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RESEARCH ARTICLE

New Approaches to Neurophysiological Diagnosis and Treatment of Diabetic Vitreal Hemorrhages

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ABSTRACT:

When bleeding from neovascularization of the disc or neovascularization of the retina may develop preretinal hemorrhage or vitreous hemorrhage. The risk of vitreous hemorrhage is higher with extensive disc or retinal neovascularization. Hemorrhages usually occur spontaneously and cause a sudden appearance of floating opacities. New approaches to neurophysiological diagnostics and treatment of diabetic vitreal hemorrhages were studied in the work. To achieve the goal, an experiment was conducted with the participation of 83 patients. For the study, the patient's demographic data, indication for injection, intrauterine injection type, systemic risk factors and ocular complications were used. It has been established that anti-VEGF injections play an important role in the treatment of patients. The method studied can be used to dynamically evaluate the function of the visual analyzer.

KEYWORDS: Panretinal Photocoagulation, Vitrectomizedeyes, Neurophysiological diagnosis, Glaucoma.

INTRODUCTION:

Diabetic retinopathy (DR) is the leading cause of vision loss in working-age populations worldwide[1-4]. These causes of vision loss are often mediated by a common pathogenetic process – functional and structural disorders of ganglion cells of the retina and optic nerve[5-6], which determines the urgency of evaluating his condition, including neurophysiological methods, one of which is the method of visual evoked response potentials (ERP)[7-8].

These cause of vision loss are often mediated by a common pathogenetic process such as functional and structural disorders of ganglionic cells of retina and optic nerve[5-6]. This state determines the sense and urgency of evaluating its condition, having used some neurophysiological methods, one of which is the well known and high useful method of visual evoked response potentials (ERP)[7-8].

Retinal ischemia is the leading factor in pathophysiology of proliferative diabetic retinopathy (PDR). Angiogenic mediators such as insulin-like growth factor-1, erythropoietin, fibroblast growth factor and vascular endothelial growth factor (VEGF) are released secondary to retinal ischemia. They lead to the formation of neovascular structures in the retina [9-11]. One of the common ways the VH arises are those neovascular structures hemorrhages. Contraction of the fibrous component can increase the tendency of neovascular structures to bleed, also often caused associated visual nerve damage and lead to loss of vision. In the most of cases VH is treated surgically. But the high risk of complications after vitrectomy, sometimes negotiates surgical procedure[12-14].

Panretinal photocoagulation (PRP) is the gold standard in PDR treatment which can reduce the risk of severe visual loss by 50-60%[15-16]. The patients who do not receive timely PRP develop serious vision loss within 5 years[17]. But 4.5% of patients show disease progression that ultimately lead to pars plana vitrectomy (PPV), although the PRP was considered adequate[18].

Photocoagulation therapy not be possible in eyes with intravitreal opacity such as VH. This condition leads to the progression of neovascular tissue and may result in persistent VH, recurrent VH, or development of TRD. Currently, in patients whose hemorrhage does not clear spontaneously, PRP is performing after clearing the media[19].

Anti-VEGF drugs prevent the formation of new vasculature by directly affecting VEGF. VEGF is a 40 kDa dimeric glycoprotein that is produced by hypoxic stimulation in different cells of the retina: vascular endothelium, retinal pigment epithelial cells, Müller cells[20].

The first VEGF-A inhibitor, bevacizumab (Avastin), was approved by the US Food and Drug Administration (FDA) in 2004 for the first-line treatment of metastatic colorectal cancer. It is a monoclonal antibody (149kDa) that binds to all isoforms of VEGF-A and is now being used as an off label intravitreal drug for the treatment of retinal vascular disorders[21]. The first VEGF-A inhibitors in ophthalmology, pegaptanib (Macugen) and ranibizumab (Lucentis), were approved in 2004 and 2006, respectively. Ranibizumab is an Fab fragment of the humanized monoclonal antibody (48kDa) and has an affinity for all VEGF isoforms. The smaller molecule compared to Bevacizumab allows better retinal penetration[22]. Aflibercept (Eylea) is a recent anti-VEGF therapy approved in 2011. This agent has shown significant gain in visual acuity and improvement in morphological outcomes[23-24]. It's estimated that concentration of VEGF was significantly higher in eyes with VH due to DR (821 ± 949 pg/ml) than in non-DR hemorrhage (2.75 ± 7.5 pg/ml, $P < 0.01$, chi-square test) or non-DR with no VH (less than detectable level, $P < 0.01$, chi-square test)[25].

Intravitreal anti-VEGF agents have been used in DR treatment for diabetic macular edema, preretinal hemorrhage, and neovascularization and as preoperative adjuvant therapy in PDR cases[26].

