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Dorsolamide May Have a Role in Unoperable Diabetic Retinopathy

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Abstract

Aim: To assess the efficacy of long term use of dorzolamide in unoperable cases of diabetic retinopathy.

Method: A collection of 33 cases of diabetic patients, that are not amenable to have surgical treatment for any reason with advanced and late stages of retinopathy exposed to the effect of dorzolamide topically administered three times a day for life with a mean period of follow up from 2012 till the time of putting the results on papers. Meanwhile, those patients also received vitamins and antioxidants supplements plus follow up with medical consultant.

Results: All patients record satisfactory stationary outcome encouraging results after 3 months of continuous use of topical dorsolamide. Variable changes in visual acuity assessed but shows no significant improvement, however most of cases retain vision that is functionally accepted.

Discussion: Long term use of topical dorsolamide have several benefits through regulating activity of elevated level of enzymes, pH status correction, improving homeostasis, enhance cell metabolism and survival.

Conclusion: The outcome result may stimulate using topical CA inhibitors in other stages of diabetic retinopathy or even as a prophylaxis to ameliorate the progressive deterioration.

Keywords: Diabetic retinopathy; Carbonic anhydrase; Carbonic anhydrase inhibitors

process is a breakdown of the blood-retinal barrier (BRB), which normally prevents water movement in the retina, thus allowing fluid to accumulate in the retinal tissue. Inflammatory processes and an increase in vascular permeability play a central role. Different mechanisms, complicated by ischemic conditions, interact in a complex manner. Diabetic retinopathy is considered as a retinal neurovascular disease in which neuronal abnormalities precede the microvascular injury. Long-term hyperglycaemia causes vascular basement membrane thickening, non-enzymatic glycosylation, free radical formation and pericyte death. These changes ultimately lead to dilated vessels, increased capillary hydrostatic pressure and formation of microaneurysms [2]. Accumulation of fluid in the macula alters cell function as well as provokes an inflammatory reparative response [3]. The retina generates a large amount of CO₂ and lactate because of its high metabolic activity. In a situation where there is an ideal autoregulation there will be no change in flow for a given change in perfusion pressure [4]. Since the unique feature of retinal circulation is not having autonomic innervation hence the blood flow is entirely dependent on autoregulation. In the strictest sense, autoregulation is defined as the ability of the vessels to maintain a constant flow to the tissues under conditions of varying perfusion pressure. This definition was later expanded to include the changes in the vascular hemodynamics to support the metabolic needs of the tissues [5]. A number of interconnecting biochemical pathways have been proposed as potential links between hyperglycaemia and diabetic retinopathy. Reduced oxygen availability leads to the activation of a core cellular response to hypoxia [6]. The reduced oxygen limits the capacity for oxidative phosphorylation as a means of producing energy [7,8]. Hypoxic cells respond to this micro environmental stress by reprogramming their metabolism to engage the glycolytic pathway which is often permanent and persists after reoxygenation. The switch to glycolysis by cells results in increased production and export of acidic metabolites, such as lactic and carbonic acids, to the extracellular space and leads to a decline in extracellular pH [9], creating a toxic microenvironment.

One consequence of extracellular acidification is the disruption of the intracellular pH, a decrease in which rapidly affects basic cellular functions (membrane integrity, metabolism and energy production) and proliferation [8,9]. Thus, cells must regulate intracellular pH as the extracellular pH declines, a process particularly critical for normal cells that

