Role of Low Molecular Weight Heparin and other Adjunctive Medical Treatement in Management of Proliferative Vitroreotinopathy

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Presented by
Victor Abd El Masseh Rasheed Botros
M.B. B.Ch.

Supervised by

Prof. Dr. Hussien Hamed Shaker
Professor of Ophthalmology
Faculty of Medicine
Ain Shams University

Dr. Mohamed Hanafy Hashem
Lecturer of Ophthalmology
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
Cairo, Egypt
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الطبيب/فيكتور عبد المسيح رشيد بطرس

تحت اشراف

الأستاذ الدكتور /حسين حامد شاكر
استاذ طب وجراحة العيون
كلية الطب - جامعة عين شمس

الدكتـــــور/محمد حنفي هاشم
مدرس طب وجراحة العيون
كلية الطب - جامعة عين شمس

كلية الطب
جامعة عين شمس
القاهرة
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PVR	*Proliferative vitroretinopathy*
RPE	*Retinal pigment epithelium*
ECM	*Extracellular matrix*
BRB	*Blood retinal barrier*
5-FU	*5-Fluorouracil*
FGF	*Fibroblast growth factor*
EGF	*Epidermal growth factor*
PDGF	*Prostaglandin derived growth factor*
EMT	*Epithelial -mesenchymal transition*
TGF	*Transforming growth factor*
IL	*Interleukin*
CTGF	*Connective tissue growth factor*
RA	*Retinoic acid*
NA	*Naproxen*
LMWH	*Low molecular weight heparin*

Introduction

Surgical repair of rhegmatogenous retinal detachment is currently successful in over 90% of cases.[1-3] Where there is a final failure to reattach the retina due to development of proliferative vitreoretinopathy (PVR) in over 75% of cases.[4]

This process is characterised by cellular proliferation on both surfaces of the detached neuroretina, on the posterior vitreous face, and within the vitreous base resulting in the formation of contractile periretinal membranes. It is estimated to occur in 5-10% of all rhegmatogenous retinal detachments.[4]

In fact, PVR process is a wound healing response in which several stages can be distinguished, including the influx of inflammatory cells, migration, proliferation of cells, and deposition and remodeling of extracellular matrix.

There is general agreement that four categories of cell can be identified

- Retinal pigment epithelial (RPE) cells have been identified by light and electron microscopy,[5] and immunohistochemically.[6] Also RPE cells within the eye may undergo metaplastic change to macrophage or fibroblast-like morphology.[7]

- Glial cells have been shown to be a part of PVR membranes.[6]
- Fibroblasts or fibrocytes. These cells contain myofibrils, and therefore be responsible for the contraction of PVR cellular membranes.[8]
- Inflammatory cells: macrophages [9] and T lymphocytes of both CD4+ and CD8+ subsets.[10]

It is generally accepted that membrane formation results from an interaction of these different cells with components of the extracellular matrix (ECM) which is formed of multiple structural proteins some of them formed by retinal cells under effect of cytokines and others reach vitreous after blood retinal barrier (BRB) break down. The cell attachment protein fibronectin has been identified as a significant component of PVR membranes.[11]

Then an excessive wound healing process and ECM remodeling takes place with fibrocellular membrane contraction resulting in retinal surface wrinkling, star-fold formation, and tractional retinal detachment.

As vitreoretinal surgical techniques have advanced the anatomical success rate of retinal surgery in severe PVR has increased from around 60% to over 90%.[12] Visual results however, are often disappointing and the value of such surgery has been questioned. As a result, there is a need to tackle the problem of PVR through some other means.

To improve anatomic and visual success rates of reattachment strategies, research has focused on the use of intravitreal pharmacologic agents directed against one or more of the stages of PVR process.

Non-specific antiproliferative agents like 5-fluorouracil (5-FU) has been shown to be effective in reducing the incidence of PVR in animal models.[13] Daunorubicin also has been tested both experimentally and clinically.[14]

Retinoic acid produces a growth arrest in RPE cell cultures and prevents the dedifferentiation of individual RPE cells[15] so reduce the rate of tractional retinal detachment when delivered to the vitreous cavity in silicone.[16] An initial report on the use of oral 13-cis retinoic acid as an adjunct to surgery in PVR has shown a promising result.[17]

Antinflammatory therapy like intravitreal injections of dexamethasone or triamcinolone can reduce intraocular cellular proliferation and tractional retinal detachment. This action may be largely mediated by a reduction in blood-retinal barrier breakdown and associated intraocular inflammation.[18]

Non-steroidal anti-inflammatory medications given perioperatively could limit the degree of blood-retinal barrier breakdown and have been shown to inhibit cellular proliferation in vitro.[19]

Modulation of fibrin production is another possible target for adjunctive treatment. Low molecular weight heparin prevent post- operative fibrin formation in addition, interferes with cell - substrate adhesion by binding fibronectin, binds growth factors including fibroblast growth factors (FGFs), epidermal growth factor (EGF), and prostaglandin derived growth factor (PDGF), and inhibits cellular proliferation including scleral fibroblasts and RPE cells. These combined activities make low molecular weight heparin a potential multi- functional drug for use in the prevention of the development of PVR.[20]

Aim of the work

To evalute the effect of variuos pharmacological agents in decreasing the incidence of tractional retinal detachement due to proliferative vitreoretinopathy (PVR) after primary rhegmatogenous retinal detachment.

- Treatment of PVR can be preventive or curative.
- After studying of the pathophysiology of PVR it has become possible to design pharmacological adjuncts to the surgical management of the condition which specifically target the cellular components and pathological processes of PVR.

Pathphysiology of PVR

The term proliferative vitreoretinopathy (PVR) is the latest and most enduring of a series of terms used to describe the migration and proliferation of cells to form fibrocellular membranes on and around the retina. It was initially thought to be a process originating within the vitreous, the contracted gel leading to retinal shortening and irreversible fibrotic contraction, hence the term massive vitreous retraction (MVR).[21]

With the introduction of closed intraocular microsurgery, direct access to preretinal and subretinal spaces confirm that PVR was in fact a process of periretinal cellular proliferation, the more clinically significant and damaging element of which was epiretinal. The term massive periretinal proliferation (MPP) was therefore coined,[22] but subsequently changed to PVR, at the behest of the Retina Society.[23]

The role of the vitreous gel in the development of PVR is comparatively small. Posterior vitreous detachment generally initiates the chain of events leading to PVR, by creating dehiscence in the internal limiting lamina and/or full thickness retinal breaks and then proliferation of cells forming contractile membranes on the posterior surface of the detached gel and at the vitreous base contributes to the forces acting on the anterior retina.

Breakdown of blood-retinal barrier is another key feature associated with PVR which trigger cell migration and proliferation of the principal cell involved in PVR being the retinal pigment epithelial (RPE) cells, glial cells, fibrous astrocytes, fibroblasts, myofibroblasts, and macrophages this influenced by the growth factors and cytokines.[24]

This also causes chemotaxis of blood-borne inflammatory cells like macrophages, lymphocytes, and polymorphonuclear cells and circulating fibrocytes which are frequently found in PVR membranes.[25]

Migration, proliferation, and dedifferentiation of these cells within a provisional extracellular matrix containing collagen, fibronectin, and other matrix proteins lead to formation of contractile membranes on the surface of the retina and beneath it.

These periretinal membrane cause development of surface wrinkling and single or multifocal star-folds(Fig.1). In the final stages, multidirectional tractional forces produced by posterior and/or anterior PVR form a narrow or closed funnel of the detached retina (Fig.2).[26]