Review

Pars Plana Vitrectomy and the Risk of Open Angle Glaucoma: Where Are We?

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Abstract: Purpose is to o review the pathogenic mechanism theories and clinical evidence on the risk of developing Open Angle Glaucoma (OAG) after Pars Plana Vitrectomy (PPV). Most existing scientific literature on the issue agree on the role of ascorbate as an oxygen scavenger within the vitreous chamber. Oxygen tension in the vitreous and anterior chamber is maximum inn proximity of the retinal surface and endothelium, respectively and steeply decreases toward the lens; on both sides, and trabeculate. Vitreous removal and, to a lesser extent, liquefaction, greatly reduces oxygen tension gradient in vitreous chamber while cataract extraction has similar effects on anterior chamber oxygen gradients. Oxygen derivatives originated from the cornea and retina are actively reduced by the vitreous gel and/or the crystalline lens. Vitreous removal and cataract extraction reduce drastically this function. Most reported clinical series confirm this hypothesis although protocol difference and follow-up length greatly impact the reliability of results.

Keywords: Ascorbate; Pars Plana Vitrectomy; Open Angle Glaucoma; Oxidative Stress; Vitreous Me-tabolism 0. How to Use This Template

1. Introduction

The vitreous plays a pivotal role in the anatomy and physiology of the eye [1], acting as a scaffold, energy damper [2], nutrients distributor [3], oxygen scavenger and more [4]. Vitreous alterations have been related to a wide spectrum of ocular diseases including retinal tears and detachment, cataract, age related macular degeneration and also different forms of glaucoma [5].

Pars Plana Vitrectomy (PPV) is a common surgical procedure aimed at removing the vitreous gel, performed for a variety of indications [6] including retinal detachment, macular puckers and holes, diabetic retinopathy and trauma [7]. Although the potential for PPV to alter ocular pressure homeostasis had been hypothesized in the early stages of vitrectomy development [8, 9] the full pathogenic mechanism has not been proposed until much later [10].

The role of PPV in the development of successive Open Angle Glaucoma (OAG) up to several years after gel removal has been lengthy debated in the past years as clinical the proposed pathogenic mechanism gained acceptance and clinical series have been published.

Purpose of present paper is to review the current lines of evidence on PPV as a cause for OAG.

2. Vitreous Physiology and Pathogenic Mechanism

Among the many and increasing number of functions and biochemical activities attributed to the vitreous, the role of ascorbate certainly plays a prominent role. Ascorbate blood concentration is 50-60 μM while is 30-40 times higher in the human vitreous (about 2mM) [11] where is actively transported by a sodium-dependent transporter named SLC23A2 present in the ciliary epithelium pigmented layer [12].

Why is so much ascorbate needed within the vitreous chamber? Shui and Coll. [13] proposed that intraocular oxygen tension is regulated in an ascorbate-dependent way: oxygen reacts with ascorbate to produce hydrogen peroxide, then converted to H2O by the action of catalase. In this scenario, the vitreous would act as a barrier to oxygen derivates strategically interposed between the highly vascularized and metabolically active retina and the delicate anterior structures extremely sensitive to oxidative stress: the lens and trabeculate meshwork.

Shui and Coll. also noticed that the liquified vitreous contains less ascorbate and consumes oxygen at a much lower rate than vitreous gel [1]. Until the vitreous is mainly in a gel status, oxygen diffusion from the retina encounters ascorbate and gets consumed as witnessed by the decreasing oxygen gradient as the distance from the retina increases [14]. When the vitreous liquefies or is replaced by aqueous as after PPV, oxygen moves transported by aqueous currents and turbulence generated by saccades and head motion [15] reaching comparable concentration throughout the eye.

This may suggest a role of vitreous liquefaction in the development of nuclear cataract, as liquified gel current increase oxygen levels close to the lens altering the physiologic gradient acting as consecutive barriers protecting the crystalline transparency.

Siegfried and Coll. [16] confirmed Chang's hypothesis by measuring oxygen tension in the anterior chamber eyes undergoing anterior segment surgery and in the vitreous chamber of eyes undergoing vitrectomy before and after vitreous gel removal. They noted a steep gradient of oxygen tension both in the anterior chamber and vitreous chamber decreasing towards the lens and trabecular meshwork until the vitreous and crystalline lens are present; after their removal that gradient disappears and oxygen tension almost equals anywhere within the eye, showing a significant increase at the trabeculate and lens.

