DOI: https://doi.org/10.25276/0235-4160-2018-1-37-47
УДК 617.735

The treatment results in patients with diabetic proliferative retinopathy who underwent vitrectomy after a ranibizumab injection. Vitrectomy after ranibizumab in diabetes

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ABSTRACT

Purpose. To evaluate the results of the combined treatment with intravitreal ranibizumab injection (IVR) followed by pars plana vitrectomy (PPV) in patients with proliferative diabetic retinopathy (PDR).

Material and methods. The study involved 69 patients with PDR had IVR followed by 23G PPV. The patients were divided into 3 subgroups: subgroup 1 – PPV 1 day after IVR, subgroup 2 – PPV 3 days after IVR, and subgroup 3 – PPV 5 or 7 days after IVR. The control group consisted of 23 patients operated on before the study started or patients who did not agree for anti-VEGF injection before vitrectomy.

Results. The regression of the pathological vessels was observed in all the subgroups with IVR injection pretreatment. Six-months post-vitrectomy a BCVA improvement was observed in the IVR groups in 87% of the patients and in 70% of the patients in the control group (p<0.203). Among the patients without renal failure the IVR groups had 4 times higher chances for the BCVA improvement than in the control group (p<0.133). After excluding the influence of the diabetes duration the odds became statistically significant (p<0.050) – over 10 times higher. Retinal detachment (RD) at the primary examination reduced the chance for BCVA improvement at 3 (p<0.020) and 6 (p<0.068) months post-vitrectomy.

Conclusions. IVR in patients with PDR cause pathological neovascularization regression, reduces intraoperative bleeding and increases the chances for BCVA improvement, especially in the groups with proper renal function and without any cardiovascular complications.

Key words: *anti-VEGF, neovascularization, proliferative diabetic retinopathy, ranibizumab, renal failure, vitrectomy.* ■

No author has a financial or proprietary interest in any material or method mentioned.

Fyodorov Journal of Ophthalmic Surgery.– 2018.– No. 1.– P. 37–47.

РЕФЕРАТ

Результаты лечения пациентов с пролиферативной диабетической ретинопатией методом витрэктомии, проведенной после инъекции Ранимизумаба (Луцентиса)

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Актуальность. Результаты лечения пациентов с пролиферативной диабетической ретинопатией методом витрэктомии, проведенной после инъекции Ранибизумаба (Луцентиса).

Материал и методы. Проведено 69 витрэктомии pars plana (PPV) 23G после инъекции ранибизумаба (IVR) у пациентов с пролиферативной диабетической ретинопатией (PDR). Пациенты группы исследования были разделены на 3 подгруппы: 1 подгруппа – PPV 1 день после IVR, 2 подгруппа – PPV 3 дня после IVR, 3 подгруппа – PPV 5-7 дней после IVR. Контрольная группа – 23 пациента с PDR, которым была проведена витрэктомия pars plana (PPV) 23G.

Результаты. Во всех 3 подгруппах группы исследования была отмечена регрессия неоваскуляризации. В группе исследования корригируемая острота зрения (BCVA) 6 мес. после IVR+PPV улучшилась в 87% случаев, а в контрольной – в 70% случаев (p<0,203). Среди пациентов группы исследования без диабетической нефропатии острота зрения улучшалась в четыре раза чаще, чем у пациентов контрольной группы (p<0,133). При исключении фактора продолжительности диабета среди пациентов группы исследования без диабетической нефропатии улучшение остроты зрения наблюдали в 10 раз чаще, чем в контрольной группе (p<0,05). Выявленная до операции тракционная

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отслойка сетчатки является статистически значимым фактором, снижающим прогноз улучшения остроты зрения в группе исследования в сроки наблюдения до 3 (p<0,02) и 6 мес. (p<0,068).

Выводы. Применение ранибизумаба перед витректомией (IVR+PPV) у всех пациентов с пролиферативной диабетической ретинопатией (PDR) вызывает разной степени выраженности регрессию неоваскуляризации, уменьшает интраоперационное кровотечение, повышает прогноз улучшения остроты зрения, в частности среди пациентов без почечной и сердечно-сосудистой патологии.

Ключевые слова: *anti-VEGF-инъекции, неоваскуляризация, пролиферативная диабетическая ретинопатия, ранибизумаб, диабетическая нефропатия, витректомия.* ■

Авторы не имеют финансовых или имущественных интересов в упомянутых материале и методах.

Офтальмохирургия.– 2018.– № 1.– С. 37–47.

