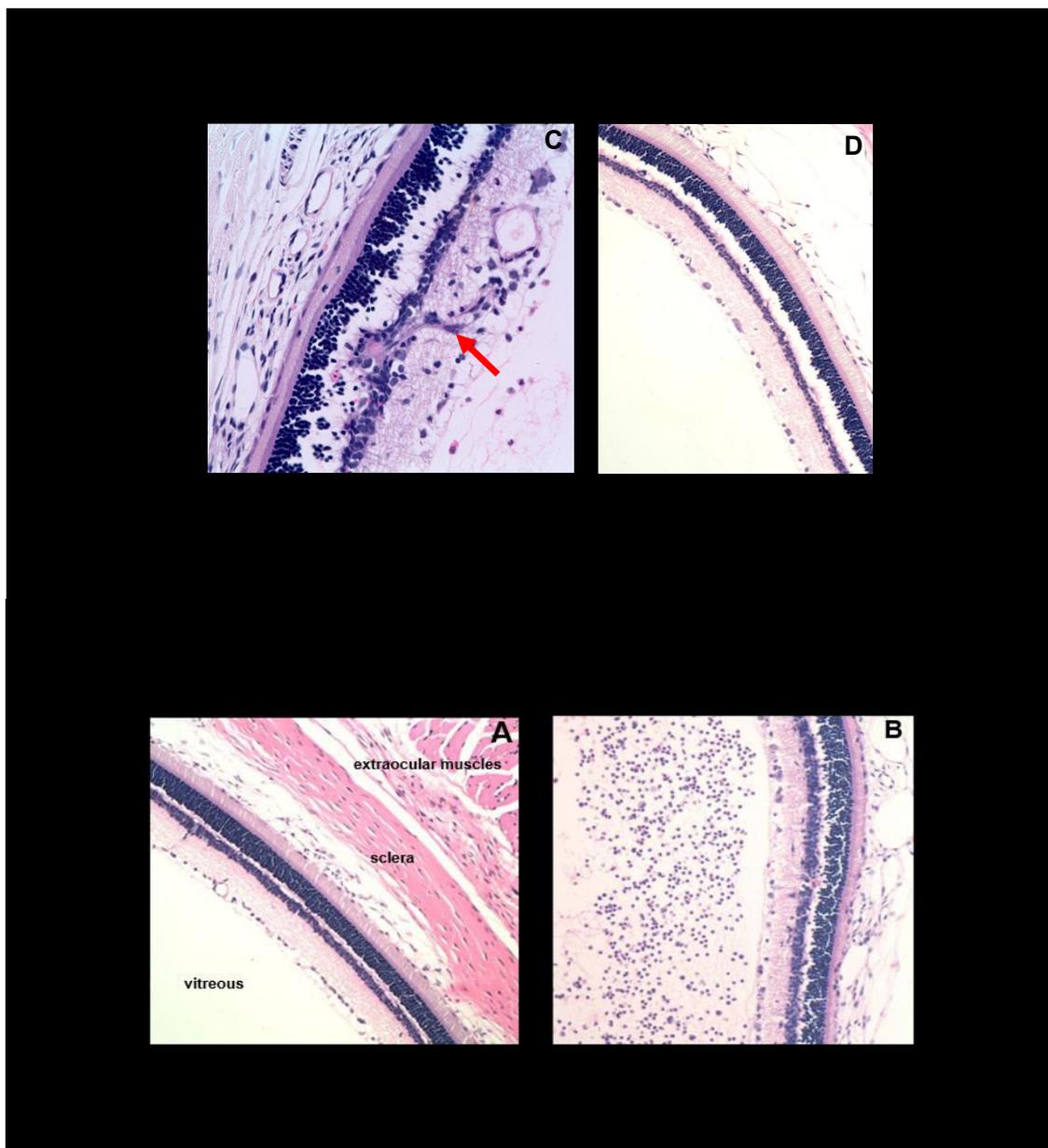
#### *Animal Model of Transient Retinal Ischemia*

First, an animal study was performed to analyse histologically whether the intravitreal administration of etamsylate has a protective effect against ischemia-reperfusion injury in a rat model of transient retinal ischemia. Animal studies were performed in accordance with the ARVO Statement for Use of Animals in Ophthalmic and Vision Research.

Ten adult Sprague-Dawley rats of both sexes were anesthetized by intraperitoneal injection of ketamine hydrochloride (50 mg/kg), diazepam (2 mg/kg) and atropine 0.1 mg/kg). Animals were divided into two groups (Group A, n=5) with 60 minutes of ischemia and 4 days of reperfusion and group B (n=5) with 60 minutes of ischemia and 14 days of reperfusion.