Anti-VEGF agents block new vessel formation and also induce regression of existing vessels [27]. So, they can theoretically prevent new hemorrhages from preexisting or new loci in VH patients. And can be successful in the treatment VH. Because of the drug's short half-life, it is expected that IVB is not effective against recurrent hemorrhage in the long term.

In a study by the Diabetic Retinopathy Clinical Research Network (DRCRnet), researchers applied intravitrealranibizumab to 125 eyes and intravitreal saline to 136 eyes of diabetic patients with VH that precluded PRP. At 16 weeks after injection, eyes injected with ranibizumab showed a greater improvement in VA, lower rate of recurrent hemorrhage and significantly higher rate of PRP completion compared to the saline-injected group[28]. However, in a later report of results at 1 year, they reported no significant differences in VA outcomes or surgery rates[29].

The ideal interval for repeated IVB injections in cases of PDR-associated VH has not been clearly established. A second injection in eyes not exhibiting signs of hemorrhage clearance 4-6 weeks after the first injection. Repeated IVB injections were administered to eyes that did not show reduced hemorrhage or developed recurrent hemorrhage in early follow-up[30]. In general, the visual acuity (VA) of PDR patients can be expected to return to pre-hemorrhage levels after the VH is completely resorbed[31].

In practice, ophthalmologists often face a situation where the nature or degree of VH does not allow ophthalmoscopically assess the condition of the fundus, retina, optic disc. The dynamics of restoration or deterioration of the function of these structures depends on the nature, massiveness, other parameters of VH. Monitoring their condition presents difficulties in diagnosis, with the outcome of VH largely dependent on the state of the structures described. One of the additional methods of evaluation, the dynamics of recovery or deterioration of the optic nerve function with VH is the VLP method. In the context of this problem – the achievement of better treatment outcomes, outcomes of VH, the authors evaluated the diagnostic significance of the early-day components of visual evoked potentials using flash stimulation.

The purpose of this article is evaluation of the outcomes of intravitreal Ranibizumab or Aflibercept use in patients with a vitreous hemorrhage (VH) secondary to proliferative diabetic retinopathy (PDR) and evaluate reasons and diagnostical effectiveness of using method of visual evoked response potentials. With the present study, we aimed to evaluate the effects of IVB on hemorrhage clearance time, need for surgery and final VA results in diabetic patients with VH.

MATERIALS AND METHODS:

During the experiment 83 eyes were examined of 83 patients (33 male, 50 female) with type 2 diabetes mellitus. Study eyes had vitreous hemorrhage from PDR with or without precluding partial panretinal photocoagulation and include at least 6 month of follow-up. Most patients had poor glycemic control with a mean HbA1C of 9,2±1.32%.

Patients were randomized into 3 groups: eyes treated with IV Ranibizumab (group 1, n=32) eyes treated with IV Aflibersept (group 2, n=29) and eyes not treated with IV injection (group 3, n=22). Mean age was 65.2±5.6 years in group 1 and 64.1±4.2 in group 2 and 61.8±4.8 in group 3 (p=0.441). Follow-up was scheduled for 1 and 4 weeks afterwards and then every 4–6 weeks for the next 12 months. At each visit, a complete ocular examination was performed.

Examination:
Initial best-corrected visual acuity (BCVA) was measured using the Snellen chart: VA during follow-up; intraocular pressure (IOP); gonioscopy; slit-lamp examination; VH status; ultrasonography; dilated examination of the contra lateral eye; visual evoked potentials; VH clearance time was defined as the time until primary vessels in the posterior pole and the optic disc were clearly visible; PRP is applied as soon as the fundus clears.

Exclusion criteria:
Vitrectomizedeyes, patients with simultaneous bilateral VH, advanced glaucoma, rubeosisiridis, tractional retinal detachment, corneal or anterior segment pathology, active ocular infection, uncontrolled systemic hypertension, history of thromboembolism, coagulation disorder.

Patients who were treated by intravitral injections injection and those who were followed without intravitreal therapy were compared in terms of visual acuity (VA) change, final VA, VH clearance time, rate of surgical intervention.

The parameters evaluated included patient's demographic data, indications for injection, type of intravitreal injection used, systemic risk factors and ocular complications.