INTRODUCTION

Despite considerable improvements in treatment, diabetic retinopathy remains great challenge for ophthalmologists. Angiogenesis, a key factor in the development of diabetic retinopathy, is a complex multi-step process. Hypoxia leads to the imbalance between the inducers and inhibitors of angiogenesis. The growth of pathological vessels is followed by fibrous tissue. Numerous pathological vessels cause intense intraoperative bleeding, which makes proliferative membrane removal a very difficult or even impossible task. In recent years, many vitreoretinal surgeons have used anti-VEGF pretreatment before pars plana vitrectomy (PPV) in patients with proliferative diabetic retinopathy (PDR). Preliminary treatment with anti-VEGF agents restricts the number of pathological vessels, considerably stimulates the regression of neovascularization and reduces intraoperative bleeding making it significantly easier to conduct a complex procedure [11, 14, 15, 16, 22, 23].

Presently, there are no generally accepted standards defining the exact time of anti-VEGF injection before PPV in PDR. Most surgeons inject anti-VEGF agents within 1-10 days before PPV, which is related to literature reports of the intensification of fibrosis processes in proliferative membranes which may lead to the development or exacerbation of tractional retinal detachment [1]. In patients who received bevacizumab injection less than 10 days before PPV, intensified fibrosis was not observed [7]. Most studies analyzed the use of bevacizumab, while only isolated reports were published on the use of ranibizumab prior to vitrectomies in PDR. It is not known whether ranibizumab enhances fibrosis to the same extent as bevacizumab or whether there are differences between the two preparations in this respect.

PURPOSE

The aim of the study was an assessment of treatment outcomes in patients with PDR who underwent vitrectomy preceded by intravitreal ranibizumab injection (IVR).

Patients and methods

Ninety-two (92) patients were analyzed. The study group consisted of patients with PDR referred to Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Clinical Department of Ophthalmology and Central Clinical Hospital of the Ministry of Interior in Warsaw for vitrectomy from Jul'2012 to Oct'2014. In our centers prior to study start in cases with PDR standard PPV were performed without anti VEGF pretreatment. Since numerous studies demonstrated that intravitreal anti-VEGF injections before vitrectomy had significantly stimulated the regression of neovascularization and reduced intraoperative bleeding, thus, making the surgery easier, the plan to form a random control group was abandoned. The control group was made up of 23 individuals who underwent vitrectomy due to PDR in 2012 before the study start (21) and patients admitted to hospital later who refused anty-VEGF injection (2) because of possible systemic adverse events. Sixty-nine (69) patients received ranibizumab as preliminary treatment before vitrectomy; the injections were given: 1 day (14 patients), 3 days (35 patients) and 5 or 7 days (20 patients) before PPV. The duration of diabetes in the study group was 5 years shorter than in the control group.

Before enrollment, all patients were informed in detail about planned course of the study and gave their informed consent to participate. The study was approved by the Ethics Committee at the Collegium Medicum in Bydgoszcz. Patients' general condition was assessed on the basis of medical records provided by each patient, a questionnaire administered to patients and a consultation conducted by internal medicine specialists and anesthesiologists. Every individuals had a detailed ophthalmological examination including: best corrected visual acuity (BCVA), the evaluation of anterior eye segment, stereoscopic assessment of posterior eye segment, intraocular pressure (IOP) measurement. In patients with sufficient visualization we obtained eye fundus photograph, OCT, and fluorescein angiography.

The patients in the study group were divided into 3 subgroups. Subjects in subgroup 1 were given intravitreal ranibizumab injection (IVR) 1 day before scheduled vitrectomy, in subgroup 2 patients were given IVR 3 days before PPV, and in subgroup 3 patients were given IVR 5 or 7 days before PPV. All patients underwent a prior or simultaneous phacoemulsification. Vitrectomies were performed by four experienced surgeons. Each surgery was filmed and the surgeon filled in a survey evaluating the course of the surgery. Check-up examinations were conducted on postoperative day 1, and then 7 days, 2-3 weeks, 7-8 weeks, 3 months, 6 months and possibly 12 months after the surgery. Visual acuity was measured after performing refraction using Snellen charts at 5m for distant vision with best correction. Check-up examination included also the evaluation of anterior and posterior segment, IOP, eye fundus photograph

and OCT. An analysis of visual outcome was undertaken with visual success and visual loss defined as a gain or reduction of 1 Snellen line. If visual acuity (VA) was less than 20/200: no light perception, light perception, hand motions, count fingers, 1/50, 2/50, 3/50 VA improvement was defined as one stage improvement.

The following were study endpoints:

BCVA improvement after 3 and 6 months.

Evaluation of the course of the surgery (intraoperative bleeding assessment). Intraoperative bleeding was assessed based on the use of alternative infusion and endodiathermy.

Preliminary statistical analysis included the comparison of the groups (the study group vs. the control group) relative to baseline parameters *(Tab. 1)*. Qualitative variables were compared using Fisher's Exact Test while quantitative variables were compared with Mann-Whitney Test. The aim of the main statistical analysis was the identification of risk factors (predictors) for study endpoints. A series of univariate and multivariate analyses (logistic regression analysis) was performed for the primary endpoint of the study, where analyzed potential risk factors for a BCVA improvement included age, duration of diabetes, type of diabetes, complications such as stroke, myocardial infarction, renal failure and baseline visual acuity.

