COMPARATIVE STUDY BETWEEN SYSTEMIC VERSUS TOPICAL APPLICATION OF TRANSEXAMIC ACID (TA) DUR9ING CORONARY ARTERY BY PASS GRAFT

Thesis

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Introduction

Neovascularization of ocular tissue is one of the most important pathologies in Ophthalmology. Neovascular glaucoma (NVG) is relatively common and serious condition which occurs as a result of iris neovascularization "Rubeosis Iridis" ***(1).***

Hypoxia appears to be the stimulus for the neovascular response in the eye. A vasoproliferative factor similar to that causing proliferative retinopathy appears to induce the growth of new blood vessels on the iris. This vasoproliferative angiogenic factor is elaborated by hypoxic retinal tissue in an attempt to revascularize these areas. The factor diffuses through the vitreous into the anterior chamber and induces a similar neovascular response to that occurring in the retina ***(2).***

Neovascularization occurs in the anterior segment which leads to formation of new vessels at the pupillary border and iris surface (neovascularization of the iris {NVI}) and over the angle of anterior chamber (neovascularization of the angle {NVA}). This leads to formation of fibrovascular membranes. These membranes may be invisible on gonioscopy, accompany NVA and progressively obstruct the trabecular meshwork causing 2ry open-angle glaucoma ***(3).***

As the disease continues, fibrovascular membranes along NVA tend to mature and contract; thereby tenting the

iris towards the trabecular meshwork and causing peripheral anterior synechiae and synechial angle closure and thus causing high intraocular pressure (IOP) ***(4)***.

Diabetic retinopathy and central retinal vein occlusion account for nearly two-thirds of patients with neovascular glaucoma ***(5).***

The current standard care includes retinal ablation and control of IOP with medical and surgical therapy **(6*).***

Recently, Bevacizumab (AVASTIN®),a recombinant antibody against vascular endothelial growth factor, was used by ophthalmologists as an intravitreal agent in the treatment of proliferative eye disease, particularly for proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO) and macular edema ***(7).***

Aim of the work

To compare the effect of multiple intravitreal injections of Bevacizumab combined with the conventional treatment of NVG versus the standard conventional treatment of NVG alone , as regarding IOP, iris and angle neovascularization and visual acuity .

Anatomy of the anterior chamber angle

The features of the outflow apparatus are as follows **(Fig.1)*(8):***

1. ***Internal scleral sulcus***
    - Sulcus
    - Schwalbe's ring
    - Scleral spur
2. ***Trabecular meshwork***
    - Uveal meshwork
    - Corneoscleral meshwork
    - Trabecular structure
    - Iris processes
    - Pericanalicular connective tissue
    - Extracellular matrix
3. ***Canal of Schlemm and collector channels***
    - Schlemm's canal
    - Endothelial lining
    - Giant vacuoles
    - Collector channels ***(8)***

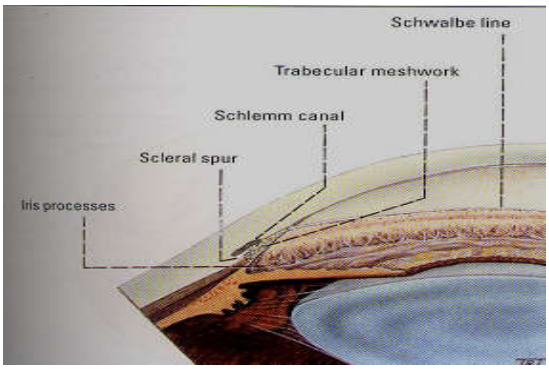

Fig.1: Structure of the angle*(1)*

Gonioscopic features of the limbus

The gonioscopic features of the limbus are usually observed with magnification, at the slit lamp. They are as follows ***(8)***:

CILIARY BAND

In the angle recess, the most posterior landmark is the dark ciliary band, which represents the anterior face of the ciliay body including the insertion of the ciliary muscle into the scleral spur. This lies at the apex of the chamber angle ***(8)***.

SCLERAL SPUR

The scleral spur is a pale, translucent narrow strip of scleral tissue which is located anterior to the ciliary band and marks the posterior boundary of the corneoscleral meshwork ***(8)***.