Introduction

It is worthy to mention the famous phrase in each study of diabetic eye diseases which states that it is a blindness leading cause in all age groups worldwide. Diabetes is now recognized as an epidemic disease and the incidence of retinopathy, a common neurovascular complication of diabetes, is expected to be at higher rates. Retinal edema occurs when fluid and protein deposits collect within, leading to thickening and swelling which distorts vision [1]. The pathophysiological

prefer an intracellular pH that is somewhat alkaline [8,10]. The combination of an increasingly acidic microenvironment and a requirement to regulate intracellular pH results in death of normal cells and accelerates degradation of the extracellular matrix [11]. Unoperable cases of diabetic retinopathy such as those who are not candidate for any type of surgical interference due to may be patient causes (refusal, multiple organs disease, anesthesia unfitness, poverty and ignorance) or hospital causes (long waiting list, insufficient tools and medical supplies and unavailability of specialized surgeon in the area), or very poor prognostic factors that down balances the benefit of interference, although many of these are eliminated with the rapid development in branches of ophthalmology but still phobia from surgery is the most common cause to refuse surgical interferences, pushes to think for alternatives that may at least give a little hope to the patient that may maintain at least the situation from progressive deterioration not forgetting that the patient always demands and asks for a possible medical way to restore his vision by an alternative choice rather than the unwanted surgical option. The most common asked question "please doctor is there any medical therapy other than surgical interference". Carbonic anhydrases (CAs) are a group of ubiquitous zinc containing metalloenzymes having the same structure but vary in activity, which function by causing rapid conversion of carbon dioxide to bicarbonate and protons (reversible hydration), thence help determine levels of them and thereby regulate intracellular and extracellular pH and volume. There are different alpha-carbonic anhydrase isoforms studied, differing widely in their cellular localization and biophysical properties. Several isoforms of carbonic anhydrase identified to be present in the eye in various cell types both the intracellular [CA I (low activity), CA II (high activity) and CA III] and the membrane bound [CA IV and CA XIV] in which the last one involved prominently in the extracellular pH regulation. CA is one of the few enzymes occupying a central role in both transport and metabolism, and as such it serves a molecular link between these two general processes. The increase in retinal blood flow with CA inhibitors may serve to enhance retinal ischemia. An elevated level in tissue pCO_2 and pH acidity is thought to cause the vascular dilatation [12].

Methods

The attending diabetic patients for assessment [33 patients] who are aware of the disease and its consequences that may even end in blindness, ask for any alternative choice of therapy to surgery regarding intravitreal injections, laser retinal photocoagulation and vitrectomy.

The most common cause of refusing surgical interferences is phobia from surgery [17 patients] and its consequences that may be noticed in other members of family having the same disease [5 patients], then comes the multiple disease entity that may challenge the surgical interference of vitrectomy [7 patients], however few cases have reached advanced stages that made the specialist to make a decision that the surgical option is of no benefit [4 patients].

During the follow up period of those patients which ranges from 4-7 years [(5 cases-7 years), (9 cases- 6 years), (10 cases- 5 years), (9 cases-4 years)], the surgical option is always mentioned to ensure memorization of rejection.

The age of the patients ranged between 56-72 years as 14 male and 19 female. Positive family history is recorded in 29 cases. Medical treatment of diabetes mellitus according to the medical consultant advice could be oral drugs, insulin injection subcutaneously or a combination.

Monthly visit assessment and examination advised to the patients, who were highly compliant. During each visit the following was done:

- Assessment of the general condition done by a specialized medical consultant through laboratory investigation of blood glucose in addition to monitoring of medical treatment to control diabetes mellitus.
- Evaluate the visual function of the patient and asking about any noticed improvement change or at least stable condition.
- Intraocular pressure measurement.
- Slit lamp examination of the anterior segment and, if needed dilated, posterior segment examination, to assess the fundus and detect any complication happening during the period of therapy.
- Fundus picture captured plus optical coherence tomography (OCT) which are non-invasive imaging tests.
- Reassurance of the patient after each visit that the condition is stable and he might at least get slight visual function improvement at continuous drug use to ensure compliances.