RESULTS

There were differences in the duration of diabetes between the study group and the control group. The duration of diabetes in the study group was 5 years shorter than in the control group (Tab. I). In the control group, right eye was operated more frequently than in the study group. Otherwise, the differences between both groups observed before the start of treatment were not statistically significant.

The regression of pathological vessels was observed in all subgroups of patients who received IVR prior to vitrectomy. Among patients operated 24 hours after IVR, 2 subjects (15%) demonstrated only partial regression of pathological vessels and in 11 subjects (85%) this regression was significant. All patients who received IVR 3, 5 and 7 days before PPV had a significant regression of pathological vessels.

No significant differences were observed in the occurrence of BCVA improvement between the study group and the control group 3 months after vitrectomy *(Tab. II)*.

Six months after the surgery, among ranibizumab-treated patients, BCVA improvement was achieved in 87% of patients while among control patients, the BCVA improvement occurred in 70% of subjects *(Tab. III)*. The BCVA improvement was also more likely when excluding the effects of age, diabetes duration, diabetes type and baseline visual acuity *(Tab. III)*. Visual acuity was compared between ranibizumab-treated patients and those without, in the selected subgroups: patients without ischemic heart disease, patients without the history of myocardial infarction, patients without history of renal failure and patients with type 2 diabetes mellitus. In all these subgroups, BCVA improvement after 6 months was more likely in ranibizumab-treated patients versus those without IVR. Among patients without signs of renal failure, ranibizumab-treated subjects were nearly 4 times more likely to experience BCVA improvement (87% vs 62%; *Tab. IV*) than subjects without IVR. Once the effect of diabetes duration has been excluded in this group of patients, BCVA improvement 6 months after PPV was over 10 times more likely in patients who received IVR before vitrectomy (OR 10.81; p<0.050; Tab. IVa). A similar correlation, at the borderline of statistical significance (p<0.071) was observed among patients without history of myocardial infarction – BCVA improvement in this group of subjects who received IVR prior to PPV was over 6 times more likely (OR 6.80) than in subjects who were not treated with ranibizumab before PPV.

The occurrence of tractional retinal detachment at baseline was associated with statistically significant reduction of chances for BCVA improvement 3 months after the surgery (47% vs 80%, *Tab. II*) and 6 months after the surgery (69% vs 91%, *Tab. III*).

Half of patients (50%) with documented renal failure experienced vision improvement 3 months after PPV, while the same was true about 78% of subjects without the diagnosis of renal failure (p<0.043; *Tab. II*); the levels of significance achieved indicate statistically significant differences in the occurrence visual improvement resulting from co-existent renal failure. This correlation was also statistically significant once the effect of diabetes duration (p<0.029; *Tab. II*) and baseline visual acuity (p<0.042; *Tab. II*) have been excluded. Once excluding the effect of age (p<0.054; *Tab. II*) and type of diabetes (p<0.065; *Tab. II*), the correlation was at the borderline of statistical significance. In the subgroup of patients without ischemic heart disease (p<0.037) and without history of myocardial infarction (p<0.039), the correlation between visual improvement observed 3 months after vitrectomy and co-existent renal failure is also statistically significant. Six months after vitrectomy, the association between VA improvement and co-existent renal failure is not statistically significant.

Three months after the surgery, BCVA improvement was statistically significantly more likely among patients without hypertension than in those with hypertension; the difference was statistically significant (93% vs 62%; p<0.047; *Tab. II*). This correlation was also observed once excluding the effect of age (p<0.032; *Tab. II*), diabetes duration (p<0.032; *Tab. II*), diabetes type (p<0.039; *Tab. II*) and baseline visual acuity > 0.5 (p<0.056; *Tab. II*). Six months after PPV, the correlation between BCVA improvement and coexistent hypertension was not statistically significant.

DISCUSSION

As the number of patients with advanced PDR is growing, the establishment of optimum management guidelines in such patients is an issue of great importance. No management standards have been established so far.

Vitrectomy has been a recognized treatment method for advanced diabetic retinopathy practiced for a few decades. It has been long emphasized that early vitrectomy has better outcomes and allows to