TRABECULAR MESHWORK

Anterior to the scleral spur is a broad band of tissue approximately 750µm in width, which is relatively featureless in the unpigmented eye and extends from scleral spur to Schwalbe's ring. The trabecular band covers the internal aspect of the canal of Schlemm. The canal may sometimes be visible during gonioscopy, when blood refluxs retrogradely into the canal, and appears as a pink strip visible through the meshwork ***(8)***.

SCHWALBE'S RING

Anterior limit of the drainage angle is termed Schwalbe's ring or line. This is a fine scalloped border at the termination of Descemet's membrane which usually lies in the plane of the posterior corneal surface but in 15-20% of normal subjects may be variably hypertrophied and project as a delicate, glistening ridge into the anterior chamber (posterior embryotoxon). It is sometimes lightly pigmented ***(8)***.

ANGLE RECESS

The apex of the angle lies in a plane 0.6-1.0 mm behind the most anterior aspect of the lens capsule. The iris therefore curves backwards peripherally at the iris root to a variable extend to form the angle recess. The width of this recess varies according to the size of the eye, depth of the chamber, state of the pupil and other factors, so that different angle widths are referred to clinically, from the

widest (encountered in the aphakic or pseudophakic eye) to the narrowest (encountered in the small, hypermetropic or microphthalmic eye) ***(8)***.

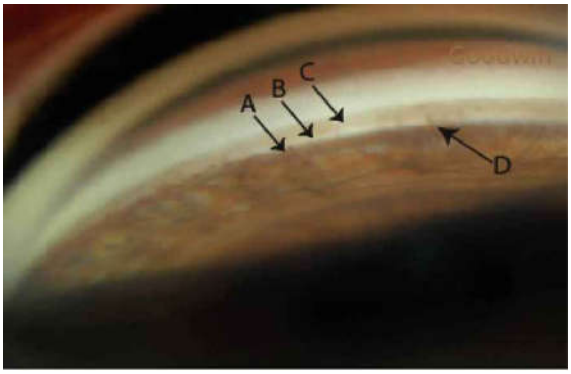

Fig.2:Structure of normal angleA=Scleral Spur,B=Trabecular meshwork,C=Schwalb line,D=Iris process*(8)*

Pathology of neovascular glaucoma

The neovascularization process begins as endothelial budding from capillaries of the minor arterial circle at the pupil. Clinically, this neovascularization appears to progress sequentially from the pupil to the periphery. However, histologically, once the process starts at pupillary margin, new endothelial buds may appear from vessels anywhere in the iris, including the major arterial circle in the iris root. These endothelial buds progress to become glomerulus- like vascular tufts ***(9)***.

These tufts leak fluorescein, confirming that they are indeed new vessels. These new vessels are essentially very thin-walled endothelial cells without a muscular layer or much adventitia or supportive tissue. There are gaps between and fenestrations in these endothelial cells, allowing leakage of fluorescein, and presumably, other substances as well(Fig.4) ***(10)***.

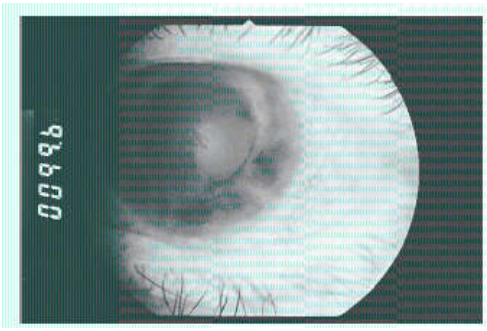

Fig.3:Iris fluorescein angiography showing leaking new vessels.***(11)***

The fibrovascular membrane consists of proliferating myofibrolasts which are fibroblasts with smooth muscle differentiation; these cells are clinically transparent and are only hinted by the flattening of the usual iris surface architecture Scanning Electron microscopy shows the uniform presence of this membrane wherever there are new vessels. Anatomically the new vessels are not on the surface of the iris but actually are beneath this layer of myofibroblasts. The presence of this membrane explains why there can be increased IOP despite the gonioscopic appearance of normal open angle or only slight neovascularization of the angle (NVA) disproportionate of the degree of IOP elevation ***(9)***.