RESULTS AND DISCUSSION:

Taking into account that the purpose of the work includes the evaluation of the diagnostic significance of Visual evoked potentials, we briefly describe the neurophysiology of this method. In this work, the VEP was not evaluated for the chess pattern of stimulation in connection with the conceptual statement of the problem of isolating the state of cells forming the structures of the optic nerve, primary projections of fibers Lemniscus lateralis – visual cortex. For such a task, it is appropriate to use flash stimulation for a flash of red light generated by a matrix of LEDs, a flash duration of up to 0.1 ms, and a stimulation period of 1000 ms. With flash stimulation, it is possible to record distinctly the so-called super-early VEP components (designation N0 or P0 due to possible biphasic response, have a development time of up to 20 ms), are generated as a result of the optic nerve response – lemniscus lateralis – primary visual cortex. Early induced responses of the nervous system (P1-N1, matching latent periods of 20-140 ms) reflect the activity of primary visual centers, the primary response of the cerebral cortex to afferent activation and the initial stages of the inclusion of modal-nonspecific brain structures in response. The components of the intermediate phase (P2-N2 – the development time of 140-160 ms) are the potential that arises from the activation and inclusion of primary associative brain zones in the processing of visual information, at this stage, the limbic-reticularly connected mechanisms of neuronal excitation development, P3 components -N3 (development time 160-270 ms and more) are mainly considered conditioned by activity of the cerebral cortex in close interaction with limbic structures and recursion of the afferent flow in associative zonestory.

Intravitreal injections were given in the operating room under the topical anesthesia. All patients gave their informed consent. 10% Povidone iodine was used for skin preparation while 5% was instilled into the conjunctival sac before and after injection in all patients. No topical antibiotics were given before and after the procedure. Visual acuity changes in the study groups is shown in Figure 1.

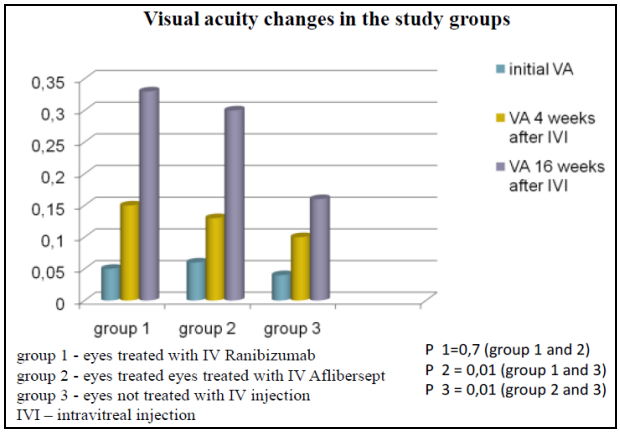

Figure 1 Visual acuity changes in the study groups

Table 1 Results dynamics

The difference between initial and final VA according Snellen chart was	VH clearance time was
0.32 ± 0,1 in group 1, 0.343 ± 0,11 in group 2 0,19 ± 0.09 in control group (p=0.01).	1.92 ± 0,4 months in group 1, 2.12 ± 0.5 months in group 2 (p=0.146), 3.13 ± 0.6 months in control group (p=0.048)

Dosage of intravitrealranibizumab given was 0.05ml (10 mg/ml) and aflibersept was given in the dosage 0.05ml (40mg/ml). Injection site varied between the superotemporal quadrant, inferotemporal and superonasal depending on the surgeon's access. Injections were given 4mm from the limbus for phakic patients and 3.5mm for pseudophakic patients. Patients were reviewed one day, one week and one month post injection, to assess their visual acuity and check intra ocular pressure (Table 1).

Dynamics of LP VIZ for early-stage components of VIZ (mean values of latent periods (LP) of early-stage components of VIZ):
Initial 28, 1 ± 2, 4; final results 24.5 ± 1, 6 in group 1,
Initial 26, 4 ± 1, 9; final results 23.9 ± 1, 6 in group 2,
Initial 28, 9 ± 2, 5; final results 28.3 ± 1, 9 in group 3,
12, 8 ± 2, 3 – healthy people.
VH clearance time shown in Figure 2.