Table I

Baseline Characteristics of Study Subjects

Таблица I

Характеристика пациентов до операции

Factor Фактор	n	IVR before PPV Группа IVR до PPV			n	Control group Контрольная группа			
		X±SD /%				X±SD /%			
Right eye Правый глаз	69	43.5	%		23	69.6	%		0.053
Left eye Левый глаз	69	56.5	%		23	30.4	%		0.053
Visual acuity Острота зрения									0.112
≤0.1		60.9	%			82.6	%		
0.1-0.5		34.8	%			13.0	%		
≥0.5		4.4	%			4.4	%		
IOP (mmHg) ВГД	61	15.8	±	4.3	19	16.1	±	4.9	0.786
BMI ИМТ	67	30.0	±	6.1	18	28.4	±	5.7	0.302
Type 1 DM Тип 1 СД	69	24.6	%		22	40.9	%		0.177
Type 2 DM Тип 2 СД	69	76.4	%		22	59.1	%		0.177
Duration of DM (years) Продолжительность СД (годы)	67	17.1	±	9.7	21	22.2	±	11.4	0.044
Age (years) Возраст (годы)	69	56.5	±	11.8	23	55.7	±	13.0	0.774
Oral antidiabetic drugs Препараты противодиабетические	45	48.9	%		12	25.0	%		0.195
Anticoagulants Антикоагулянты	28	10.7	%		10	30.0	%		0.310
Insulin units/24h Инсулин/24h	69	47.9	±	25.5	21	47.7	±	25.1	0.971
HbA1 (%) HbA1 (%)	39	7.7	±	1.2	4	9.9	±	1.4	
Laser duration Лазеротерапия (месяцы)	48	39.9	±	43.7	7	20.0	±	16.7	0.242
Diabetic foot Диабетическая стопа	68	23.5	%		22	9.1	%		0.221
Renal failure Нефропатия	68	27.9	%		22	40.9	%		0.294
Dysesthesia Невралгия	66	18.2	%		22	9.1	%		0.503
Hypertension Гипертензия	68	75.0	%		22	72.7	%		1.000
Ischemic heart disease ИБС	67	16.4	%		22	4.6	%		0.280
Myocardial infarction Инфаркт миокарда	67	9.0	%		22	0.0	%		0.330
Stroke Инсульт	66	10.6	%		23	4.4	%		0.675
Hiperlipemia Гиперлипидемия	66	47.0	%		21	38.1	%		0.616

Abbreviations: IOP intraocular pressure, DM – diabetes mellitus.
Примечание: ВГД – внутриглазное давление, ИМТ – индекс массы тела, СД– сахарный диабет, HbA1 – гликированный гемоглобин, ИБС – ишемическая болезнь сердца, PPV – витректомия pars plana, IVR – инъекции ранибизумаба.

Table II

Predicted improvement of visual acuity 3 months after PPV depending on different factors in all patients and after excluding the influence of: age, diabetes duration, diabetes type and baseline visual acuity

Таблица II

Прогнозирование улучшения остроты зрения 3 мес. после витректомии в зависимости от исследуемых факторов среди всех пациентов при исключении влияния по очереди: возраста, продолжительности сахарного диабета и исходной остроты зрения (ОЗ)

Factor Фактор	VA Improvement ОЗ до операции			Age Возраст		DM duration СД Продолжительность		DM type СД Тип		VA >0.5 ОЗ>0.5	
		OR	p	OR	p	OR	p	OR	p	OR	p
Baseline VA: Исходная ОЗ:											
<0.1	79%	3.39	0.061	3.41	0.061	3.50	0.061	3.52	0.057	5.66	0.019
0.1-0.4	53%	1.00		1.00		1.00		1.00		1.00	
≥0.5	33%	0.44	0.534	0.48	0.590	0.51	0.614	0.57	0.677	0.16	0.255
IVR time: IVR время:											
Control group Контрольная группа	82%	1.93	0.476	2.01	0.451	2.16	0.431	3.04	0.266	2.04	0.443
1 day before PPV 1 день до PPV	67%	0.86	0.844	0.89	0.884	0.79	0.760	1.04	0.959	0.91	0.902
3 days before PPV 3 день до PPV	70%	1.00		1.00		1.00		1.00		1.00	
5 days before PPV 5 дней до PPV	64%	0.77	0.726	0.84	0.820	0.72	0.662	0.89	0.874	0.83	0.802
IVR time [1 day] IVR время [1 день]		0.97	0.884	0.96	0.832	0.98	0.904	0.96	0.857	0.97	0.901
Treatment: Лечение:											
Control group Контрольная группа	82%	1.00		1.00		1.00		1.00		1.00	
IVR-treated subgroups IVR-группа	67%	0.46	0.356	0.46	0.354	0.40	0.318	0.32	0.206	0.45	0.346
DM type [2 vs 1]: СД тип [2 vs 1]:											
Type 1 DM Тип 1 СД	59%	1.00		1.00		1.00				1.00	
Type 2 DM Тип 2 СД	75%	2.10	0.226	2.10	0.312	2.09	0.303		.	2.09	0.233
DM duration [year] СД продолжительность [годы]		0.99	0.612	0.99	0.594		.	0.99	0.936	0.99	0.736
Age [year] Возраст (годы)		1.02	0.509		.	1.00	0.458	1.01	0.995	1.01	0.549
Sex [W vs M] Пол [Ж vs M]											
Men мужчины	76%	1.00		1.00		1.00		1.00		1.00	
Women женщины	61%	0.48	0.210	0.41	0.149	0.45	0.181	0.44	0.176	0.48	0.221
HbA1 before PPV [1%] HbA1 до PPV [1%]		1.16	0.609	1.19	0.535	1.35	0.346	1.19	0.550	1.16	0.602
Renal failure Нефропатия											
-	78%	1.00		1.00		1.00		1.00		1.00	
+	50%	0.28	0.043	0.29	0.054	0.25	0.029	0.31	0.065	0.28	0.042

