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Research Article

Current Approach of Ingredients Interactions on Ocular Perfusion Pressure in Glaucoma

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Abstract

Purpose : To determine and to investigate the cross-sectional relationship between ocular perfusion pressure (OPP), pulsatile ocular blood flow (POBF) versus diastolic blood pressure (DBP), vascular systemic and local risk factors.

Method: In retrospective metanalysis included 91 consecutive patients, mean age 55.7 ± 10.7, divided in: Control Group 21 patients, with normal tension glaucoma (NTG) 24 and with POAG 31, 16 of them with vascular disorders POAG1: with Transient Ischemic Attack (TAI) 5 patients, hemodynamic crisis 5 patients, Raynaud's syndrome 3 patients, sleep apnea syndrome 3, 15 in POAG2 without evident vascular disorders and severe myopic group (SMG) > 7.0D with myopic changes, disc haemorrhage and peripapillary atrophy, 15 patients. We performed a baseline glaucoma examination, focusing on hemodynamic parameters. T-test and linear regressions for statistical analysis.

Results : Our findings indicated that when treated the BP-related factors as continuous variables and added them to the model one at a time, the multivariate-adjusted for every 10-mm Hg decrease in DBP OPP and DPP. OPP fluctuation shows significant difference among groups. SMG showed a mean decrease of OBF = 26.5%, PA = 29.5% from control group. In NTG, OBF reduced to 49% with circadian fluctuations to 4.2 and mean decrease OPP = 40% from control group. NTG, had a significantly faster progression of visual field defects in the central 10 degree area. In NTG and POAG1 compared to CG had significantly thinner RNFL 79.9 ± 8.1 vs 89.8 ± 7.5, as well as inferior at inferotemporal quadrant with MD in SAP -0.4 ± 0.3. After antiglaucoma selective therapy we concluded that Dorzolamide+Brimonidine combined therapy with IOP- 33.5% and OPP +31% had the best results, demonstrated bilateral effect in IOP reduction and OP improvement, With added therapy Nilvadipine 60 mgr and Ginkgo biloba 150 mg, Visionace the hemodynamic parameters further improved ≥ 11.6%,

Keywords: *Vascular Dysregulation; Ocular Perfusion Pressure; Pulsatile Ocular Blood Flow; Diastolic Blood Pressure; Pulse Amplitude; Factor Risk; Selective Therapy*

Abbreviations

VDR: Vascular Dysregulation; CG: Control Group; OPP: Ocular Perfusion Pressure; POBF: Pusatile Ocular Blood Flow; PA: Pulse Amplitude; DPP: Diastolic Perfusion Pressure; DBP: Diastolic Blood Pressure; NTG: Normal Tension Glaucoma; POAG: Primary Open-Angle Glaucoma; SMG: Severe Myopic Group; RNFL: Retinal Nerve Fibre Layer

Introduction

Vascular theory for glaucoma pathogenesis that has been postulated for decades is justified [1]. Investigations of vascular theory in Glaucoma, changed the treatment strategy. Have discussed as multi etiologic the presence of a progressive optic neuropathy in the context of normal or no, IOP suggests an underlying vascular insufficiency. Studies have showed that alterations in ocular hemodynamics correlated with general "vasogenic factors" play a significant role in the glaucoma pathogenesis. Vascular dysregulation (VDR) as a Circadian fluctuations of OPP and interactions influence of factors risk is a contributing factor in the glaucomatous optic neuropathy pathogenesis [2,3]. Nevertheless Glaucoma continue to remained "iceberg" [4].

Purpose

To determine and to investigate the cross-sectional relationship between ocular perfusion pressure (OPP), pulsatile ocular blood flow (POBF) versus diastolic blood pressure(DBP), vascular systemic and local risk factors. Interpreting study of interactions between them, analysing the prognostic of the consequences and their complex treatment.

Method

In retrospective metanalysis included 91 consecutive patients, mean age 55.7 ± 10.7, mean baseline IOP 21,5 ± 1,3 mmHg in follow up 2010 - 2013 divided in: Control Group 21 patients, with normal tension glaucoma (NTG) 24 and with POAG 31, 16 of them with vascular disorders POAG1 (with cerebral ischemic changes 5 patients, hemodynamic crisis 5 patients, Raynaud's syndrome 3 patients, sleep apnea syndrome 3), 15 in POAG2 without evident vascular disorders and severe myopic group (SMG) > 7.0D with myopic changes, disc haemorrhage and peripapillary atrophy, 15 patients. Main exclusion criteria were previous eye surgery or laser therapy. We performed a baseline glaucoma examination, focusing on hemodynamic parameters observation : monitoring of POBF (PARADIGM), with circadian OBF fluctuations, pulse amplitude (PA), ocular perfusion pressure (OPP) calculation, diastolic perfusion pressure (DPP), HOLTER for nocturnal blood pressure dipping and general examination MRI, colour duplex ultrasound carotid arteries examination (CDUCA). The area under ROC (Receiver Operating Characteristic) curves were plotted for RNFL parameters. The correlation between circadian POBF, OPP fluctuations and visual field (VF) Humphrey scores, mean deviation(MD) and corrected pattern standard deviation (CPSD) at initial presentation were analyzed. T-test and linear regressions using for statistical analysis. The importance of vascular risk factors has been assessed in the context of typical options of groups [5]. On the basis of current knowledge, time-dependent models taking account of various forms of interaction have been developed. All predictor variables were combined in a single regression model, to assess their joint effects on the outcome variables by multivariate modelling.