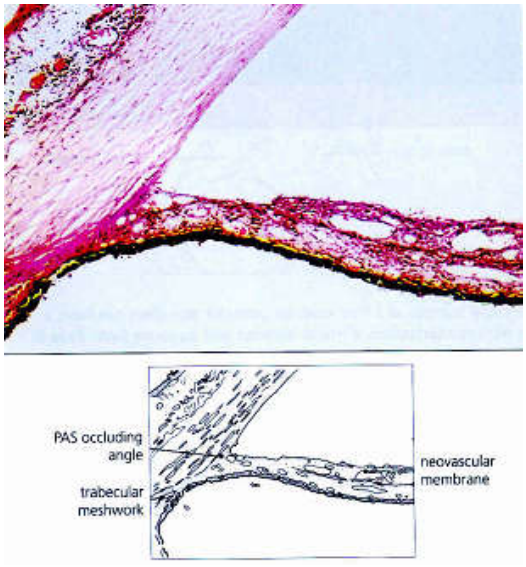

Fig.4 Histological examination of the iris demonstrate peripheral anterior synechia and neovascular membrane *(13)*

The contractility of the myofibroblast explains the smoothness of the iris surface, the formation of peripheral anterior synechia (PAS) and ultimately synechial angle closure(Fig.4) ***(12)***.

As the fibrovascular membrane continues to contract on the surface of the iris, the posterior pigment layer of the iris is pulled around the pupillary margin onto the anterior surface, causing ectropion uveae and pupillary distortion **(Fig.5)*(13).***

Before total synechial angle-closure, the membrane can obstruct the trabecular meshwork and produce secondary open-angle glaucoma. Further contraction results in synechial angle-closure with iridocorneal touch. When the neovascularization process is stopped, such as with PRP, the new vessels regress, but synechial angle-closure remains ***(9)***.

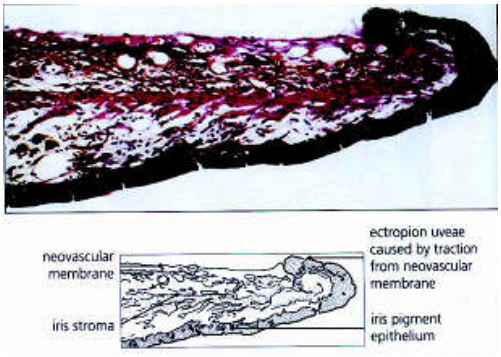

Fig.5 Histological examination demonstrates ectropion uvea *(13).*

Pathogenesis of NVG

The most commonly accepted theory for the pathogenesis of neovascular glaucoma is that ischemia of the retina liberates an angiogenic factor (or factors) that diffuses forward and causes new vessel formation on the iris and in the angle. Capillary occlusion or ischemia appears to be the initiating event in this process, which seems to be similar to the production of an angiogenic factor or factors by solid tumors ***(14)***.

Imre (1972) suggested that the factors necessary to the development of NVI are:

- The presence of living cells to ensure active metabolism.
- A low O2 tension to promote anaerobic metabolism.
- Poor venous drainage to permit accumulation of anaerobic metabolism.***(15)***.

Weiss (1977) suggested that anterior segment ischemia may also be an essential factor in pathogenesis NVI and also pointed out that the vessels in the ciliary body can not be observed directly.

Agent that have been postulated as potential angiogenic factors include: prostaglandins, biogenic amines and activated macrophages ***(2)***.

An important angiogenic factor is vascular endothelial growth factor (VEGF). In 1990s, Anthony Adamis, M.D, in the Folkman laboratory discovered that natural occurring angiogenic protein VEGF was the critical factor in development of new blood in eye disease .By inhibiting VEGF, scientists hypothesized they could prevent formation of new blood vessels in eye***(17)***

A multitude of other substances involved in angiogenesis are under investigation. These include :insulin like growth factors I and II, insulin like binding proteins 2 and 3,platelet derived growth factor(PDGF) and interleukin-6(IL-6) ***(18).***

Studies showing a greatly increased incidence of NVI and NVG after cataract extraction with removal of the posterior capsule support the presence of diffusable vasoproliferative factor from the posterior segment of the eye. Extracapsular cataract extraction with maintenance of post capsule was less likely associated with NVI which suggests that the capsule may serve as a barrier against angiogenic factors***(19).***

Angiogenesis

The process of new blood vessel formation is crucial in normal physiologic development and wound healing as well as in disease pathogenesis. Technically, this process can be divided into vasculogenesis, or the formation of a primitive vascular network, followed by angiogenesis, or