Factor Фактор	VA Improvement ОЗ до операции			Age Возраст		DM duration СД Продолжительность		DM type СД Тип		VA >0.5 ОЗ>0.5	
		OR	p	OR	p	OR	p	OR	p	OR	p
Hypertension Гипертензия (АД)											
-	93%	1.00		1.00		1.00		1.00		1.00	
+	62%	0.12	0.047	0.11	0.045	0.09	0.032	0.10	0.039	0.13	0.056
Ischemic heart disease ИБС											
-	72%	1.00		1.00		1.00		1.00		1.00	
+	67%	0.78	0.785	0.63	0.626	0.80	0.810	0.62	0.612	0.79	0.802
Myocardial infarction Инфаркт миокарда											
-	70%	1.00		1.00		1.00		1.00		1.00	
+	67%	0.84	0.892	0.76	0.831	0.95	0.968	0.64	0.731	0.97	0.978
Stroke Инсульт											
-	71%	1.00		1.00		1.00		1.00		1.00	
+	50%	0.41	0.388	0.39	0.365	0.39	0.369	0.30	0.259	0.45	0.447
Tractional RD Тракционная ОС											
-	80%	1.00		1.00		1.00		1.00		1.00	
+	47%	0.22	0.020	0.22	0.020	0.17	0.015	0.19	0.014	0.23	0.024
Baseline VA Исходная ОЗ:											
≤ 0.5	67%	1.00		1.00		1.00		1.00			
> 0.5	82%	2.18	0.356	2.120	0.375	2.150	0.370	2.160	0.365		.

Abbreviations: VA visual acuity, IVR – intravitreal ranibizumab, RD retina detachment.
Примечание: СД– сахарный диабет, HbA1 – гликированный гемоглобин, ИБС – ишемическая болезнь сердца, ОС – отслойка сетчатки, PPV – витректомия pars plana, IVR – инъекции ранибизумаба.

maintain good visual acuity for longer [3, 13, 19, 20]. The removal of vitreous body and its replacement with BSS solution with lower viscosity supports oxygen transport to ischemic areas and accelerates the clearance of cytokines including VEGF from the vitreous cavity [9, 17]. This results in the reduction of edema and neovascularization at the posterior pole. Endophotocoagulation performed during vitrectomy causes a further decrease in VEGF levels.

Many vitreoretinal surgeons have been using anti-VEGF pretreatment before PPV for more than 5 years. Anti-VEGF pretreatment restricts the number of pathological vessels [14, 15]. This finding was also confirmed in our study. Significant regression of pathological vessels was observed in 100% of patients who received IVR 3 and 5 days before PPV. On the other hand, among patients operated one day after IVR, 11 (85%) demonstrated significant regression of pathological vessels and 2 (15%) had partial regression. The regression of pathological vessels allowed for less traumatic and easier removal of proliferative membranes, even within the area of tractional retinal detachment. Reduced bleeding from pathological vessels of proliferative membrane allowed for much better visualization. Numerous literature reports support the claim that the administration of anti-VEGF before vitrectomy reduces the duration of surgery and improves its effectiveness by stimulating the regression of neovascularization and consequently, reduced intraoperative bleeding makes the surgery easier to perform [11, 16, 22, 23].

In surgeries without anti-VEGF pretreatment, bleeding often made the removal of proliferative membranes and traction release impossible. When the bleeding was severe, the coagulation of the vessel was very difficult due to poor visualization. One of the methods to restrict bleeding was the use of high intraocular pressure, but this method also limited blood flow through normal vessels resulting in retinal hypoxia what may cause irreversible cell damage and have a negative effect on the visual acuity [5].