Results

Our findings indicated that when treated the BP-related factors as continuous variables and added them to the model one at a time, the multivariate-adjusted for every 10-mm Hg decrease in DBP ($p = 0.02$), OPP ($p = 0.058$), and DPP ($p = 0.02$). PA is positively correlated with the coefficient of ocular rigidity, $p \leq 0.01$. In NTG, PA = 1.2 ± 0.35, in POAG1 PA = 1.6 ± 0.55, no statistical differences, $p > 0,005$, contrary with CG, PA = 1.95 ± 0.57, POAG2 PA = 1.87 ± 0.76, P = 0,002. Measurement of POBF showed significant reduction between CG and subjects with NTG and POAG2, $p < 0,005$ represents a difference of approximatively 32%. In supine posture reduction of POBF was 22% in NTG and POAG2 while in CG 16%. Patients with POAG had a significant lower blood flow velocity at baseline, $p < 0,01$. During NBPD, modulations of blood pressure affected perfusion pressure, there was a statistically significant difference in OPP of the control group and NTG, POAG1, SMG, $p < 0,05$. For these parameters there was no a significant difference among the groups except POAG2, NTG with OPP 43.3 ± 5.2 mmHg, SMG with 44.1 ± 5.0 mmHg, POAG1 with 44.5 ± 4.9 mmHg while in POAG2 46.3 ± 5.3 mmHg but OPP fluctuation shows significant difference among groups, $p = 0.007$, NTG with 18.3 ± 5.6 mmHg and SMG 17.5 ± 5.8 mmHg had larger fluctuations, $p < 0.001$. IOP circadian fluctuation was within this range 5.1 ± 2.0 CG, 5.4 ± 2.3POAG2 with 5.7 ± 2.5 in NTG, SMG, POAG1, without distinction $p > 0.05$. SMG showed a mean decrease of OBF = 26.5%, PA = 29.5% from control group, significantly correlated with axial length (AL), $p < 0,001$. The regression coefficient was negative $r^2 = -0.850$, indicating that the IOP decreased with increasing OBF. Choroidal blood flow that is substantially reduced, have implications of the optic nerve and chorioretinal alterations [2,3]. It's important the significant reduction in this group of OPP = 24,7% with circadian OBF fluctuations = 2,76 (18%) related with flow velocities. These demonstrated in severe myopic glaucoma group with myopic alterations and peripapillary atrophy [5] with mean OBF reduction 42.3%, PA = 55%, OPP = 33.8% and circadian OBF fluctuations 22.7%, while in severe myopic glaucoma group with vascular disorders was found significant interaction between IOP, ocular vascular disorders and OBF, OPP reduction respectively 47.4% and 39.7%. Myopia is more prevalent in the POAG. Our outcomes suggest that NTG, OBF reduced to 49% with circadian fluctuations to 4.2 (23%) and mean decrease OPP = 40% from control group ($p < 0,001$) showed significantly primary vascular dysregulation related and with vasospasm phenomenon. Vascular insufficiency