Using a transorbital approach, unilateral retinal ischemia was produced occluding the retinal central artery with a micro clip. Retinal perfusion was obtained by declamping the micro clip. At reperfusion, an Intravitreal injection of etamsylate (18.75 mg/10 $\mu$ l) was performed in the vitreous behind the dorsal limbus, using a 35-gauge needle mounted to a 10 $\mu$ l Hamilton syringe, under the guidance of a surgical microscope. Injections were performed slowly over 2 minutes.

After the reperfusion period, animals were euthanized by anesthetic overdose and eyeballs were extracted and processed for histological studies and microscopic sections were stained with hematoxylin-eosine (Fig. 2) and compared with histological findings in non-operated rats. Histological stained sections revealed leukocytes infiltration into the vitreous and neovessels in the retina in non-treated animals (Fig. 2). In treated animals, histological sections showed no signal of leukocytes infiltration nor angiogenesis (Fig. 2). This study illustrates the role of etamsylate in preventing vitreous inflammation and retinal angiogenesis in a rat model of retinal transient ischemia.



**Figure 2:** Hematoxylin-eosine staining of normal eye (A) and experimental eyes (B, C, D) (400x). Note the leukocyte infiltration in the vitreous (B) and angiogenesis in the inner layers of retina (C, arrow); D shows the normal aspect in a treated rat.

Having demonstrated the efficacy and safety of etamsylate in inflammation and angiogenesis produced by retinal ischemia and reperfusion in animals and considering the availability of a commercial formulation of etamsylate, we proceeded to evaluate the off-label efficacy of an intravitreal injection of etamsylate in patients with retinal inflammation and angiogenesis-dependent conditions.

#### *Intravitreal Etamsylate Administration Procedure in Humans*

Our studies followed the principles outlined in the Declaration of Helsinki and were performed with patient's consent after the approval of the Hospital Pio XII Ethical Committee (Madrid). Patients received a single intravitreal solution of etamsylate (150 $\mu$ l) in the affected eye. Etamsylate was administered as a 12.5% solution of diethylammonium 2,5-dihydroxybenzene sulfonate (dicynone, Sanofi-Aventis, Paris) in the operating room. Intravitreal injection of etamsylate was given according to Standard of Care (SoC) techniques in modern visual practice. Briefly, a sterile lid speculum was placed and local anaesthesia was administered. The conjunctive and ocular adnexa were prepared with povidone-iodine. A 30-gauge needle was used for a single intravitreal injection, which was applied 4.0 mm from the limbus.

We report here a new treatment for degenerative retinal diseases as well as for anterior ocular segment conditions, consisting of etamsylate administered as a single intravitreal injection as well as eye drops.

## Results

### *Macular Degeneration*

Retinal degenerative diseases may be classified as Age-Related Macular Degeneration (AMD) and inherited macular degeneration (Stargardt disease). AMD represents a leading cause of blindness, resulting in permanent damage to retinal cells that are essential for maintaining normal vision. AMD is expected to affect close to 300 million people by 2040, which represents a significant public health concern and a substantial economic burden [23]. AMD is classified into two groups based on the absence or presence of neovascularization: non-exudative or non-neovascular (dry) AMD and exudative or neovascular (wet) AMD [24]. Dry AMD accounts for approximately 90 % of cases of AMD, whereas 10% of cases are associated with wet AMD [25].

### *Dry AMD*

Dry AMD is characterized by an inflammation process and is classified into three clinical stages: early, intermediate and late or advanced stage. The advanced form of dry AMD is characterized by Geographic Atrophy (GA) [26]. Dry AMD is characterized by the accumulation of insoluble extracellular aggregates called drusen that are yellowish subretinal deposit made of proteins, lipids and cellular debris. Up to date, no treatment was approved for dry AMD. Patients with dry AMD treated with a single injection of etamsylate showed improvement of visual acuity and normalization of histologic structures of the retina [27-29].

### *Geographic Atrophy*

Geographic Atrophy (GA) is the defining lesion of the atrophic subtype of late dry AMD [28]. GA is characterized by the loss of an area of the Retinal Pigment Epithelium (RPE) that grows overtime [30]. GA is estimated to affect more than 5 million people worldwide and is typically bilateral and relentlessly progressive [31,32]. No treatment is available to prevent its recurrence or restore vision to affected areas. Intravitreal injection of etamsylate resulted in a significant reduction of GA [33].

### *Wet AMD*

Wet AMD is characterized by pathological neovascularization. Patients with this condition have also shown clinical improvement after receiving intravitreal injection of etamsylate [34,35].

### *Diabetic Retinopathy*

The number of patients with diabetes worldwide is scaling beyond previous reports and is projected to reach to 700 million patients by the year 2045 as compared to 463 million in 2019 [36]. Diabetic retinopathy is the most common neovascular complication prevalent in around 35% of patients with diabetes. A single intravitreal injection of etamsylate provides improvement of visual acuity and macular anatomy [37].