All our patients had PPV not later than 7 days after IVR. In patients with tractional retinal detachment prior to IVR the worsening of retinal detachment was not observed in any patient after ranibizumab injection until vitrectomy. All vitreoretinal surgeons taking part in this study admitted that the removal of proliferative membranes was easier and more accurate in patients with

Table III

Predicted improvement of visual acuity 6 months after PPV depending on different factors in all patients and after excluding the influence of: age, diabetes duration, diabetes type and baseline visual acuity

Таблица III

Прогнозирование улучшения остроты зрения 6 мес. после витректомии в зависимости от исследуемых факторов среди всех пациентов при исключении влияния по очереди: возраста, продолжительности сахарного диабета и исходной остроты зрения

Factor Фактор	VA Impr % ОЗ до операции %			Age Возраст		DM duration СД Продолжительность		DM type СД Тип		VA ≥0.5 ОЗ≥0.5	
		OR	p	OR	P	OR	p	OR	p	OR	p
Baseline VA: Исходная ОЗ:											
<0.1	91%	3.87	0.110	3.98	0.108	3.67	0.127	3.65	0.130	2.84	0.339
0.1-0.4	71%	1.00		1.00		1.00		1.00		1.00	
≥0.5	67%	0.80	0.870	1.07	0.965	0.76	0.840	0.84	0.903	0.32	0.478
IVR time: IVR время:											
Control group Контрольная группа	70%	0.72	0.712	1.29	0.809	0.39	0.358	0.92	0.940	0.42	0.459
1 day before PPV 1 день до PPV	90%	2.77	0.396	4.73	0.227	3.18	0.344	3.80	0.307	1.87	0.635
3 days before PPV 3 день до PPV	76%	1.00		1.00		1.00		1.00		1.00	
5 days before PPV 5 день до PPV	100%	--		--		--		--		--	
IVR time [1 day] IVR время [1 день]:		1.30	0.428	1.34	0.400	1.32	0.406	1.31	0.421	1.38	0.439
Treatment: Лечение:											
Control group Контрольная группа	70%	1.00		1.00		1.00		1.00		1.00	
IVR-treated subgroups IVR-группа	87%	2.91	0.203	2.58	0.271	5.00	0.101	3.25	0.190	5.01	0.128
DM type [2 vs 1] СД тип [2 vs 1]											
type 1 DM тип 1 СД	79%	1.00		1.00		1.00				1.00	
type 2 DM тип 2 СД	85%	1.58	0.572	1.03	0.976	2.28	0.401		.	3.62	0.194
DM duration [year] СД продолжительность [годы]		1.01	0.788	1.01	0.864		.	0.98	0.502	0.98	0.643
Age [year] Возраст [годы]		1.03	0.322		.	1.04	0.278	1.07	0.354	1.07	0.105
Sex [W vs M] Пол [Ж vs M]											
Men мужчины	80%	1.00		1.00		1.00		1.00		1.00	
Women женщины	89%	1.92	0.457	1.64	0.581	1.97	0.444	1.99	0.435	2.51	0.435
HbA1 before PPV[1%] HbA1 до PPV[1%]		0.44	0.075	0.63	0.287	0.45	0.097	0.49	0.146	0.47	0.095
Renal failure Нефропатия											
+	81%	1.00		1.00		1.00		1.00		1.00	
-	91%	2.33	0.453	3.26	0.309	2.30	0.463	3.05	0.348	1.04	0.977

Factor Фактор	VA Impr % ОЗ до операции %			Age Возраст		DM duration СД Продолжительность		DM type СД Тип		VA ≥0.5 ОЗ≥0.5	
		OR	p	OR	P	OR	p	OR	p	OR	p
Hypertension Гипертензия											
-	83%	1.00		1.00		1.00		1.00		1.00	
+	83%	1.00	1.000	1.05	0.957	1.01	0.991	1.03	0.976	0.65	0.744
Ischemic heart disease ИБС											
-	82%	1.00		1.00		1.00		1.00		1.00	
+	88%	1.53	0.710	1.13	0.916	1.51	0.722	1.38	0.780	0.55	0.635
Myocardial infarction Инфаркт миокарда											
-	84%	1.00		1.00		1.00		1.00		1.00	
+	67%	0.37	0.440	0.27	0.324	0.33	0.405	0.30	0.363	0.24	0.297
Stroke Инсульт											
-	83%										
+	100%										
Tractional RD Тракционная ОС											
-	91%	1.00		1.00		1.00		1.00		1.00	
+	69%	0.21	0.068	0.21	0.070	0.22	0.083	0.22	0.073	0.70	0.784
Baseline VA Исходная ОЗ											
≤0.5	87%	1.00		1.00		1.00		1.00			
>0.5	88%	1.04	0.976	0.87	0.907	0.99	0.991	1.12	0.97		

Abbreviations: VA visual acuity, IVR – intravitreal ranibizumab.
Примечание: СД – сахарный диабет, HbA1 – гликированный гемоглобин, ИБС – ишемическая болезнь сердца, ОС – отслойка сетчатки, PPV – витректомия pars plana, IVR – инъекции ранибизумаба.

ranibizumab pre-treatment. This observation is consistent with the findings reported by other authors [7, 15, 16]. There was no need for alternative infusion (pressure 60 mmHg). Endodiathermy was used in all control subjects, in 71% of cases in IVL group 1 day before PPV and only in 27% of cases in groups IVL 3 and 5 before PPV.