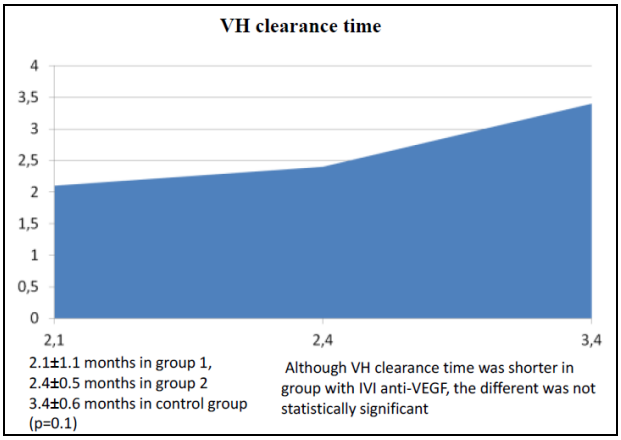

Figure 2 VH clearance time

In the study of VLPs, diagnostic features, such as asymmetry and decrease in the level of (μV) of responses, increased response time of early-day components and the restoration of late cortical components were also noted. An increase in LP was detected, starting with super early components (24.9 ms ± 1.9). A significant increase in the recovery time of the cortical potential in the occipital cortical leads (320.6 ± 34.9) in this contingent of patients is probably also due to damage to the ganglion cells. Significant differences of late cortical responses with an increase in LPPs mean their diagnostic significance not only as markers of the violation of cortical neurodynamics, but reflects a probable connection with the consequences of VH. Additional interpretation of the changes in the neurophysiological response of brain integrative systems as a result of the primary lesion of ganglion cells and optic nerve structures seems relevant for further study and application as a possible new marker in the neurophysiological diagnosis of primary peripheral visual impairment.

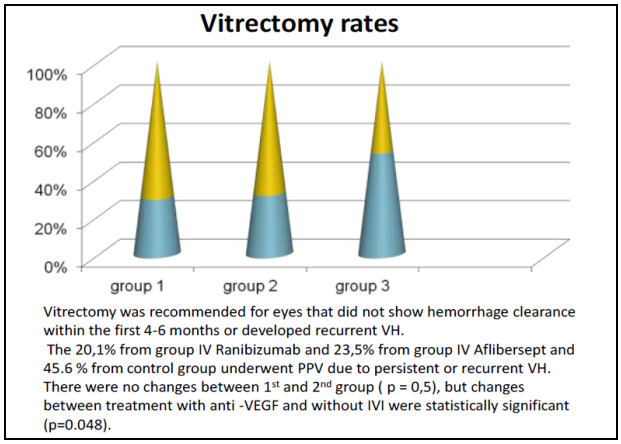

Figure 3 Vitrectomy rates

The impairment of the function of the optic nerve from the data of the early-day components of visual evoked potentials in this study was highly consistent with clinical, ophthalmoscopic disorders and manifested itself in the form of asymmetry of the latent periods of response of a healthy and compromised eye, showing a clear dynamics during the treatment. At the same time, the changes in the time of development of the components of the VIZ primarily reflect stable, mainly structural changes in the generator structures, the level of the amplitude of the VLV responses to the outbreak is more dynamic for all levels of generation, depending on changes in the functional state, pharmacological effects and other dynamic factors.