### *Cystoid Macular Edema*

Cystoid Macular Edema (CME) is a common cause of visual loss that is the result of cystic accumulation of extracellular intraretinal fluid predominantly in the outer plexiform and inner nuclear layers of the retina, as a result of the breakdown of the blood retinal barrier. We described clinical improvement after intravitreal etamsylate injection in a patient suffering CME [38].

### *Vitreous Hemorrhages*

Hemorrhages into vitreous are clinical condition of proliferative diabetic retinopathy which in some patients is re-absorbed. However, sometimes it requires pars plana vitrectomy to remove the hemorrhage that may lead to retinal tears, retinal detachment, hemosiderosis bulb and glaucoma, causing a further reduction in vision [39,40].

Proliferative diabetic retinopathy, ocular traumas and other ophthalmic disorders sometimes lead to the rupture or leakage of the retinal blood vessels, with resulting in bleeding into the vitreous and is typically manifested as opacification of the vitreous that leads to loss of visual acuity. The prognosis for vitreous hemorrhage depends on the underlying illness in patients with proliferative diabetic retinopathy as the base disease. According to statistics, there are around 450.000 cases each year of vitreous

hemorrhages in USA and the only available alternative until now for treating such hemorrhage is surgery. We have reported efficacy of etamsylate injection in reduction of vitreous haemorrhage caused by proliferative diabetic retinopathy [41].

#### *Central Serous Retinopathy*

Central Serous Retinopathy (CSR) is a self-limiting disorder leading to serous neurosensory elevation of the retina. Patients who do not resolve spontaneously can develop chronic CSR with Retinal Pigment Epithelium (RPE) and photoreceptor damage, resulting in permanent visual impairment [42]. We have reported that intravitreal injection of etamsylate improved visual acuity and neurosensory detachment secondary to chronic serous retinopathy [43].

#### *Stargardt Disease*

Stargardt disease is an inherited macular degeneration characterized by a significant loss in the central vision during the first or second decade of the life. Atrophic changes in the central retina are associated with degeneration of photoreceptors and underlying Retinal Pigment Epithelium (RPE) and yellow flecks are extending from the macula. Intravitreal injection of etamsylate shows improvement of visual acuity after treatment [44].

#### *Optic Neuritis*

Optic neuritis is an acute inflammatory condition of the optic nerve. The aetiology for optic neuritis varies including inflammation, exposure to toxins and genetic disorders [45]. Intravitreal injection of etamsylate improves visual acuity after one month of treatment [46].

#### *Retinal Vein Occlusion*

Retinal Vein Occlusion (RVO) that can occur either on the Central Retinal Vein (CRVO) or Branch of the Retinal Veins (BRVO) is caused by thrombus formation, external compression or disease of the vein wall. Population based studies suggest that about 16 million adults are affected by RVO. Macular oedema caused by leakage of fluid from capillaries in the central macular area and macular ischemia subsequent to RVO result in significant visual loss. Neovascularization caused by retinal ischemia also leads to visual impairment as a late complication of RVO and results in vitreous hemorrhage and neovascular glaucoma. The main purpose of the RVO treatment using anti-angiogenic and anti-inflammatory drugs is to decrease the duration of oedema and thus, to prevent photoreceptor damage, whether or not spontaneous improvement occurs [47,48]. We have reported a patient with occlusion of two branches of the central retinal vein in whom visual acuity and retinal histology improved two months after etamsylate injection [49].

#### *Dry Eye*

Dry eye syndrome is a condition that affects the surface of the cornea and the conjunctive due to a shortage of lacrimal fluid. As result, the surface of the eye is not well lubricated, which can lead to eye inflammation that promotes discomfort, vision problems and injuries to the cornea and conjunctiva. We have reported that etamsylate eye drops could be a novel therapy to treat drying disease of the eye [50].

#### *Pterygium*

Pterygium is an epithelial ocular hyperplasia associated with fibrovascular growth. This biologic process is associated to cellular proliferation, remodelling of the connective tissues, inflammation and angiogenesis. We have documented prompt regression of pterygium after topical etamsylate eye drops application [51-54].

#### *Rationale*

We initially performed animal experiments in retinal transient ischemia using intravitreal etamsylate. After demonstration of the efficacy and safety of intravitreal injection of etamsylate in this condition, we studied patients with several retinal diseases characterized by excessive inflammation and angiogenesis. Intravitreal injection of etamsylate in these conditions showed an important clinical benefit without adverse effects. We also showed the improvement of ocular inflammation and angiogenesis with etamsylate eye drops.

### Conflict of Interest

The authors declare no conflicts of interest that may have influenced the research, authorship or publication of the article.

### Informed Consent Statement

Informed consent was taken from the patient.

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### Authors' Contributions

PC wrote the article and performed animal studies. JA prepared the iconography and reviewed the manuscript. FC performed animal interventions. LO performed the clinical treatment. All authors read and approved the manuscript.

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