Three months after vitrectomy, no statistically significant differences were observed in the occurrence of BCVA improvement between the control group and ranibizumab-treated group, while there was a clear correlation between coexisting renal failure or hypertension and the chances for BCVA improvement. In patients with normal renal function, vision improvement was more frequent 3 months after PPV than in patients with the diagnosis of renal failure (78% vs 50%), while patients without hypertension were statistically significantly more likely to obtain BCVA improvement than subjects with hypertension (93% vs 62%). On the other hand, 6 months after vitrectomy, the correlation between BCVA improvement and coexistent renal failure as well as the correlation between BCVA improvement and coexistent hypertension were not statistically significant.

Six months after vitrectomy, BCVA improvement was more frequent among patients who received ranibizumab before PPV than in the control group (87% vs 70%) but this difference was not statistically significant. BCVA improvement was compared in patients with ranibizumab pre-treatment and patients undergoing vitrectomy without IVR in selected subgroups: without ischemic heart disease, without the history of myocardial infarction, without renal failure and with type 2 diabetes mellitus. In the group of patients without renal failure, subjects with IVR before the surgery were 4 times more likely to achieve BCVA improvement 6 months after the surgery than patients from the control group (87% vs 62%). When excluding the effect of diabetes duration, patients with ranibizumab pre-treatment were over 10 times more likely to achieve BCVA improvement 6 months after PPV than patients without IVR and this difference was statistically significant ($p<0.050$). The study group and the control group had different baseline duration of diabetes, which was 5 years shorter in the study group than in the control group.

A question arises whether additional factors worsening therapy outcomes occur in patients with renal failure. Kidney insufficiency considerably increases the risk of cardiovascular diseases. Apart from classic risk factors

Table IV

Predicted improvement of visual acuity 6 months after PPV depending on different factors in patients without renal failure and after excluding the influence of: age, diabetes duration, diabetes type and baseline visual acuity

Таблица IV

Прогнозирование улучшения остроты зрения 6 мес. после витректомии в зависимости от исследуемых факторов среди пациентов без почечной недостаточности при исключении влияния по очереди: возраста, продолжительности сахарного диабета и исходной остроты зрения (ОЗ)

Factor Фактор	VA impr % ОЗ до операции %			Age возраст		DM duration СД Продолжительность		DM type СД тип		V≥0,5	
		OR	P	OR	P	OR	p	OR	p	OR	p
Baseline VA: Исходная ОЗ											
<0.1	88%	3.29	0.198	3.77	0.167	2.97	0.256	3.46	0.193	1.37	0.811
0.1-0.5	70%	1.00		1.00		1.00		1.00		1.00	
>0.5	50%	0.43	0.590	0.68	0.818	0.39	0.563	0.53	0.701	0.14	0.278
IVR time: ИВР время											
Control group Контрольная группа	63%	0.61	0.592	1.35	0.798	0.14	0.153	0.36	0.509	0.35	0.382
1 day before PPV 1 день до PPV	100%										
3 days before PPV 3 день до PPV	73%	1.00		1.00		1.00		1.00		1.00	
5 days before PPV 5 день до PPV	100%										
IVR time [1 day] IVR время [1 день]:		1.12	0.759	1.09	0.824	1.13	0.753	1.10	0.809	1.22	0.737
Treatment: Лечение:											
Control group Контрольная группа	62%	1.00		1.00		1.00		1.00		1.00	
IVR-treated subgroups ИВР-группа	87%	3.90	0.133	3.15	0.234	10.81	0.050	8.79	0.101	8.06	0.076
DM type [2 vs 1] СД тип [2 vs 1]											
type 1 DM тип 1 СД	75%	1.00		1.00		1.00		1.00		1.00	
type 2 DM тип 2 СД	83%	1.60	0.622	0.90	0.928	3.31	0.357	3.76		3.76	0.239
DM duration [year] СД продолжитель.[годы]		1.01	0.711	1.01	0.751		.	0.99	0.394	0.99	0.789
Age [year] Возраст [годы]		1.04	0.258		.	1.05	0.204	1.09	0.253	1.09	0.071
Sex [W vs M] Пол [Ж vs M]											
Men мужчины	79%										
Women женщины	86%	1.58	0.618	1.37	0.736	1.65	0.586	1.67	0.577	1.69	0.674
HbA1 before PPV [1%] HbA1 до PPV [1%]		0.00	0.544	0.02	0.741	0.00	0.586	0.00	0.694	0.00	0.553
Renal failure: нефропатия -	81%										