Results

An important point is that refusal of surgical options play a major factor in continuous use of topical dorzolamide. Assessment and evaluation of the patient during each visit and comparing the results with the previously obtained shows:

- All patients report stabilization of visual function and/or at least mild improvement 3 months after starting the treatment and agree to continue the therapy for ever, meanwhile the patient advised to stick to other ways of management regarding strict control of diabetic status, topical and systemic vitamin and antioxidants supplement plus improving the psychological attitude and behavior.
- Three cases died during the follow up period and those were above 70 years old with accepted functional vision during life activities.
- Less frequent attacks of vitreous hemorrhages 3 months after starting the therapy as those patients were having 2-3 attacks per year and after treatment this lessens to 1 attack per 2 years.
- Most patients were happy and satisfied with using such medical treatment with no side effects apart from burning sensation after dorzolamide instillation at the end of one month of opening the drop bottle.
- Improved mental and psychological status of the patient as they are using a medication that could be alternative to surgery.

- Hazy unclear view of fundus pictures and irregular retinal outlines in OCT which is definitely obtained from those patients are of no value except to memorize the findings in the posterior segment examination using the high magnification lens with the slit lamp.

Discussion

Diabetes mellitus is a disease that affects the neurovascular tissue in vital organs with its stressful and inflammatory effects leading to hypoxia causing progressive deterioration that continues despite the measures applied for therapy. In a study by Gao et al. it was shown that diabetic patients had significantly higher concentrations of CA than healthy controls. Carbonic anhydrase is a hypoxia-inducible enzyme that is over expressed by cells and is a component of the pH regulatory system to overcome the deleterious effects of a high rate of glycolytic metabolism [13]. Elevated levels of extracellular CA I in vitreous from individuals with diabetic retinopathy, suggesting that retinal hemorrhage and erythrocyte lysis is the major contributor. Upregulation of these proteins have been reported in the diabetic vitreous by other authors [14,15]. The rate-limiting step in CO₂ transport for which CA is important occurs at the site of the membrane [16]. The finding of intense CA XIV activity in the retinal pigment epithelium and Müller cells suggests that CA XIV is the retinal target of CA inhibitors. The membrane-bound isoform CA XIV has been found in the ciliary body, retinal pigment epithelium, and Müller cells [17].

CA inhibitors can have beneficial effect in diabetic retinopathy by different suggested mechanisms and those are reducing aqueous humour secretion, inducing vasodilatation, improving blood flow to the ocular region, inhibiting platelet aggregation and reducing vascular permeability [18]. Prior publications by Wolfensberger and coworkers [19-22] have suggested that inhibition of a membranebound CA present at the retinal pigment epithelium is sufficient to enhance subretinal fluid absorption and retinal adhesiveness in individuals with macular edema and other retinal conditions. A greater degree of inhibition of carbonic anhydrase forces retinal vascular autoregulation to its limits.

All these evidences helped to choose dorzolamide as the drug that can be used in those patients as alternative to surgery although it need a long time to establish the desired effect.

Conclusion and Recommendations

Although rapid development occur in the branches of ophthalmology but still there are cases that require more search for thoughts of possible alternatives. Results show that continuous long term three times daily use of easily topically administered drug already used in other eye diseases (dorzolamide) with almost no side effects is desirable in those patients who are neither candidate nor amenable to surgical options, meanwhile there are accepted outcomes as maintaining or stabilizing the visual function by reducing or preventing the deleterious progressive deterioration of diabetic retinopathy. However, more of collaborate work up

between advanced medical centers that have the non-invasive laser Doppler velocimetry, which is not available in our area, to enlarge number of patients with frequent follow up assessment for long periods required to confirm the results obtained. Further investigative workup is required to determine the effectiveness and the exact mechanism of action of carbonic anhydrase inhibitors in different stages of diabetic retinopathy or even as a prophylaxis measure.

In summary, this study may not be considered conclusive because of the small number of patients, however high efforts in collecting such unusual cases and the long-time follow-up period may only be a personal contribution for finding a valid medical approach to unoperable cases of diabetic retinopathy. So, these preliminary results seem to suggest that dorzolamide could be proposed for medical treatment in unoperable cases of diabetic retinopathy in order to reduce the need for surgical treatments and to prevent the inadvertent vision loss. Moreover, encouraging application of topical CA inhibitors for other earlier stages of diabetic retinopathy mandates exclusive research study.

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