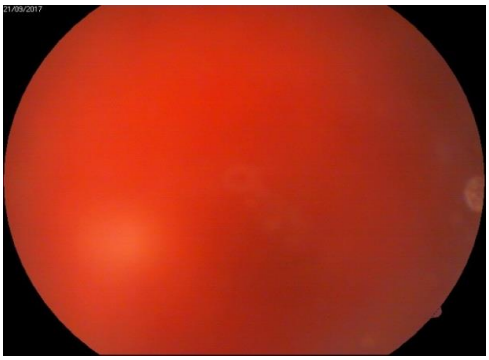

Figure4 Recurrent diabetic vitreous hemorrhageBCVA – light perception

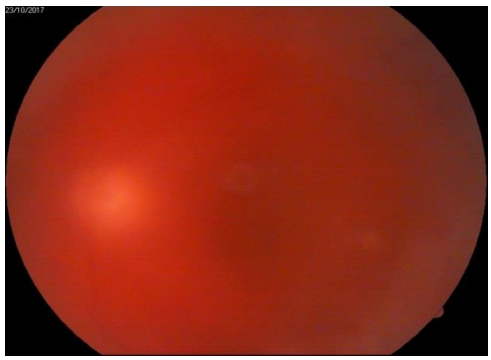

Figure5 3 days after intravitrealRanibizumab injection

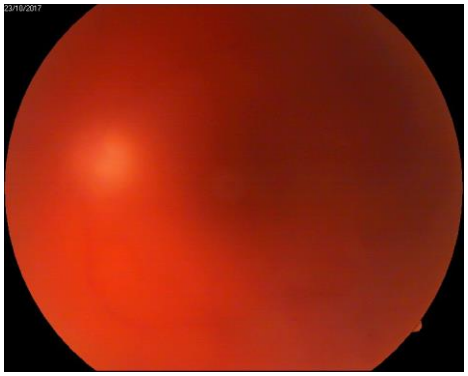

Figure6 7 days after intravitreal Ranibizumab injection

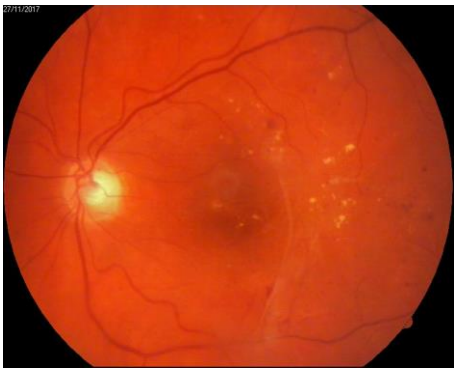

Figure7 1 month after intravitreal Ranibizumab injection BCVA 20/ 200

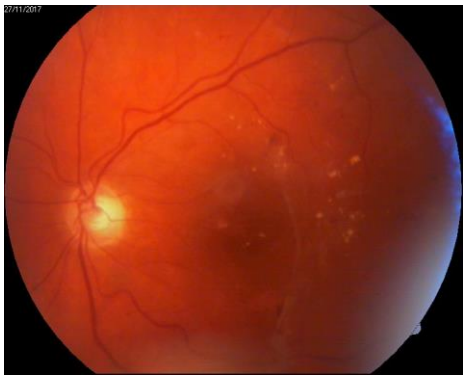

Figure8 1 year after intravitreal Ranibizumab injection BCVA 20/ 100

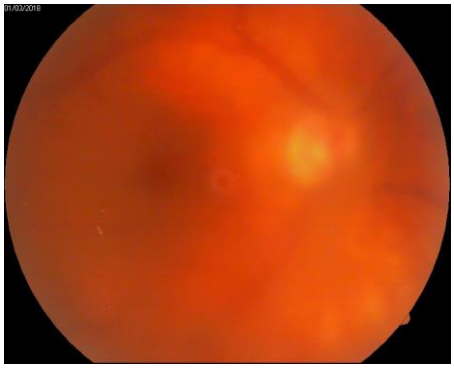

Figure9Partial diabetic vitreous hemorrhage BCVA 20/200

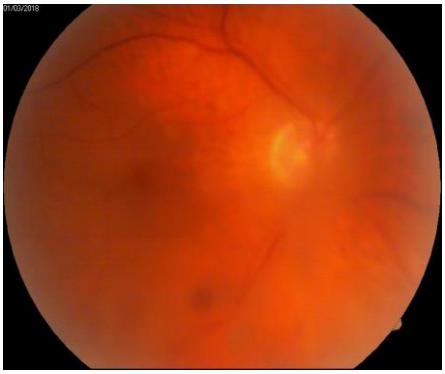

Figure10 7 days after intravitrealAflibercept injection

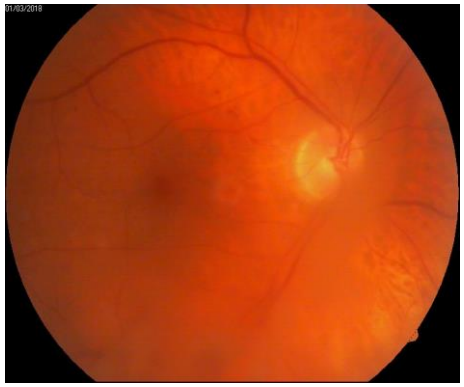

Figure11 1 month after intravitrealAflibercept injection BCVA 20/40

Vitrectomy was recommended for eyes that did not show hemorrhage clearance within the first 4-6 months or developed recurrent VH. The 20,1% from group 1 and 23,5% from group 2 and 45.6 % from control group underwent PPV due to persistent or recurrent VH (p=0.048) (Figure 3).

IVI decreases the number of cases requiring surgery. Clinical examples before treatment and after two different patients are presented in Figures 4-11.

CONCLUSION AND FUTURE PROSPECTIVE:

This study showed important role IV anti VEGF injections in the management of patients with VH secondary to PDR. IV injections was found effective in the changes of BCVA in compare with no IVI. Determined that Intravitreal injection of anti–VEGF can reduce vitrectomy rates (and risks associated with vitrectomy). Although VH clearance time was shorter in group with IVI, the different was not statistically significant.

During the study, the diagnostic signs of the VEP were determined. This is an asymmetry and a decrease in the level of responses, an increase in the response time of early-day components, and the restoration of late cortical components. It has been established that the change in the development time of the components of the VIZ

mainly reflects stable, structural changes in the generator structures, the level of the amplitude of the VLV responses to the outbreak is more dynamic for all levels of generation, depending on changes in the functional state, pharmacological effects and other dynamic factors.

The VLP research method is informative at VH and can be included in the diagnostic plan if the eye structures are difficult to visualize and for the dynamic evaluation of the visual analyzer function.

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