Factor Фактор	VA impr % ОЗ до операции %			Age возраст		DM duration СД Продолжительность		DM type СД тип		V≥0,5	
		OR	P	OR	P	OR	p	OR	p	OR	p
Hypertension: гипертензия											
-	82%	1.00		1.00		1.00		1.00		1.00	
+	81%	0.93	0.941	0.88	0.890	0.95	0.953	0.90	0.905	0.48	0.650
Ischemic heart disease ИБС											
-	81%	1.00		1.00		1.00		1.00		1.00	
+	80%	0.96	0.973	0.59	0.686	0.93	0.952	0.80	0.858	0.33	0.424
Myocardial infarction Инфаркт миокарда											
-	82%	1.00		1.00		1.00		1.00		1.00	
+	67%	0.43	0.516	0.32	0.397	0.37	0.459	0.36	0.450	0.20	0.261
Tractional RD Тракционная ОС											
-	92%	1.00		1.00		1.00		1.00		1.00	
+	64%	0.15	0.046	0.15	0.050	0.16	0.063	0.15	0.053	0.38	0.511
Baseline VA Тракционная ОС											
≤0.5	88%	1.00		1.00		1.00		1.00			
> 0.5	83%	0.68	0.761	0.35	0.462	0.65	0.735	0.55	0.651		.

Abbreviations: VA visual acuity, IVR – intravitreal ranibizumab.
Примечание: СД – сахарный диабет, HbA1 – гликированный гемоглобин, ИБС – ишемическая болезнь сердца, ОС – отслойка сетчатки, PPV – витректомия pars plana, IVR – инъекции ранибизумаба.

for cardiovascular diseases (such as age, male sex, hypertension, left ventricular hypertrophy, smoking, diabetes and lipid disorders), the role of the so-called new risk factors is being underlined more and more often. The latter include inflammatory reaction, oxidative stress, endothelial cell dysfunction, protein loss, activation of sympathetic system and insulin resistance [12]. Patients with renal failure have endothelial cell dysfunction which increases while the impairment of renal function becomes more severe, oxidative stress markers are present in serum and higher activity of proinflammatory factors is observed, particularly in patients on dialyses [18]. Oxidative stress, endothelial cell dysfunction, insulin resistance and increased activity of proinflammatory factors promote the progression of diabetic retinopathy [4, 8]. Therefore, patients with renal failure should be considered at higher risk of diabetic retinopathy progression.

In our patients, the presence of tractional retinal detachment was associated with statistically significant reduction of the chances for BCVA improvement: by 78% 3 months after PPV and by 79% 6 months after PPV and these results are at the borderline of statistical significance. This correlation occurs particularly when detachment involves the posterior pole. In the detached retina, apoptosis of photoreceptors takes place as a consequence of the separation of neurosensory retina from RPE and choroidal capillaries which results in irreversible functional deterioration, also after retinal re-attachment [2, 6, 10, 21].

An important issue is the effect of anti-VEGFs on the development and progression of tractional retinal detachment. In a multicenter study of 211 patients with PDR who received bevacizumab prior to vitrectomy, Arevalo et al. found the development or progression of tractional retinal detachment in 5.2% of patients [1]. These authors emphasized that the natural course of proliferative retinopathy involved cycles of neovascular proliferation and regression, the proliferation of fibrous tissue co-occurring with pathological vessels as a consequence of these processes, traction occurs between fibrovascular membranes and posterior hyaloid membrane on the one hand, and retina on the other. Thus, the development of tractional retinal detachment in patients with advanced proliferative retinopathy may be the result of both rapid regression of pathological vascularization coexisting with increased fibrosis and the shrinkage of proliferative membranes and posterior hyaloid membrane as well as natural course of the disease. The authors conclude that the benefits associated with anti-VEGF pretreatment may save more eyes with advanced PDR. Vitrectomy should be preferably performed after full antiangiogenic effect had been achieved and fibrotic processes are still not very intense.

CONCLUSIONS

Our findings are not conclusive as to the optimum time of ranibizumab injection before surgery. The surgeons

admitted that visualization of the patches of adhesions between the proliferative membrane and retina was very difficult due to bleeding in control group. On the first day after IVR, eye fundus assessment showed considerable restriction of pathological vessels in the majority of cases. In some neovascular vessels, blood flow was maintained and they had to be closed with endodiathermy which was still much easier to perform than in patients without ranibizumab pre-treatment due to better visualization. Three days after the injection, pathological vessels with blood flow were rare. The intensification of tractional retinal detachment was not observed among patients who underwent PPV. However, we cannot exclude the expansion of areas with no or limited perfusion. As mentioned before, many systemic factors associated with diabetes severity contribute to BCVA improvement. The identification of optimum time interval between ranibizumab injection and vitrectomy requires further research. The experience gathered so far seems to support day 1 and day 3 after the injection.

Our findings clearly show that patient's general status has an enormous effect on the development and progression of retinopathy as well as on treatment outcomes. It is important to remember about persisting effect of previous poor glycemic control (metabolic memory) on the development of chronic complications of diabetes, therefore good visual acuity after surgery may be achieved and maintained only with close cooperation between patient, diabetologist and ophthalmologist.

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Поступила 24.12.2017