Oxygen has been linked to apoptosis in trabecular meshwork cells [17] which would represent the very last piece of the pathogenic mechanism puzzle although the same reasoning brings to believe vitrectomy might be beneficial for ischemic retinal diseases.

3. Clinical Evidence

The very first to report OAG increase after PPV were probably Stangos and Coll. in 2004 [18] who observed OAG doubling (from 19.7% to 38%) nine months after PPV although they did not comment this finding that was later on underlined by Chang in his 2006 Jackson Lecture when he presented data related to 453 eyes followed for an average 56.9 months and proposed the oxidative theory. He also pointed out that phakic eyes had a significantly longer time between PPV and glaucoma diagnosis compared to pseudo-phakic patients as if the lens acted as oxygen scavenger itself while developing a cataract.

Luk and Coll. [19] confirmed this hypothesis having followed 101 patients for an average 51 months after PPV for macular surgery and found a 7.9% prevalence of OAG with a significant difference between phakic (2%) and pseudo-phakic (13%).

Not all data concurred: Yu and Coll. in 2010 [20] retrospectively reviewed the records of 441 patients followed for an average 79 months and found 4.31% OAG after PPV versus 2.49% in the controls concluding the difference was not statistically significant, in agreement with Mi et al who in 2015 [21] retrospectively analyzed 234 eyer after epiretinal membrane peeling and PPV at least 2 years after surgery and found no evidence of increased OAG prevalence.

Koreen et al. [22] in 2012 followed 286 eyes with more than 6 months follow-up after PPV and found an overall 11.6% of OAG with highly statistically significant difference between phakic patients 1.4% and pseudo-phakic patients (16%). In that very series there was no difference between those who underwent cataract extraction before, at the time of PPV or later on, therefore the lens itself proved a protective factor against the onset of OAG.

Govetto et al. [23] in 2014 also found a significant difference in the rate of OAG of 312 eyes (8.9% of vitrectomized Vs 2% of non-vitrectomized eyes) between 3 and 6 years after PPV while Fujikawa [24] found an increase in intraocular pressure after PPV for macular hole but not for epiretinal membrane (ERM) 12 months after surgery, possibly due to the shortness of follow-up or the less complete vitrectomy usually performed in ERM cases. It is conceivable that if a significant amount of peripheral vitreous is left in place, as is the case for many surgeons performing macular surgery, this allows a residual oxygen-binding effect postponing the insurgence of cataract and trabecular meshwork damage.

Yamamoto [25] found a significant increase in IOP only for patients undergoing PPV for retinal detachment compared to MH and ERM who did not show such an increase after an average 23 months follow-up and the PROVE study [26] demonstrated a significant increase in IOP and decrease in OCT measured Retinal Nerve Fiber Layer (RNFL) thickness 12 months after PPV for macular surgery although the shortness of follow-up and peeling maneuvers may act as confounders.

Miele and Coll. in 2018 [27] conducted a meta-analysis on the issue, pooling seven paired studies of cases versus controls and a mean follow-up of 12 months. Only 4 studies reported OAG data on 851 patients and the prevalence were 7.8% among PPV patients and 4.8% of controls, with a 1.67 odds ratio. Ocular hypertension was found in 5.8% and 3.1% of patients, respectively. The study concluded there is an increase in the risk for OAG after PPV but protocol inconsistency prevented conclusive evidence with available data.

4. Conclusions

There is enough convincing experimental evidence to believe that the vitreous gel plays a pivotal role in oxygen gradient maintenance throughout the vitreous chamber and that vitreous liquefaction and more overtly vitrectomy determine an abrupt loss of such gradient. There also is evidence that after vitrectomy the crystalline lens itself, if present, acts as an oxygen scavenger paying the price of speeding the cataract process.

After cataract removal both barriers resisting to oxygen derivatives spreading throughout the eye, fail to work and the trabecular meshwork becomes a very likely target for oxidation that has been proved to trigger trabecular cell apoptosis.

Most surgical series reported after Chang's Lecture proposed the pathogenic mechanism have been largely confirming (with a few exceptions) the oxidation theory and the role of the crystalline lens. The only available meta-analysis pointed out the lack of standardization and the need for longer follow-up on similar series in order to be able to shed more light on the issue. The risk of OAG should nonetheless be overtly discussed with patients as PPV indications expand to include less invalidating conditions such as vitreous floaters.

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