due to abnormal autoregulation as a major factor in glaucoma deterioration [6,7]. NTG, high fluctuation group had a significantly faster progression of visual field defects in the central 10 degree area, showed deterioration in both hemifields, arcuate form (similar with this of anterior ischemic neuropathy). A positive correlation between MD and OBF ($r = 0.34$, $p < 0.01$) was identified. Circadian OPP fluctuation showed positive associations with VF indices at alterations progress of NTG $p < 0.05$. Ocular perfusion pressure standard deviation at baseline and primary vascular dysregulation were significant predictors of future VF progression in NTG. In NTG and POAG1 OPP were very sensible and fluctuated depending on the intra or extraocular disorders, CCT and IOP changes (P = 0,001), showed the abnormality autoregulation. In POAG1 the OBF and OPP were lower ≥ 10% than POAG2 (P < 0,001), explained by correlated of vascular risk factors. We observed progressive visual held defects MD ≥ -8.5 ± 2.1dB, CPSD > 5.50, of the baseline with progression of visual field defects in the peripheral 20 to 32 degree area ($p = 0.005$), identified to NTG and POAG1 group. It is also important to note that eyes with more severe VF loss require more aggressive therapy to slow rates of progression. OPP standard deviation at baseline were significant predictors of future VF progression in these groups. MD < -6.0 dB, identified i POAG2, without new defects to VF. We identified that NTG and POAG1 compared to CG had significantly thinner RNFL 79.9 ± 8.1 vs 89.8 ± 7.5, $p < 0.001$ as well as inferior at inferotemporal quadrant with MD in SAP -0.4 ± 0.3 vs within normal limits in CG. The OBF and PA were lower in NTG than POAG1 respectively 8.7 ± 1.6, 1.6 ± 0.5, vs 9.6 ± 0.9, 2.1 ± 0.7 but without statistical differences, p = 0,001. The areas under the ROC curve were 0.724 (0.669 - 0.779) in NTG and POAG1 vs 0.848 (0.775 - 0.921) in CG. We have got a good concordance between OCT and OBF findings [1], showed OBF reduced 7.3 ± 1.5 (-24.3%), PA 1.6 ± 0.4 (-24.8%), $p < 0.01$. It's important that in POAG2 10 cases (66.5%) remained stable, with POBF changes 10% but PA reduced 12.5%, in 5 cases (33.5%), remarked POBF reduced 25%, PA 22% preceded for further progression. The peripapillary OCT thickness demonstrated a statistically significant correlation between RNFL loss and OBF insufficiency $p < 0.01$, confirmed interaction between them. The OCT and OBF analyzer reflect true structural changes preceding the appearance of functional changes. A linear regression model indicated that 10μm change in CCT resulted deviation of IOP 0,46-0,95 mmHg and POBF measurement deviation 0,48 - 0,87 μl/sec ($r = 0,650$). NTG group had thinner CCT 513 ±25μm than CG, p = 0,001. By analyzing a negative correlation existed between CCT and IOP, $p < 0,001$ and the relationship between CCT and POBF readings were positive, p = 0,001. It's characteristic a statistical negative correlation $[r]^2 = -0.85$, between IOP and POBF. OBF showed interaction to others risk factors. After antiglaucoma selective switched therapy we concluded that: Dorzolamide with IOP reduction from base line 21.75%, Brimonidine with 26.25%, Latanoprost 26.8% as monotherapy and Dorzolamide/Timolol fixed combination 30.9% associated POBF improved = 36%, PA improved = 25.5% OPP = 27.5%. Dorzolamide+Brimonidine combined therapy with IOP- 33.5% and OPP +31% had the best results, demonstrated two-sided effect in IOP reduction and OPP improvement, $p = 0.001$. With added therapy Nilvadipine 60 mgr, Ginkgo biloba 150mg, Visionace and Neurozan the hemodynamic parameters further improved ≥ 11.6%, shows beneficial effect over RGC. Calcium channel blockers (CCB) as Nilvadipine 60 mgr cause vasodilation in microcirculation (anti-vasospasm effect) and play role in lower IOP, while Ginkgo Biloba at neuroprotection therapy, they have together a beneficial effect in NTG, POAG1, SMG prognosis.

Discussion

Glaucoma is multifactorial disease and thinking for some are "unifactorial", reflected in therapeutic method. Several pressure- independent mechanisms are responsible for the glaucoma progression. Mechanical and vascular factors coupled. Separating glaucoma risk factors from glaucoma causal factors is not easy. Substantial progress has been made with regard to understanding risk factors and functional consequences of glaucoma [2,8]. Systemic vascular dysregulation can be primary or secondary of nature and can be combined with local ones. Vascular factor demonstrated strong connections between blood pressure changes, ocular perfusion pressure (OPP) and consecutive glaucomatous damages. VD distinguished in primary vascular dysregulation (PVD) formerly called vasospastic syndrome and secondary vascular dysregulation (SVD) [6,7,9,10]. The vascular factor reflected with association between nocturnal blood pressure dipping (NBPD), ocular blood flow fluctuations and unstable OPP as a reference point. In backstage NBPD prepared and finally played "ocular drama". Increased intraocular pressure and ischemia at the post-laminar optic nerve head affects retinal ganglion cell axons is starting of affection, vascular dysregulation and peripheral autonomic failure with ocular perfusion pressure falls below and its fluctuations, accompanied of abnormal autoregulation is progressing factor [3,9,11]. There is evidence of an abnormal association between NBPD and OPP in glaucoma patients. Therefore in patients with sympathetic dysfunction DBP shows further reduction, $p = 0.001$. NBPD characterized potent factor risk, where lower diastolic blood pressure and diastolic perfusion pressure respectively as predictor of glaucoma progres-

sion. Normally blood pressure follows a circadian pattern characterized by a decline of 10% from day to night [9]. Patients with peripheral autonomic failure offer the opportunity to demonstrated NBPD [11-13]. Blood pressure decreases by more than 20% in hypertensive patients is dipping [11,13,14]. Low blood pressure (LBP) and low OPP correlated with Glaucoma prevalence or glaucoma aggravation as well. Low diastolic perfusion pressure(DPP) and his fluctuations is a risk factor for glaucoma progression. It is interesting to note that although found a strong association between low DBP, OPP fluctuations and POAG progression. Perfusion pressure is defined as the difference between arterial and venous pressure [12,15,16]. OPP may more closely reflect the level of blood flow to the optic nerve. NBPD combined with factor risk local and systemic is a perfect set up for glaucoma development, showed a substantial interaction. Conjunction of VD to NBPD with that of NTG determined faster progression of glaucoma, but in SMG and POAG1 showed more permanent alterations. POBD was found to be associated with systolic and pulsatile components of blood velocities and pulsatile component of blood choroidal flow [7,16,17]. POBF estimated major parts of choroidal blood flow but don't know exactly which vascular bed is most important in terms of the glaucoma pathogenesis : retrobulbar, retinal, choroidal circulation or all together. OPP is directly proportional with BP mean and inversely proportional with IOP or laconically OPP is equal with the difference between DPB and IOP. DPP is the difference among DBP and IOP. For OPP calculation used the formula mean BP (where the BP was as one third of the systolic blood pressure plus two thirds of the diastolic blood pressure (DBP) minus IOP [3,6,18]. The sample size was also relatively small, and thus had limited power to detect accurately differences between the groups. Exit of dilemma for the management of NBPD. There are no guidelines to define the standard of nocturnal hypotension. For as long as cardiologist tweaking target blood pressure to new lows. Contradictory concepts between two specialties remained "Achilles heel". Trying to have an "beneficial solution" to NBPD correction, that indicated new relationship betwixt cardiologist and ophthalmologist. On the future it's important to know how other glaucomatous risk factor affected!

Conclusion

Vascular dysregulation compounded in a "domino effect" with IOP and OPP fluctuations, played a great role in glaucoma aggravation. Non-correct evaluation maybe attach it to "irreversible functional reaction". OPP depends on systemic and local pitfall and malicious factors. Choroidal blood flow that is substantially reduced, have implications of the optic nerve and chorioretinal alterations [6,16]. Decreased choroidal blood flow have role and in the development of choroidal neovascularisation in aged macular degeneration (AMD) [14,17]. NBPD not only is an important expression of vascular deterioration but also analytically verifies glaucoma vascular theory. Observed how is converted a extraocular novel factor risk to the intraocular strong. In NBPD a vascular imbalance that leads to OPP reduction and insufficient autoregulation. Big circadian fluctuations of OBF with OPP instable and reduction 40% are significant predictor of progression [5,19,20]. It' characteristic a statistical negative relation between IOP and OBF. OBF showed interaction to others risk factors [19,20]. Overnight intensive glaucoma treatment combined neuroprotective (nilvadipine, ginkgo biloba) and selective anti-glaucomatous eyedrops (excluded betablockers) is necessary. Not neglected careful treatment of vascular dysregulation. Circadian of OPP fluctuations have a positive association with glaucoma severity [5,11]. NBPD and peripheral autonomic failure with ocular perfusion pressure falls below and its fluctuations, accompanied of abnormal autoregulation are aggravation, progressing factor. Interactions and interference of factors risk represent a complicated and powerful impact in glaucoma progression. Individual risk can be defined by a time dependent model in which interaction between risk factors is determinative. Glaucoma therapy targets not only to the IOP lowering but to improve as if possible OBF and OPP. New focus on glaucoma management suggested. Interdisciplinary cooperation is indispensable. Intimate cooperation between cardiologist and ophthalmologist is mandatory… "The Tango danced by two". If cardiologists have come to believe that aggressive treatment of patients with high blood pressure will lead to better outcomes, "the game is lossed". Knowing that blood pressure goes down at night when IOP rises [11,12], cardiologist must avoid using betablockers nightlase and ophthalmologist in this time don't use betablockers eyedrops that secondary lowered blood pressure. Maltreatment of this clinical situation is more dangerous that its negligence. It's not be wrong for the ophthalmologist in clinical practice to keep with him a sphygmomanometer. Best treatment is customized treatment [20,21]. Multifactorial Glaucoma in multi-physiognomic Glaucoma advised multitherapeutic choice. Glaucoma puzzle offer surprises. Maybe clinical translation of regenerative medicine and gene/cell therapy to be "gold key".

Conflict of Interest

Don't have any financial or conflict of interest.

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